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Risk of hospitalization among patients with epilepsy using long versus short half-life adjunctive antiepileptic drugs

Joyce A. Cramer [a], Tingjian Yan [b], Ryan Tieu [b], Russell L. Knoth [c], Contessa Fincher [c], Manoj Malhotra [c], Jiyoon Choi [c,*]

[a] Houston, TX, USA
[b] Partnership for Health Analytic Research, LLC, 280 S. Beverly Dr., Ste. 404, Beverly Hills, CA 90212, USA
[c] Eisai Inc., 100 Tice Blvd., Woodcliff Lake, NJ 07677, USA

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ABSTRACT

Introduction: While antiepileptic drugs (AEDs) remain the primary treatment for epilepsy, many patients continue to have seizures. Uncontrolled seizures may be related to AED half-life, since short half-life (SHL) AEDs require more frequent dosing compared with the simplified regimens of long half-life (LHL) AEDs. Long half-life AEDs may also improve seizure control by extending missed dose forgiveness periods. The value of LHL AEDs may be assessed as reduced healthcare utilization. The study's objective was to examine the impact of adding an LHL versus SHL adjunctive AED on the risk of hospitalizations in patients with uncontrolled epilepsy.
Methods: This was a retrospective, longitudinal cohort study using the Symphony Health Solution Patient Integrated Dataverse. Patients ≥12 years old with uncontrolled epilepsy (≥2 medical claims ≥30 days apart) were identified during a study period (8/1/2012–7/31/2017). Patients were selected if they were subsequently initiated an adjunctive AED (excluding modified release formulations), and the prescription date served as the index. Patients were stratified into two mutually exclusive cohorts based on the index AED half-life (≤20 versus >20 h). Poisson regressions with robust error variances were performed for the relative risks (RRs) of all-cause, epilepsy-related, and injury-related hospitalizations.
Results: A total of 4984 patients were identified (2705 in the LHL and 2279 in the SHL cohort). Compared with those in the SHL cohort, patients in the LHL cohort were significantly younger [mean (SD, years): 43.9 (18.5) versus 49.2 (17.2), $p < 0.001$] and were less comorbid [mean (SD) of Charlson comorbidity index: 1.2 (1.8) versus 1.8 (2.2), $p < 0.001$]. In the one-year postindex date, adjusting for group differences, the risks of both all-cause and epilepsy-related hospitalizations were significantly lower in the LHL cohort than in the SHL cohort [all-cause: 0.84 (95% CI: 0.76–0.93), $p = 0.0006$; epilepsy-related: 0.83 (0.73–0.94), $p = 0.0046$].Injury-related hospitalizations did not differ between LHL and SHL cohorts.
Conclusion: In patients with uncontrolled epilepsy who were initiated on an adjunctive AED, the choice of an LHL versus SHL was associated with significantly lower risks of all-cause and epilepsy-related hospitalizations.

1. Introduction

Epilepsy affects approximately 3 million adults and 470,000 children in the United States (US) [1]. The Centers for Disease Control and Prevention (CDC) estimates that the total (indirect and direct) cost of epilepsy in the US is $15.5 billion per year [1]. Despite the existence of more than 30 FDA-approved antiepileptic medications, between 20 and 30% of patients have uncontrolled, drug-resistant, or refractory disease [2–5]. Patients with uncontrolled epilepsy use more healthcare resources (e.g., have longer hospital stays, more ED and inpatient visits) and have higher costs than those with stable disease [4,6–8].

To achieve epilepsy control, changes in AED monotherapy are often the first approach. The use of long half-life (LHL) antiepileptic drugs (AEDs) is one such change, and these drugs have been shown to reduce healthcare utilization and costs when used as primary monotherapy [9], with a variety of potential explanations for their effect on cost and utilization. For example, LHL AEDs remain in the patient's system longer, require less frequent dosing, are associated with better adherence [9], and offer greater dosing flexibility [10] compared with short half-life (SHL) AEDs. Use of LHL monotherapy may mitigate the effect of missed doses [9–11]. However, for many individuals with epilepsy, simply changing monotherapy does not adequately control seizures, and

* Corresponding author at: Eisai, Inc., 100 Tice Blvd., Woodcliff Lake, NJ 07677, Room 2A132, USA.
E-mail address: jiyoon_choi@eisai.com (J. Choi).

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whether these benefits are also associated with long-acting AEDs as adjunctive, rather than single agent, therapy is not known.

In the current study, using healthcare insurance claims data, we compared the risk of hospitalization in patients with uncontrolled epilepsy who initiated adjunctive treatment with LHL AED with the risk in those who were treated with SHL AED therapy.

2. Materials and methods

2.1. Data source and study design

This was a retrospective, longitudinal cohort study using the Symphony Health Solution (SHS)'s Patient Integrated Dataverse (IDV®) over the period of August 1, 2012 to July 31, 2017. The database cross-sectionally covers about three-fourths of the US population (or about 260 million lives) annually. It includes claims submitted to all payer types, including commercial plans, Medicare Part D, cash, assistance programs, and Medicaid [12]. It captures approximately 70% of US retail and specialty pharmacy claims (including 55% of mail orders), 55% of professional claims, and 30% of hospital claims. The data are deidentified in compliance with the Health Insurance Portability and Accountability Act. As this study utilized deidentified administrative claims, institutional review board approval was not required.

2.2. Study population

We included patients with uncontrolled epilepsy who initiated an adjunctive AED. Patients were deemed to have a diagnosis of epilepsy if they had at least two medical claims at least 30 days apart for epilepsy [9] [International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes of 345.xx (epilepsy) or 780.39 (other convulsions); ICD-10-CM codes of G40.xxx or R56.9] in any diagnosis field during the study period from 8/1/2012 to 7/31/2017. Uncontrolled epilepsy was defined as being treated with an AED 90 days before adding on a new AED agent.

Two mutually exclusive cohorts of patients with epilepsy were established: adjunctive LHL AED cohort and adjunctive SHL AED cohort. For the LHL cohort, patients with at least one claim for an adjunctive LHL AED agent (see Appendix 1 for the list of AED agents) were identified during the identification (ID) period between 8/1/2013 and 7/31/2016. The SHL cohort consisted of patients who were not in the LHL cohort and had at least one claim for an adjunctive SHL AED agent during the ID period. The earliest occurrence (first date) of a claim for a LHL or SHL AED in the ID period was considered the index date. The adjunctive AED observed on the index date was defined as the index therapy. Patients were excluded if they had claims for the index AED therapy during the 12 months prior to the index date (1-year washout period). Use of nonindex AED therapy in the baseline period was allowed. The criteria used to ensure that the index AED was used as an adjunct to a nonindex AED were 1) having at least one nonindex AED in the 90 days prior to and the 90 days after the index date and 2) having at least 60 overlapping days' supply between index and nonindex AEDs within the 90 days from the index date [4].

Patients were excluded if they 1) had multiple AEDs on the index date, or 2) were treated with any combination of 2 or more nonindex AED half-life categories [e.g., LHL + extended or delayed release (ER/DR), SHL + ER/DR, or LHL + SHL] during the 90 days prior to the index date. Additionally, to create the study cohort, we excluded patients on AEDs commonly used for other indications using a cutoff of 5%. As a result, we further excluded patients who were treated with gabapentin and clonazepam as these drugs were frequently prescribed for the treatment of pain and anxiety, respectively, and >5% of the patients were on these medications.

To ensure patients had preexisting epilepsy, the first diagnosis of epilepsy had to be before or on the index date. Patients were required to be at least 12 years of age and have continuous medical and drug data coverage for 12 months before and at least 12 months after the index date. Because the SHS data do not contain health plan enrollment data or information about patients' inclusion criteria in the database, algorithms to determine continuous data coverage were developed separately for medical and drug claims by assessing gaps in consecutive claims that indicate potentially incomplete data. Patients were considered to have continuous medical or drug data coverage if the interval between any two consecutive medical claims or drug dispensing records was no more than 120 days during the study period. Similar algorithms have been used in previous studies [13–15]. Patients were followed for at least one year until the end of data coverage or study period. Fig. 1 presents the study timeline.

2.3. Outcome measure

The outcomes of interest included in the study were all-cause, epilepsy-related, and injury-related hospitalizations during the 1-year postindex period. Epilepsy-related hospitalization was defined as any hospitalization with a primary diagnosis of epilepsy (ICD-9-CM code 345.xx or ICD-10-CM code G40.xxx). Injury-related hospitalization was defined as any hospitalization with a primary diagnosis of bone fracture or head injury (ICD-9-CM codes 800.xx-829.xx, 850.xx-854.xx, 873, 949.01 or ICD-10-CM codes S01, S06, S09, S12, S14, S22, S32, S42, S49.0-.1, S52, S59.0-.2, S62, S72, S79.0-.1, S82, S89.0-.3, S92,

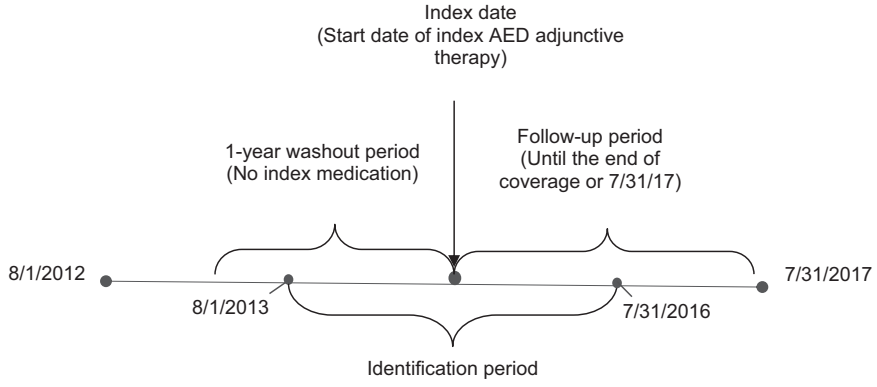

Fig. 1. Study timeline. We included patients diagnosed as having uncontrolled epilepsy during the study period (8/1/2012–7/31/2017), and who initiated an adjunctive antiepileptic drug (AED) during the identification (ID) period (8/1/2013–7/31/2016). The earliest occurrence (first date) of a claim for a long- or short-acting AED in the ID period was considered the index date. The adjunctive AED observed on the index date was defined as the index therapy. Patients were excluded if they had claims for the index AED therapy during the 12 months prior to the index date (1-year washout period). Patients were followed for at least one year until the end of data coverage or study period.

S99.0-.2) [16,17]. Because of the incompleteness of SHS inpatient data, we reported the relative risk of the above hospitalizations.

2.4. Covariates

Baseline covariates potentially related to illness severity were examined using data in the 1-year preindex period. These included: sociodemographics (age, sex, and insurance type), Charlson comorbidity index (CCI) [18,19], epilepsy type, epilepsy-related events (head injury, fractures, and implantation of a vagus nerve stimulator), preindex AEDs, and other comorbidities of interest (brain tumor, depression, PTSD, headache, hyperlipidemia, and hypertension). Unlike in our patient identification algorithm (which required two claims 30 days apart for the target condition), we identified patients as having epilepsy-related events and other comorbidities of interest by the presence of a single code for the relevant condition. Additionally, as previous studies suggest that suboptimal medication adherence levels are associated with poor health outcomes [4,6,11,20], we included adherence to any AED during the 1-year follow up period as a covariate. Medication adherence was measured by proportion of days covered (PDC). Proportion of days covered was calculated as the number of available days of any AED therapy divided by 365 [21]. The days' supply as reported on the prescription claim was used to calculate the PDC.

2.5. Statistical analysis

Descriptive analyses were performed to assess differences between LHL and SHL AED cohorts across baseline covariates. Specifically, chi-square tests were used for categorical variables, and two sample t-tests were used for continuous variables. Poisson regression models with robust error variances [22] for the relative risk of all-cause, epilepsy-related, and injury-related hospitalization, adjusting for the above baseline variables and PDC of any AED during the follow-up period.

2.6. Subgroup analyses

Because the study main population comprised patients who received mixed AEDs (e.g., LHL + SHL, ER/DR + LHL, or ER/DR + SHL), we conducted subgroup analyses in patients 1) who were previously treated with a LHL AED and had an adjunctive LHL AED (pure LHL–LHL) and 2) who were previously treated with a SHL AED and had an adjunctive SHL AED (pure SHL–SHL).

3. Results

3.1. Patient selection and baseline characteristics

During the 5-year study period, there were 2,724,675 patients with at least 2 medical claims 30 days apart for epilepsy. Of these, 493,845 initiated an adjunctive AED during the ID period. After excluding patients who had taken the same AED in the year prior to the index date, there were 151,191 individuals who newly started an adjunctive AED. Of whom, 86,031 had a qualifying diagnosis of epilepsy on or before the index treatment. After excluding patients with less than 12-month continuous enrollment before and after the index date, those under 12 years old, and those treated with multiple AEDs during the 90 days prior to or ER/DR on the index date, our final study sample consisted of 4984 patients: 2279 in the LHL cohort and 2705 in the SHL cohort (Fig. 2).

Significant differences in baseline characteristics were noted between patients in the LHL and SHL cohorts. The LHL cohort was significantly younger [mean (SD): 43.9 (18.5) vs. 49.2 (17.2); $p < 0.001$], and females made up 67.6% of the LHL cohort compared with 63.7% of the

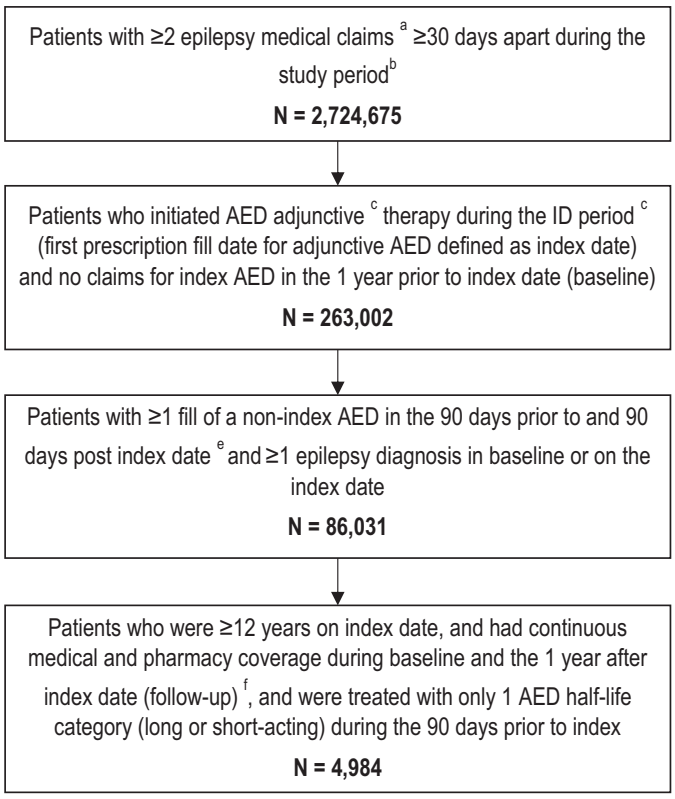

Fig. 2. Patient attrition. During the 5-year study period, there were 2,724,675 patients with ≥2 medical claims 30 days apart for epilepsy. After applying exclusion criteria, the final sample included 4984 patients (≥12 years) who were treated with one category of antiepileptic drug (long- or short-acting).

Table 1
Baseline[a] patient demographics and clinical characteristics.

	Index AED		p-Value
	Long (LHL)	Short (SHL)	
N	2279	2705	
Age, mean (SD)	43.9 (18.5)	49.2 (17.2)	<0.001
Age group, n (%)			<0.001
12–17	288 (12.6)	152 (5.6)	
18–34	461 (20.2)	435 (16.1)	
35–49	524 (23.0)	648 (24.0)	
50–64	686 (30.1)	911 (33.7)	
65+	320 (14.0)	559 (20.7)	
Sex, n (%)			0.003
Female	1541 (67.6)	1722 (63.7)	
Male	738 (32.4)	983 (36.3)	
Plan type, n (%)			<0.001
Commercial[b]	445 (19.5)	504 (18.6)	
Medicare	728 (31.9)	1041 (38.5)	
Medicaid	826 (36.2)	862 (31.9)	
Unknown	280 (12.3)	298 (11.0)	
Charlson comorbidity index, mean (SD)	1.2 (1.8)	1.8 (2.2)	<0.001
Number of chronic conditions, mean (SD)	4.1 (2.0)	4.6 (2.1)	<0.001
Epilepsy/seizure type on index date[c], n (%)			<0.001
Generalized	219 (9.61)	208 (7.69)	
Focal/partial onset	1513 (66.39)	1878 (69.43)	
Unspecified/Other	210 (9.21)	300 (11.09)	
Unknown	337 (14.79)	319 (11.79)	
Head injury, n (%)	189 (8.29)	275 (10.17)	0.023
Fractures, n (%)	177 (7.77)	263 (9.72)	0.015
Implantation of vagus nerve stimulator (VNS), n (%)	62 (2.72)	43 (1.59)	0.006
Cerebrovascular disease/stroke, n (%)	418 (18.34)	672 (24.84)	<0.001
Brain tumor, n (%)	95 (4.17)	169 (6.25)	0.001
Depression, n (%)	759 (33.30)	833 (30.79)	0.058
Posttraumatic stress disorder (PTSD), n (%)	100 (4.39)	77 (2.85)	0.003
Headache, n (%)	701 (30.76)	735 (27.17)	0.005
Hyperlipidemia, n (%)	836 (36.68)	1181 (43.66)	<0.001
Hypertension, n (%)	970 (42.56)	1415 (52.31)	<0.001

AED: antiepileptic drug.
[a] Patient demographics (e.g., age, sex, region, plan type) were reported on the index date (start of adjunctive AED treatment). Baseline comorbid conditions (including Charlson comorbidity index, number of HCUP chronic conditions) were reported during the 1 year prior to the index date.
[b] Plan types include commercial, cash, employer group, pharmacy benefits manager, processors, third party administrator, and workers compensation.
[c] If no claim for epilepsy diagnosis on index date, the closest claim within ±90 days of index was used.

SHL cohort ($p = 0.003$). The proportion of commercial, Medicaid, and Medicare patients also differed ($p < 0.001$) (Table 1).

There were statistically significant group differences in the type of AED used in the year prior to initiating the index adjunctive treatment and in comorbid illness. In the LHL cohort, the most common preindex AED were SHL (46.8%), followed by LHL (28.0%) and ER/DR (25.2%); whereas a higher percentage of patients in the SHL cohort were previously treated with LHL AED (38.0%), followed by SHL (37.6%) and ER/DR (24.4%). Charlson comorbidity index was lower in the LHL than in the SHL cohort [mean (SD): 1.2 (1.8) vs. 1.8 (2.2); $p < 0.001$], as was the HCUP chronic condition indicator [mean (SD): 4.1 (2.0) vs. 4.6 (2.1); $p < 0.001$] (Table 1). Additionally, a lower percentage of patients in the LHL cohort had head injury, fractures, cerebrovascular disease/stroke, brain tumors, hyperlipidemia, and hypertension ($p < 0.05$). During the 1-year follow-up period, the LHL cohort had a mean (SD) PDC of any AED of 0.97 (0.07) while the SHL cohort had 0.96 (0.08) ($p < 0.05$).

3.2. Risk of hospitalization

In the 12 months following initiation of adjunctive AED, the unadjusted risks of all-cause and epilepsy-related hospitalizations were lower in the LHL cohort than in the SHL cohort [all-cause relative risk (RR): 0.81 (95% CI, 0.73–0.89), $p < 0.001$; epilepsy-related: 0.82 (0.72–0.94), $p = 0.003$]. Controlling for baseline differences, patients in the LHL cohort continued to have a lower risk of being hospitalized, for any and epilepsy-related reasons, than those in the SHL [all-cause: 0.84 (95% CI, 0.76–0.93), $p = 0.0006$; epilepsy-related: 0.83 (0.73–0.94), $p = 0.0046$]. Differences in injury-related hospitalizations between the LHL and SHL cohorts were not statistically significant (Table 2).

3.3. Subgroup analysis

We identified 637 patients in the pure LHL–LHL cohort, and 1018 patients in the pure SHL–SHL cohort (Supplemental Table 1). Consistent with the main findings, the adjusted RR of inpatient hospitalization was lower in the LHL–LHL cohort than in the SHL–SHL cohort, although the difference was not statistically significant [0.86 (95% CI, 0.72–1.02); $p = 0.0870$] (Supplemental Table 2).

4. Discussion

In patients with uncontrolled epilepsy initiating adjunctive AED treatment, the choice of a long-acting AED is associated with lower risks of all-cause and epilepsy-related hospitalizations. This was true even controlling for whether the previous therapy was long- or short-acting.

For patients with uncontrolled epilepsy, treatment options include an alternative AED monotherapy or adjunctive treatment [23,24]. While AED selection is based on many clinical factors (e.g., seizure type, age, potential drug interactions, adverse effects, comorbidities), our data suggest that when adding an adjunctive AED, an LHL medication should be considered. The potential of LHL AEDs as a monotherapy to decrease healthcare utilization and costs in patients with epilepsy [9], including in those with refractory epilepsy [4], has been shown in previous studies. In a 2014 study using US claims data, Cramer et al. reported that patients with epilepsy treated with LHL AED monotherapy had a lower economic burden compared with those treated with SHL AED monotherapy [9]. However, in a prior study, the differences in risks of both all-cause and epilepsy-related hospitalizations were not statistically significant between SHL and LHL AED monotherapy users. Our study differed from this prior study in that (1) we focused on patients who used AEDs as adjunctive therapy instead of monotherapy and (2) we used a different data source with more recent years of data and more recently approved AEDs.

Reducing healthcare utilization and cost in patients with uncontrolled disease is particularly important given its association with worse clinical outcomes, higher utilization, and higher costs [4,6,17,20,25–28] than in patients with stable disease. The finding of lower hospitalization risk in patients treated with adjunctive LHL AEDs is particularly relevant to reducing cost since hospitalization is a significant driver of healthcare costs [9,29]. For example, one study using survey data reported that hospitalization accounted for one-third of the total cost in patients with epilepsy [30]. A different study using survey data found that inpatient care comprised 68% of costs for patients with newly diagnosed epilepsy [29].

Table 2
Adjusted[a] healthcare utilization during the 1-year follow-up.

	Risk of inpatient hospitalization: RR (95% CI)	p-Value	Risk of epilepsy related inpatient hospitalization: RR (95% CI)	p-Value	Risk of injury related inpatient hospitalization: RR (95% CI)	p-Value
Age group						
12–17 vs. 65 +	1.68 (1.32–2.14)	<0.0001	2.04 (1.51–2.77)	<0.0001	0.91 (0.26–3.14)	0.8838
18–34 vs. 65 +	1.22 (1.00–1.50)	0.0508	1.30 (0.99–1.70)	0.0560	0.40 (0.13–1.27)	0.1204
35–49 vs. 65 +	1.09 (0.92–1.28)	0.3217	1.12 (0.89–1.40)	0.3289	0.60 (0.26–1.40)	0.2359
50–64 vs. 65 +	1.05 (0.91–1.22)	0.4675	1.04 (0.85–1.28)	0.7139	1.01 (0.51–2.00)	0.9832
Female vs. male	0.96 (0.86–1.06)	0.3776	0.92 (0.80–1.05)	0.2114	0.48 (0.30–0.77)	0.0024
Insurance type						
Medicare vs. commercial	1.11 (0.96–1.28)	0.1742	1.03 (0.85–1.26)	0.7346	1.49 (0.66–3.36)	0.3352
Medicaid vs. commercial	1.13 (0.98–1.31)	0.0831	1.16 (0.97–1.40)	0.1078	0.95 (0.43–2.11)	0.8940
Unknown vs. commercial	0.97 (0.81–1.18)	0.7905	0.93 (0.72–1.19)	0.5590	1.17 (0.45–3.03)	0.7458
Charlson comorbidity index (baseline)	1.11 (1.09–1.13)	<0.0001	1.08 (1.05–1.11)	<0.0001	1.14 (1.02–1.27)	0.0163
Epilepsy/seizure type on index						
Generalized vs. partial/focal	0.85 (0.71–1.03)	0.0960	0.89 (0.70–1.12)	0.3236	0.77 (0.28–2.11)	0.6166
Unknown vs. partial/focal	0.87 (0.78–0.98)	0.0236	0.69 (0.59–0.82)	<0.0001	0.82 (0.45–1.50)	0.5291
Head injury (y vs. n)	1.36 (1.21–1.53)	<0.0001	1.44 (1.22–1.69)	<0.0001	1.53 (0.81–2.90)	0.1872
Fractures (y vs. n)	1.06 (0.91–1.24)	0.4278	0.92 (0.74–1.16)	0.4883	2.25 (1.26–4.00)	0.0058
Implantation of vagus nerve stimulator (VNS) (y vs. n)	1.21 (0.89–1.64)	0.2331	1.24 (0.84–1.82)	0.2783	1.57 (0.40–6.19)	0.5204
Brain tumor (y vs. n)	1.11 (0.92–1.33)	0.2795	1.22 (0.95–1.55)	0.1131	1.30 (0.49–3.45)	0.5979
Depression (y vs. n)	1.31 (1.18–1.45)	<0.0001	1.37 (1.20–1.57)	<0.0001	1.93 (1.14–3.26)	0.0151
Posttraumatic stress disorder (PTSD) (y vs. n)	0.77 (0.63–0.94)	0.0118	0.83 (0.62–1.11)	0.2163	1.09 (0.27–4.35)	0.8994
Headache (y vs. n)	1.10 (0.99–1.22)	0.0636	1.09 (0.95–1.26)	0.2116	0.92 (0.52–1.64)	0.7845
Hyperlipidemia (y vs. n)	1.02 (0.91–1.14)	0.7718	0.99 (0.85–1.16)	0.9323	0.69 (0.39–1.22)	0.2021
Hypertension (y vs. n)	1.27 (1.12–1.43)	0.0002	1.23 (1.04–1.45)	0.0158	0.84 (0.45–1.56)	0.5738
PDC of any AED during follow-up	0.99 (0.99–1.00)	0.0045	1.00 (0.99–1.01)	0.8155	0.99 (0.97–1.01)	0.2875
Preindex AED						
Long vs. short	0.96 (0.86–1.07)	0.4913	1.06 (0.91–1.23)	0.4414	1.08 (0.61–1.90)	0.7949
ER/DR vs. short	0.92 (0.81–1.04)	0.1587	1.09 (0.93–1.28)	0.3064	1.11 (0.60–2.04)	0.7346
Index AED long vs. short	0.84 (0.76–0.93)	0.0006	0.83 (0.73–0.94)	0.0046	0.97 (0.59–1.57)	0.8868

AED: antiepileptic drug; PDC: proportion of days covered; RR: relative risk.
[a] Adjusted by age group, gender, insurance type, Charlson comorbidity index, epilepsy/seizure type on index, baseline epilepsy related events (head injury, fractures, VNS), baseline comorbid conditions (brain tumor, depression, PTSD, headache, hyperlipidemia, hypertension), PDC of any AED during follow-up (for number of office visits and risk of hospitalization), and preindex AED.

4.1. Limitations

This study had several limitations. First, as administrative claims data are designed for payment, not research, clinical information is lacking. Claims do not include details regarding why a certain AED may have been prescribed, nor do they include measures of disease severity, length of time the subjects had epilepsy, or contraindications to medications. As a result, the groups we studied undoubtedly were different in ways we could not measure. We controlled for measurable differences using regression. However, unmeasured differences in the study database, such as disease severity and contraindications to medications [31], may have been responsible for the choice of LHL vs. SHL AEDs. These differences may explain the lower hospitalization risks found in the LHL cohort. Second, the SHS database includes inpatient data from 30% of hospitals in the US, but hospital encounter data would be missing if a patient in our study was admitted to a hospital that was not one of the hospitals included in the SHS database. In our analysis, we assumed that the missing data were randomly distributed across the study population and reported the relative risk of hospitalization instead of absolute rates. If this assumption was incorrect, our findings would be biased, although we have no method of estimating the direction or magnitude of this bias. Third, patients were considered to have continuous data coverage during periods with at least two refills of any AEDs within a 120-day period. This may have resulted in higher medication adherence overall, as the majority of patients with low adherence (i.e., those who filled every 180 days) were excluded from the study. This exclusion may further support the finding of greater risk of hospitalization in patients on adjunctive SHL AED therapy because it reduces the likelihood that hospitalizations were attributable to poor adherence [11].

5. Conclusions

Patients treated with an adjunctive LHL AED were significantly less likely to be hospitalized than those treated with an adjunctive SHL AED. The benefits of selecting an LHL AED as adjunctive therapy should be considered for appropriate patients with uncontrolled epilepsy. The observed reduction in utilization would likely reduce cost and improve the economic burden associated with this chronic disease.

Declaration of competing interest

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Appendix 1. List of long half-life, extended/delayed-release, and short half-life AED agents

AED half-life categories*	Generic name	Brand name
Long	Perampanel	Fycompa
Long	Ethosuximide (ESM)	Zarontin
Long	Phenobarbital (PB)	Luminal
Long	Phenytoin (PHT), regular release	Dilantin
Long	Topiramate (TPM), regular release	Topamax
Long	Zonisamide (ZNS)	Zonegran
Long	Felbamate (FBM)	Felbatol
Long	Clobazam	Onfi
Long	Clonazepam (CLZ)	Klonopin
Long	Lamotrigine (LTG), regular release	Lamictal
Long	Carbamazepine (CBZ), regular release	Tegretol
Extended release	Carbamazepine (CBZ), extended release (ER)	Carbatrol
Extended release	Divalproex (DVP), extended release (ER)	Depakote ER
Extended release	Levetiracetam (LEV), ER	Keppra
Extended release	Phenytoin (PHT), ER	Dilantin
Extended release	Lamotrigine (LTG), ER	Lamictal XR
Delayed release	Divalproex (DVP), delayed release (DR)	Depakote Sprinkle Capsules
Short	Vigabatrin (VGB)	Sabril
Short	Gabapentin (GPT)	Neurontin
Short	Lacosamide (LCM)	Vimpat
Short	Acetazolamide	Diamox
Short	Eslicarbazepine acetate	Aptiom
Short	Piracetam	Nootropil
Short	Rufinamide	Banzel
Short	Valproic Acid	Depakene
Short	Brivaracetam	Briviact
Short	Diazepam	Valium
Short	Ethotoin	Peganone
Short	Ezogabine	Potiga
Short	Fosphenytoin Sodium	Cerebyx
Short	Methsuximide	Celontin
Short	Stiripentol[a]	Diacomit
Short	Divalproate or valproex (DVP), regular release	Depakote
Short	Levetiracetam (LEV), regular release	Keppra
Short	Oxcarbazepine (OXC)	Trileptal
Short	Pregabalin (PGB)	Lyrica
Short	Primidone (PRM)	Mysoline
Short	Tiagabine (TGB)	Gabitril

[a] Not approved by FDA.
* Half-life cutoff: 0–20 h (short); 20+ (long).

Appendix 2. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2019.106634.

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