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The direct cost of seizure events in severe childhood-onset epilepsies: A retrospective claims-based analysis

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ABSTRACT

Objective: The objective of the study was to assess the direct cost of medically treated seizure events in severe childhood-onset epilepsies. Lennox–Gastaut syndrome (LGS), Dravet syndrome (DS), and tuberous sclerosis complex (TSC) are representative conditions associated with frequent intractable seizures.
Methods: Commercial and Medicaid insurance claims from 2010 to 2015 were queried to identify patients with possible LGS, possible DS, or TSC, having ≥2 years of continuous insurance from the date of first epilepsy/seizure diagnosis or antiepileptic drug (AED) fill (index date). Utilization and cost data in patients with and without seizure events requiring acute treatment were evaluated for two years postindex. Medically treated seizure events resulting in minor, moderate, severe, and no injury were included. Average costs were normalized to 2017 dollars at 3% per annum and reported for each cohort, by insurance type and degree of injury.
Results: Among 9754 patients, 55.4–58.8% of LGS, 47.7–55.8% of DS, and 13.7–28.0% of TSC cohorts had ≥1 medically treated seizure event, depending on insurance type. Events during two-year postindex averaged 2.8–3.3 in LGS, 3.1–3.3 in DS, and 1.9–2.2 in TSC; cost per event averaged $8147–$14,759 in LGS, $4637–$8751 in DS, and $5335–$9672 in TSC. In patients with events, average all-cause costs per-patient-per-year (PPPY) were $71,512–$84,939 in LGS; $31,278–$43,758 in DS; and $42,997–$48,330 in TSC.
Conclusions: Patients with intractable seizures having at least one medically treated seizure event incur substantial all-cause costs. Our results can be used to inform cost effectiveness and budget impact models to estimate the value of existing and future treatments for these and similar conditions.

1. Introduction

Epilepsy is the fourth most common neurological condition and afflicts approximately 3.4 million patients in the United States [1], with an incidence of approximately 150,000 new cases each year [2]. Recurrent, unprovoked seizures are the defining feature of epilepsy and often result in injury, emergency intervention, hospitalization, and intensive care [3]. Approximately 30% of patients with epilepsy in the general population have drug-resistant seizures that are persisting despite treatment with at least two adequately dosed and tolerated antiepileptic drugs (AEDs) [4]. Lennox–Gastaut syndrome (LGS), Dravet syndrome (DS), and tuberous sclerosis complex (TSC) represent three conditions associated with substantially higher rates of treatment-resistant seizures, ranging from 65% in TSC [5] to >80% treatment resistance in LGS [6] and DS [7].

Lennox–Gastaut syndrome is a rare, severe, and drug-resistant epilepsy syndrome characterized by multiple generalized seizure types (including tonic, atonic, and generalized tonic–clonic seizures) that place patients at significant risk for facial and head injuries and increased risk of status epilepticus and sudden unexpected death in epilepsy (SUDEP); additionally, LGS is characterized by moderate to severe cognitive impairment [8–10]. Similarly, DS is also a rare treatment-resistant epilepsy syndrome associated with severe generalized seizures of multiple forms, developmental delays, and increased risk of status epilepticus and SUDEP [11–13]. In TSC, patients suffer from multiorgan, nonmalignant tumors throughout the body, resulting in significant neurological, renal, pulmonary, and dermatological effects; and seizures specifically are common and typically drug-resistant [14].

Adult patients with drug-resistant epilepsy and recurrent seizures require more healthcare services (more emergency department (ED) visits, hospitalizations, physician visits, and longer hospital stays) and generate significantly higher epilepsy-related medical service and

Abbreviations: LGS, Lennox–Gastaut syndrome; DS, Dravet syndrome; TSC, tuberous sclerosis complex; SUDEP, sudden unexpected death in epilepsy; PPPY, per-patient-per-year; ICD, International Classification of Disease; AED, antiepileptic drug; ED, emergency department; IP, inpatient; OP, outpatient; SD, standard deviation.

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pharmacy costs when compared with patients with well-controlled epilepsy ($23,238 vs $13,839, respectively, claims data from 2007 to 2009) [3]. Claims analyses of patients with possible DS reported average per-patient-per-year (PPPY) all-cause costs of $30,094 and $32,572 (2017 US dollars) in patients with commercial coverage and Medicaid, respectively [15]. Studies specifically examining all-cause healthcare costs of epilepsy in patients with LGS have yielded PPPY averages ranging from $28,241 to $40,000 depending on patient age [16], to a high of $73,486 in a specific subpopulation with LGS [17]. Another claims analyses of patients with possible LGS reported average PPPY all-cause costs of $65,026 and $63,930 (2017 US dollars) in patients with commercial and Medicaid coverage, respectively [18]. In each of these instances, patients with uncontrolled epilepsy, LGS, or DS demonstrated significantly greater costs than matched comparisons (patients with controlled epilepsy and/or populations without epilepsy).

Estimates of total PPPY medical costs provide some understanding of the direct economic impact of uncontrolled epilepsy, but lack specific cost implications for seizure reduction, the primary outcome for most epilepsy trials. While one study estimated costs associated with drop seizures in LGS, it relied exclusively on physician survey data to estimate the proportion of seizures requiring hospitalization [19]. Using a retrospective medical insurance claims analysis, the current study examines the healthcare costs resulting from medically treated seizure events with and without injury in three populations with epilepsy associated with some of the highest rates of treatment resistance and seizure-associated healthcare utilization: LGS, DS, and TSC. Evaluating the direct cost of seizures in treatment-resistant epilepsies increases understanding of the cost implications of these serious, chronic conditions and may contribute to determining cost-effective selection of therapy in patient populations with high seizure rates and high burden of care.

2. Methods

2.1. Study design

Truven Health Analytics MarketScan® Research Databases were queried for US health insurance claims data (commercial and Medicaid) among patients with medical and drug coverage between October 2010 to September 2015. These databases include claims for healthcare services and outpatient (OP) pharmacy prescriptions across the continuum of care for approximately 90 million employees, dependents, and retirees with private insurance nationally or for Medicaid enrollees from seven diverse states; the proportion of patients in capitated managed care (28% of Medicaid patients and 13% of commercial patients in this study) may not be representative.

2.2. Patient selection

Patients with claims evidence for an International Classification of Diseases, ninth revision (ICD-9) diagnosis of epilepsy or related conditions (345.*, 759.5, or 780.32) having medical and drug coverage throughout their enrollment period were selected for further consideration. A requirement of two years of continuous insurance was applied from the date of first epilepsy/seizure diagnosis or fill of any AED in the data set (index date). Thus, the study population includes a mix of newly diagnosed patients and patients with established epilepsy. Inclusion and exclusion criteria were applied to select three mutually exclusive cohorts—LGS, DS, and TSC for a series of related studies [15,18,20].

First, the TSC cohort was identified using the ICD-9 diagnosis code 759.5; comorbid TSC with LGS occurred but was rare and had little impact. Patients with Down syndrome or brain neoplasms were excluded (Supplemental Appendix 1). Next, the LGS and DS cohorts were identified from among the patients without TSC. Patients with intractable epilepsy (ICD-9345.01, 345.11, 345.81, or 345.91), intellectual disability/developmental delay (Supplemental Appendix 1), and ≥1 prescription for a selected AED (Supplemental Appendix 2) with no diagnoses indicative of other etiologies were evaluated for LGS or DS.

Patients meeting all of the following criteria were assigned to the possible DS cohort: a) no diagnoses atypical in DS (Supplemental Appendix 1), b) no repeated use of drugs generally contraindicated in DS (more than two prescriptions for over 30 days' supply of sodium channel blockers carbamazepine, lacosamide, lamotrigine, oxcarbazepine, rufinamide, or eslicarbazepine acetate, which are not recommended for use in DS due to the potential to exacerbate seizures in this population), and c) either prescriptions for ≥2 distinct AEDs (Supplemental Appendix 2) filled within 90 days of the index date or a diagnosis of febrile seizures (ICD-9780.31 or 780.32).

From the remaining sample of patients with refractory epilepsy, intellectual disability/developmental delay, and AED use, patients with possible LGS were identified using predictive modeling as described previously [18]. Briefly, patient demographic and clinical characteristics predictive of the use of rufinamide, an approved therapy for LGS considered unlikely to be used for other reasons in patients with refractory epilepsy and intellectual disability/developmental delay, were used to develop separate predictive models of possible LGS disease, by insurance type. The predictive models were applied to patients not assigned to the TSC or DS cohorts; patients who met the threshold of predicted LGS were assigned to the LGS cohort. Patients with a prior injury with ongoing care at the index date or lacking sufficient cost or utilization data were excluded.

2.3. Cost and seizure event variables

In order to distinguish seizure-related care from regular medical management (maintenance care), all-cause (service and drug) insurance claims were evaluated during a two-year postindex period to identify medically treated seizure events with and without injury. A seizure without injury was defined as an ED visit or an inpatient (IP) admission that started in the ED, in which a specified ICD-9 code for epilepsy or convulsion (345.x1, 345.10, 345.2, 345.3, 345.60, 780.3x) and no injury diagnosis code was present. Costs for seizure events without injury were accumulated through hospital discharge.

A seizure with injury was defined by the conjunction of any ICD-9 code for epilepsy or convulsion (345.* or 780.3*) and a diagnosis code for injury. Seizure-related injuries were classified as minor, moderate, or severe according to the level of injury sustained, based on injury categories established by Clements and colleagues [21], as shown in Supplemental Appendix 3.

All-cause costs for seizure events with injury were accumulated for postinjury seizure periods of 10, 30, or 90 days, varying by injury severity. Minor modifications to the Clements et al. time period criteria were added, including extending the postinjury seizure period through hospital discharge or end of repeated services with the specific injury diagnosis code and truncating at the point a new seizure occurred in the ED/IP setting, if earlier [21]. During the postinjury seizure period, nonemergency OP claims in which both seizure and injury diagnoses were present were considered ongoing care of the prior injury (not new seizure events).

Each patient's baseline mean all-cause cost per day of services and drugs not in IP or ED settings was calculated by averaging costs during the first and last 30-day segments of the two-year postindex period that was free of medically treated seizures and related postinjury care. Seizure-related costs were calculated as the all-cause cost of services and drugs during the postinjury seizure period minus the patient's baseline average cost per day, applied to nonhospital days of the seizure period.

All-cause costs not specifically attributable to seizure events, including baseline costs, were classified as maintenance care costs. Costs of all OP prescription drugs, including AEDs and rescue drugs, were included in maintenance care costs because the timing of

prescription fills precludes reliable attribution of these costs to specific seizure events.

Average cost per medically treated seizure event was evaluated within each disease cohort by insurance type and by degree of injury. In addition, average all-cause costs PPPY were evaluated for two years postindex within each disease cohort by insurance type and for patients with at least one medically treated seizure event (Event) and those with no such seizure event (No Event). In the Event group, costs were divided into seizure event costs and maintenance costs.

Costs are presented from the health plan perspective as the average total allowed cost (cost after discounts, before application of deductibles, copays, coinsurance, and coordination of benefits), and calculated PPPY, normalized to 2017 dollars at 3% per annum.

3. Results

3.1. Patient demographics and characteristics

Across the three epilepsy syndromes, 9754 patients met inclusion criteria: 5999 with possible LGS; 989 with possible DS; and 2766 with TSC (Table 1). Patients in the LGS cohort in both insurance groups had an average age of 13 years; patients in the DS cohort had an average age of 12 years in the commercial-insured group and 17 years in the Medicaid group; and patients with TSC had an average age of 27 years in the commercial-insured group and 26 years in the Medicaid group. Depending on insurance type, medically treated seizure events were observed in 55.4–58.8% of LGS, 47.7–55.8% of DS, and 13.7–28.0% of patients with TSC.

A total of 4519 patients had 13,440 medically treated seizure events. Depending on insurance type, among those with medically treated seizure events, patients in the LGS cohort averaged 2.8 (±2.8) to 3.3 (±3.5) events, patients in the DS cohort averaged 3.1 (±3.4) to 3.3 (±3.4) events, and patients in the TSC cohort averaged 1.9 (±1.8) to 2.2 (±2.3) events during the postindex period. The majority of medically treated seizure events in all cohorts did not result in injuries (Supplemental Appendix 4).

3.2. Cost per medically treated seizure event

Combining all medically treated seizure events (resulting in no injury and all levels of injuries), the average cost per event, depending on insurance type, was $8147 (±43,218) to $14,759 (±43,600) for the LGS cohort; $4637 (±26,826) to $8751 (±16,028) for the DS cohort; and $5335 (±24,445) to $9672 (±24,071) for the TSC cohort (Fig. 1 and Supplemental Appendix 5). Medically treated seizure events resulted in IP admission for 28–42% of events without injury and 6–18% events with injury in most cohorts (0–33% in the small DS commercial cohort). In general, the cost of seizures with injuries increased as severity of injury increased, except in the case of patients with DS covered under commercial insurance, where there were many fewer patients.

3.3. Annual all-cause costs

Patients with medically treated seizure events in both insurance groups had substantial annual all-cause average costs of $71,512 (±$94,213) to $84,939 (±$109,786) in LGS; $31,278 (±$49,239) to $43,758 (±$52,589) in DS; and $42,997 (±$63,505) to $48,330 (±$63,505) in TSC, where the proportion of annual costs attributable to events, depending on insurance type, were 19–24% in LGS, 24–31% in DS, and 14–19% in TSC. The annual average costs of medically treated seizure events in patients with at least one event were $13,252 (±$47,046) to $20,455 (±$45,423) in LGS; $7540 (±$25,886) to $13,584 (±$20,446) in DS; and $5927 (±$20,642) to $9174 (±$18,165) in TSC (Fig. 2 and Supplemental Appendix 6).

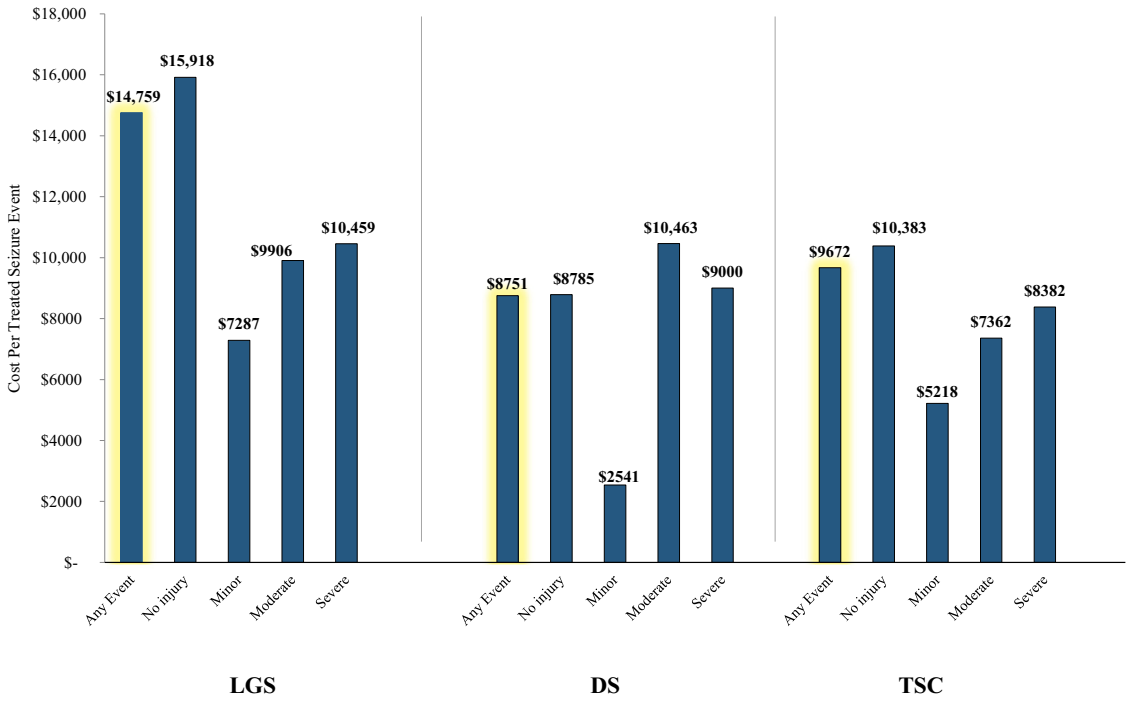
Depending on disease and insurance type, patients with seizure events averaged 0.5 (±1.0) to 1.1 (±1.3) IP admissions, 1.3 (±1.4) to 2.3 (±2.5) ED visits, 4.7 (±10.6) to 10.1 (±25.2) hospital OP visits,

Table 1
Demographics and seizure events, by disease cohort and insurance type.

	Lennox–Gastaut syndrome			Dravet syndrome			Tuberous sclerosis complex		
	All patients	Patients with Event(s)	Patients with No Event	All patients	Patients with Event(s)	Patients with No Event	All patients	Patients with Event(s)	Patients with No Event
Commercial insurance									
n (%)	2269 (100)	1258 (55.4)	1011 (44.6)	321 (100)	153 (47.7)	168 (52.3)	1622 (100)	223 (13.7)	1399 (86.3)
Age, mean year (SD)	13 (9.8)	12 (10.1)	15 (9.4)	12 (10.8)	11 (12.1)	14 (9.2)	27 (18.6)	18 (15.9)	28 (18.6)
Age, range year	0–62	0–59	0–62	0–62	0–62	1–53	0–63	0–63	0–63
Male, n (%)	1203 (53.0)	695 (55.2)	508 (50.2)	178 (55.5)	84 (54.9)	94 (56.0)	754 (46.5)	112 (50.2)	642 (45.9)
# AEDs at index, mean (SD)	2.02 (1.24)	2.08 (1.31)	1.95 (1.14)	1.97 (0.88)	1.82 (1.05)	2.10 (0.66)	0.56 (0.90)	1.14 (1.17)	0.47 (0.82)
# events PPPY, mean (SD)	0.77 (1.23)	1.63 (1.71)	N/A	0.74 (1.41)	1.55 (1.72)	N/A	0.13 (0.46)	1.39 (1.37)	N/A
# events per patient during postindex period, mean (SD)	1.54 (2.47)	2.77 (2.75)	N/A	1.48 (2.83)	3.10 (3.43)	N/A	0.26 (0.92)	1.90 (1.75)	N/A
Total # of events during postindex period	N/A	3487	N/A	N/A	475	N/A	N/A	423	N/A
No injury events	N/A	2846	N/A	N/A	405	N/A	N/A	329	N/A
Minor injury events	N/A	118	N/A	N/A	13	N/A	N/A	23	N/A
Moderate injury events	N/A	304	N/A	N/A	36	N/A	N/A	39	N/A
Severe injury events	N/A	219	N/A	N/A	21	N/A	N/A	32	N/A
Medicaid insurance									
n (%)	3730 (100)	2192 (58.8)	1538 (41.2)	668 (100)	373 (55.8)	295 (44.2)	1144 (100)	320 (28.0)	824 (72.0)
Age, mean year (SD)	13 (10.5)	12 (10.9)	15 (9.9)	17 (15.5)	13 (15.3)	21 (14.6)	26 (19.9)	24 (17.9)	27 (20.6)
Age, range year	0–60	0–60	0–60	0–69	0–61	1–69	0–89	0–66	0–89
Male, n (%)	1969 (52.8)	1207 (55.1)	762 (49.5)	380 (56.9)	226 (60.6)	154 (52.2)	555 (48.5)	158 (49.4)	397 (48.2)
# AEDs at index, mean (SD)	2.15 (1.18)	2.13 (1.21)	2.18 (1.13)	1.96 (0.92)	1.78 (1.07)	2.18 (0.62)	0.97 (1.15)	1.44 (1.28)	0.79 (1.04)
# events per year, mean (SD)	0.96 (1.56)	0.95 (0.87)	N/A	0.91 (1.51)	1.63 (1.74)	N/A	0.31 (0.78)	1.11 (1.13)	N/A
# events during postindex period, mean (SD)	1.91 (3.12)	3.25 (3.49)	N/A	1.82 (3.02)	3.25 (3.42)	N/A	0.62 (1.55)	2.22 (2.25)	N/A
Total # events during postindex period	N/A	7131	N/A	N/A	1213	N/A	N/A	711	N/A
No injury events	N/A	5443	N/A	N/A	1018	N/A	N/A	457	N/A
Minor injury events	N/A	363	N/A	N/A	43	N/A	N/A	51	N/A
Moderate injury events	N/A	740	N/A	N/A	84	N/A	N/A	136	N/A
Severe injury events	N/A	585	N/A	N/A	68	N/A	N/A	67	N/A

Note: SD = standard deviation.

a. Costs per event for commercial-insured patients



b. Costs per event for Medicaid-insured patients

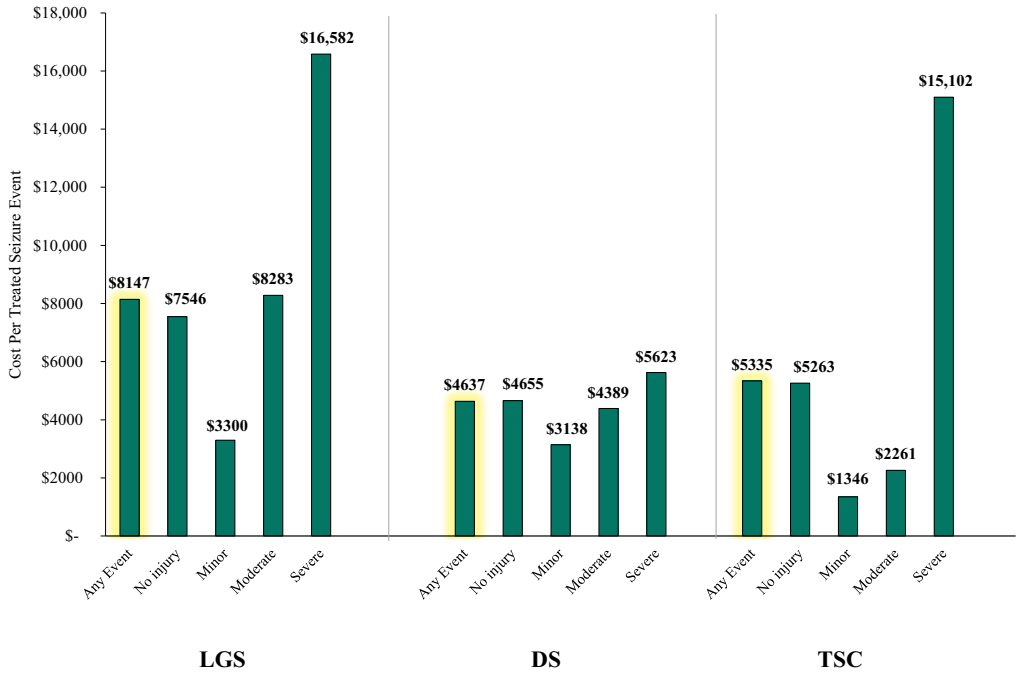


Fig. 1. Cost per medically treated seizure event by injury category for each disease cohort and insurance type (highlighted—cost for patients with and without injury): a (top) commercial-insured patients, b (bottom) Medicaid-insured patients. Refer to Supplemental Appendix 4 for related data.

6.7 (±7.3) to 15.4 (±21.9) physician visits, and 13.1 (±14.3) to 29.1 (±16.4) AED prescription fills PPPY, Table 2.

Depending on disease cohort and insurance type, patients with medically treated seizure events had a mean cost PPPY of $9056 (±$30,014) to $34,929 (±$67,542) for IP admissions; $968 (±$1474) to $3473 (±$4114) for ED visits; $2158 (±$4892) to $12,841 (±$27,857) for hospital OP visits; and $2105 (±$3903) to $10,209 (±$23,837) for AEDs, Table 3.

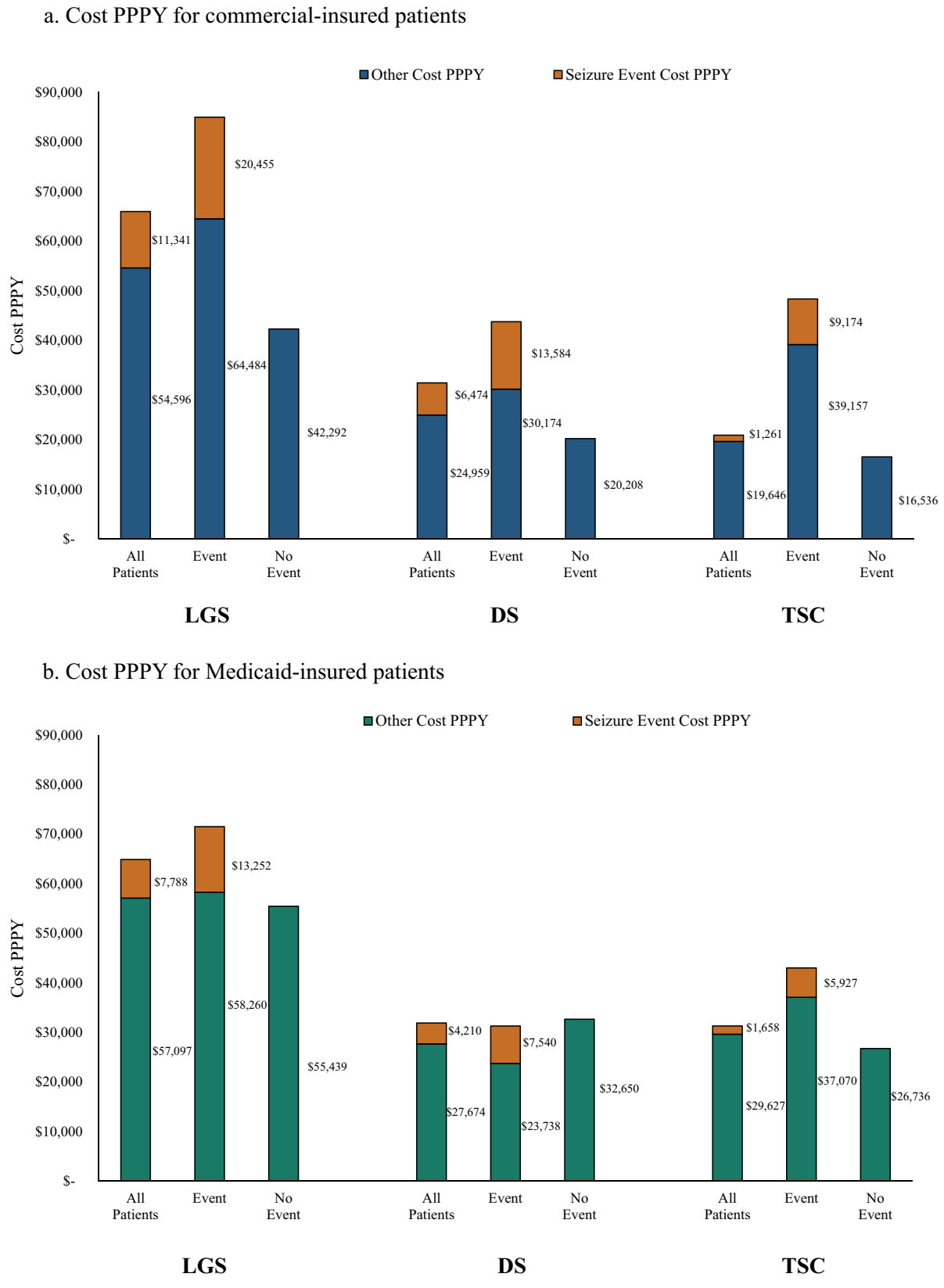


Fig. 2. Cost PPPY for patients with and without medically treated seizure events and the impact of events on costs, by disease cohort and insurance type: a (top) commercial-insured patients, b (bottom) Medicaid-insured patients. Refer to Supplemental Appendix 5 for related data.

Inpatient admissions generated 21% to 45% of total costs among patients with medically treated seizure events and 4% to 23% of total costs among patients with no seizure events, Table 3. Depending on disease cohort and insurance type, 37–57% of patients with seizure events were admitted to the hospital from the ED at least once during the two-year postindex period.

Table 2
Average all-cause utilization PPPY, by disease cohort and insurance type.

			Service utilization PPPY by category, mean (SD)							Drug fills PPPY by type, mean (SD)		
	Seizure status	n	Inpatient admissions	ED visits	Hospital OP visits	Physician visits	Other OP	Home health	Equipment/ Supply	AEDs	Rescue drugs	Other drugs
LGS												
Commercial	All patients	2269	0.7 (1.1)	1.1 (1.6)	8.2 (22.2)	13.5 (19.6)	9.6 (19.6)	16.2 (46.8)	4.0 (9.3)	23.1 (14.5)	1.5 (4.4)	22.3 (26.1)
	Event	1258	1.1 (1.3)	1.7 (1.9)	10.1 (25.2)	15.4 (21.9)	10.9 (20.8)	18.1 (50.2)	4.5 (10.1)	24.4 (15.1)	2.0 (5.1)	24.9 (28.5)
	No Event	1011	0.3 (0.5)	0.3 (0.6)	5.9 (17.4)	11.1 (15.8)	8.0 (17.9)	13.8 (42.1)	3.4 (8.1)	21.6 (13.7)	0.9 (3.1)	19.2 (22.2)
Medicaid	All patients	3730	0.6 (1.0)	1.4 (2.1)	6.1 (14.9)	8.0 (10.0)	49.1 (81.0)	81.5 (126.2)	2.5 (6.0)	28.5 (16.1)	1.9 (4.2)	35.7 (40.3)
	Event	2192	0.8 (1.4)	2.1 (2.4)	7.4 (17.0)	9.0 (10.8)	48.6 (81.8)	76.5 (122.7)	2.7 (6.4)	29.1 (16.4)	2.3 (4.5)	37.2 (41.9)
	No Event	1538	0.2 (0.4)	0.4 (0.0)	4.4 (11.0)	6.6 (8.0)	49.7 (81.5)	88.7 (130.6)	2.3 (5.5)	27.7 (15.0)	1.3 (3.6)	33.6 (37.8)
DS												
Commercial	All patients	321	0.5 (0.8)	1.0 (1.5)	7.0 (20.3)	10.7 (11.5)	9.1 (20.1)	5.7 (20.0)	1.0 (3.0)	18.9 (11.5)	1.0 (3.2)	15.0 (16.3)
	Event	153	0.8 (1.0)	1.8 (1.8)	8.0 (17.4)	12.4 (11.1)	11.1 (19.9)	5.7 (26.9)	0.8 (2.2)	17.6 (11.0)	1.5 (4.3)	15.1 (14.4)
	No Event	168	0.2 (1.0)	0.2 (0.4)	6.1 (22.6)	9.2 (11.6)	7.3 (20.2)	5.6 (23.0)	1.1 (4.0)	20.0 (11.2)	0.5 (1.2)	14.8 (17.9)
Medicaid	All patients	668	0.4 (0.7)	1.4 (2.1)	3.8 (8.3)	6.4 (9.4)	43.1 (84.2)	44.4 (97.8)	0.7 (2.7)	21.3 (13.1)	1.0 (2.4)	27.7 (35.9)
	Event	373	0.6 (0.9)	2.3 (2.5)	4.7 (10.6)	6.7 (7.3)	30.1 (62.9)	34.8 (84.1)	0.8 (3.4)	20.1 (14.1)	1.4 (2.7)	27.3 (37.7)
	No Event	295	0.1 (0.2)	0.3 (0.5)	2.5 (3.4)	6.0 (11.5)	59.4 (103.0)	56.4 (111.8)	0.6 (1.6)	22.7 (11.7)	0.4 (1.8)	28.1 (33.4)
TSC												
Commercial	All patients	1622	0.2 (0.4)	0.4 (0.9)	3.0 (5.9)	9.1 (12.7)	5.8 (15.1)	1.2 (10.6)	0.4 (1.8)	5.4 (9.9)	0.1 (0.6)	11.4 (17.1)
	Event	223	0.5 (0.7)	1.3 (1.4)	4.7 (8.9)	13.3 (18.8)	7.6 (16.5)	2.1 (7.9)	0.8 (3.6)	13.1 (14.3)	0.6 (1.3)	14.1 (21.4)
	No Event	1399	0.1 (0.4)	0.3 (0.8)	2.7 (5.2)	8.4 (11.3)	5.5 (14.9)	1.0 (10.9)	0.3 (1.4)	4.2 (8.4)	0.1 (0.4)	11.0 (16.3)
Medicaid	All patients	1144	0.3 (0.7)	1.0 (1.9)	3.8 (6.8)	7.5 (16.3)	44.9 (90.2)	34.0 (84.2)	0.8 (2.7)	11.6 (14.9)	0.4 (1.2)	26.6 (37.6)
	Event	320	0.5 (1.0)	1.7 (1.9)	5.3 (9.2)	8.4 (9.0)	49.2 (97.6)	40.2 (88.2)	1.0 (2.5)	18.0 (17.2)	0.8 (1.8)	27.9 (33.0)
	No Event	824	0.2 (0.5)	0.7 (1.8)	3.2 (5.5)	7.2 (18.3)	43.2 (87.2)	31.6 (82.5)	0.8 (2.8)	9.2 (13.2)	0.2 (0.7)	26.1 (39.3)

4. Discussion

While the economic burden of some difficult to treat epilepsies has been described [15,18,20], details on the direct cost of seizures in LGS, DS, and TSC are lacking. Patients with one or more medically treated seizure event covered under either commercial or Medicaid insurance had substantial annual all-cause costs of at least $72,000 in LGS, $31,000 in DS, and $42,000 in TSC, where 14–31% of costs (depending on disease and insurance type) were attributable to seizure events.

Using US health insurance claim data, Cramer et al. reported that adults with uncontrolled epilepsy (added AEDs to existing therapy) had higher annual overall (medical and pharmacy) costs and epilepsy-related costs than those with well-controlled epilepsy (no change in AED therapy) over a one-year period [3]. Similarly, using German health insurance data, Strzelczyk et al. reported that patients with severe drug-refractory epilepsy had increased rates of hospitalization, with increased morbidity and mortality rates compared with the general population [22].

Although the design of this study limits direct comparisons between disease cohorts, event types, and insurance types, we observed several interesting patterns that have clinical relevance. The lower proportion of medically treated seizure events in patients with TSC could be explained by the relatively lower rates of treatment resistance [5,23] and a relatively lower frequency of seizures. The higher utilization of maintenance services by patients with vs without seizure events regardless of insurance type suggests that patients experiencing seizures require more ongoing care than patients who have not experienced seizures requiring medical treatment. Similarly, the generally higher all-cause costs for both maintenance care and seizure events in patients with vs without events (with the exception of Medicaid-insured patients with DS, where costs were similar) likely reflect the reported increased cost of care associated with severe drug-resistant epilepsy syndromes [3]. Patients with at least one medically treated seizure event incurred $7000 to $25,000 PPPY more in IP care costs than those without seizure events. The PPPY cost of ED visits was also substantially higher among patients with vs without events in all cohorts.

In the populations with LGS and TSC covered under commercial insurance, medically treated seizure events that did not involve injuries were more costly than events with injury, which may be due to the relatively higher rates of hospitalization in these types of events. These differences emerged despite the inclusion of an extended period of time around the episode of the seizure with injury; 10 days for minor injury, 30 days for moderate injury, and 90 days for severe injury, with the latter including head and skull fracture, burns, and cortex lacerations.

In the Medicaid-insured populations, patients with seizure events had lower utilization of hospital and physician visits, higher utilization of home health and other OP services, and generally lower all-cause costs compared with commercial-insured patients with seizure events. It is possible that home health services may be a substitute for acute care, with unknown differences in treatment quality and acute and long-term clinical outcomes. It is also possible, however, that higher utilization of home health services may help stabilize or even reduce the need for other services by addressing problems before they require interaction with other acute care settings, like emergency rooms and physician offices. Further exploration of the qualitative and quantitative features of services offered through home health may be worthwhile. For example, long-term exercise therapy may have some benefits in individuals with epilepsy. In a preclinical study, daily swimming exercises for 30 days reduced the learning and memory deficits in epileptic rats [24]. Comparable positive effects were identified in another study of learning and memory in rats in terms of long-term potentiation upon exposure to aerobic exercise [25]. Additionally, a single noncontrolled study of 10 children with benign epilepsy with centrotemporal spikes who completed 5 weeks of supervised exercise and 30 weeks of subsequent home-based exercise showed significant improvement in neurocognitive and psychological domains [26].

5. Limitations

The general limitations of using ICD coding are well-established [27], however, given the lack of distinct ICD-9 diagnosis codes for LGS and DS, the necessarily exploratory methodologies identifying representative populations with LGS and DS are not yet validated. Future studies validating identification methods for LGS, DS, and similar conditions in claims data will be important.

Table 3
Average all-cause costs PPPY, by disease cohort and insurance type, (service costs, table a and drug fill and total costs, table b).

a.			Service costs PPPY by category, mean (SD)						
	Seizure category	n	Inpatient admissions	ED visits	Hospital OP visits	Physician visits	Other OP	Home health	Equipment/Supply
LGS									
Commercial	All patients	2269	$23,623 ($56,494)	$2148 ($4601)	$10,458 ($24,409)	$2972 ($10,549)	$2306 ($7197)	$8605 ($38,165)	$1846 ($5044)
	Event	1258	$34,929 ($67,542)	$3469 ($5748)	$12,841 ($27,857)	$3483 ($12,874)	$2917 ($8837)	$9722 ($39,765)	$1994 ($5502)
	No Event	1011	$9555 ($33,644)	$505 ($1241)	$7491 ($18,874)	$2337 ($6550)	$1546 ($4253)	$7215 ($36,046)	$1663 ($4403)
Medicaid	All patients	3730	$14,346 ($55,442)	$836 ($1819)	$3525 ($16,371)	$864 ($2233)	$9065 ($23,864)	$23,430 ($41,921)	$1359 ($2703)
	Event	2192	$20,681 ($61,771)	$1272 ($1898)	$4208 ($20,956)	$962 ($2440)	$9144 ($25,210)	$21,492 ($39,840)	$1346 ($2661)
	No Event	1538	$5318 ($43,352)	$214 ($1493)	$2551 ($4756)	$724 ($1890)	$8952 ($21,809)	$26,191 ($44,588)	$1378 ($2763)
DS									
Commercial	All patients	321	$10,847 ($28,133)	$1811 ($3290)	$5769 ($11,643)	$2154 ($3255)	$1817 ($4479)	$1540 ($8445)	$438 ($1644)
	Event	153	$19,875 ($38,279)	$3473 ($4114)	$6982 ($13,967)	$2641 ($3771)	$2398 ($5677)	$991 ($3086)	$294 ($1083)
	No Event	168	$2625 ($6340)	$297 ($702)	$4665 ($8922)	$1711 ($2635)	$1287 ($2918)	$2040 ($11,290)	$569 ($2018)
Medicaid	All patients	668	$5694 ($23,135)	$810 ($1647)	$1728 ($1647)	$574 ($961)	$7566 ($20,646)	$10,390 ($26,767)	$276 ($1076)
	Event	373	$9056 ($30,014)	$1357 ($2023)	$2158 ($4892)	$601 ($708)	$5388 ($17,755)	$7940 ($25,180)	$313 ($1173)
	No Event	295	$1444 ($6479)	$119 ($347)	$1185 ($3123)	$540 ($1208)	$10,320 ($23,548)	$13,488 ($28,390)	$230 ($938)
TSC									
Commercial	All patients	1622	$5226 ($19,684)	$902 ($2892)	$4951 ($9795)	$1885 ($4828)	$1210 ($9963)	$475 ($7116)	$141 ($1230)
	Event	223	$13,769 ($26,772)	$2992 ($5329)	$8974 ($11,878)	$3040 ($6635)	$2723 ($19,778)	$645 ($3498)	$341 ($2586)
	No Event	1399	$3865 ($17,943)	$568 ($11,878)	$4309 ($9265)	$1700 ($4449)	$969 ($7249)	$448 ($7534)	$109 ($828)
Medicaid	All patients	1144	$4062 ($17,487)	$520 ($1482)	$2086 ($5299)	$767 ($3448)	$8178 ($23,402)	$8061 ($23,815)	$203 ($931)
	Event	320	$9085 ($29,520)	$968 ($1474)	$2719 ($4079)	$716 ($970)	$9118 ($25,380)	$8771 ($21,381)	$332 ($1374)
	No Event	824	$2111 ($8563)	$346 ($1450)	$1840 ($5686)	$787 ($4018)	$7812 ($22,594)	$7786 ($24,702)	$153 ($681)

b.			Drug fill costs PPPY by type, mean (SD)			Total costs PPPY, mean (SD)		
	Seizure category	n	AEDs	Rescue drugs	Other drugs	Total services	Total drugs	Total costs
LGS								
Commercial	All patients	2269	$8526 ($13,662)	$755 ($3070)	$4698 ($18,299)	$51,958 ($88,914)	$13,979 ($23,987)	$65,937 ($96,223)
	Event	1258	$9144 ($14,464)	$974 ($3395)	$5467 ($18,431)	$69,354 ($101,479)	$15,585 ($25,239)	$84,939 ($109,786)
	No Event	1011	$7756 ($12,559)	$482 ($2585)	$3742 ($18,096)	$30,311 ($63,955)	$11,980 ($22,184)	$42,292 ($69,147)
Medicaid	All patients	3730	$6488 ($11,740)	$813 ($2526)	$4159 ($15,717)	$53,425 ($79,152)	$11,460 ($21,552)	$64,885 ($86,000)
	Event	2192	$6914 ($12,982)	$980 ($2640)	$4512 ($18,923)	$59,106 ($86,008)	$12,406 ($25,184)	$71,512 ($94,213)
	No Event	1538	$5882 ($9672)	$574 ($2334)	$3655 ($9407)	$45,329 ($67,406)	$10,110 ($14,824)	$55,439 ($71,687)
DS								
Commercial	All patients	321	$4130 ($5375)	$516 ($2013)	$2411 ($8020)	$24,376 ($38,308)	$7057 ($9962)	$31,433 ($41,835)
	Event	153	$3813 ($5448)	$860 ($2822)	$2432 ($9522)	$36,653 ($48,409)	$7105 ($11,314)	$43,758 ($52,589)
	No Event	168	$4418 ($5308)	$203 ($553)	$2392 ($6382)	$13,195 ($20,376)	$7013 ($8581)	$20,208 ($23,884)
Medicaid	All patients	668	$2488 ($4440)	$360 ($1038)	$1998 ($4726)	$27,039 ($42,876)	$4845 ($6904)	$31,884 ($45,174)
	Event	373	$2105 ($3903)	$523 ($1299)	$1838 ($5164)	$26,811 ($46,934)	$4467 ($6890)	$31,278 ($49,239)
	No Event	295	$2972 ($5002)	$153 ($483)	$2199 ($4105)	$27,327 ($37,194)	$5324 ($6903)	$32,650 ($39,510)
TSC								
Commercial	All patients	1622	$3087 ($12,019)	$64 ($390)	$2965 ($14,713)	$14,790 ($32,935)	$6117 ($20,148)	$20,907 ($40,657)
	Event	223	$10,209 ($23,837)	$255 ($703)	$5380 ($21,999)	$32,486 ($52,979)	$15,844 ($34,153)	$48,330 ($63,505)
	No Event	1399	$1952 ($8240)	$34 ($302)	$2580 ($13,155)	$11,969 ($27,461)	$4566 ($16,370)	$16,536 ($33,722)
Medicaid	All patients	1144	$3150 ($10,815)	$142 ($626)	$4115 ($18,875)	$23,878 ($38,111)	$7407 ($23,252)	$31,284 ($46,777)
	Event	320	$6433 ($17,298)	$288 ($803)	$4567 ($17,095)	$31,708 ($43,499)	$11,288 ($27,327)	$42,997 ($56,090)
	No Event	824	$1875 ($6376)	$85 ($531)	$3939 ($19,530)	$20,837 ($35,365)	$5899 ($21,291)	$26,736 ($41,778)

6. Conclusions

In our study, patients with intractable seizures having at least one medically treated seizure event utilized high levels of healthcare services and drugs and had substantial all-cause costs. It will be important to identify emerging treatments that improve burden of illness and to understand their role in possibly potentiating some of the long-term negative consequences of drug-resistant epilepsy conditions. Our results can be used to inform cost effectiveness and budget impact models to estimate the value of existing and future treatments for LGS, DS, TSC, and similar conditions.

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Disclosures of conflicts of interest

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Ethical publication statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2019.01.045.

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