

Risk of Hospitalization in Patients with Uncontrolled Epilepsy Treated with a Long Versus Short Half-Life Adjunctive Antiepileptic Medication

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BACKGROUND AND OBJECTIVE

Background

- Despite the existence of more than 30 FDA-approved antiepileptic drugs (AEDs), 20-36% of patients have uncontrolled, drug-resistant, or refractory disease.¹
- The use of long half-life (LHL) AEDs as primary monotherapy has been shown to reduce healthcare utilization and costs when used as primary monotherapy.²
- Whether these benefits are also associated with long-acting AEDs as adjunctive, rather than single agent, therapy is not known.

Objective

- To examine the impact of adding a LHL versus short half-life (SHL) adjunctive AEDs on the risk of hospitalization in patients with uncontrolled epilepsy.

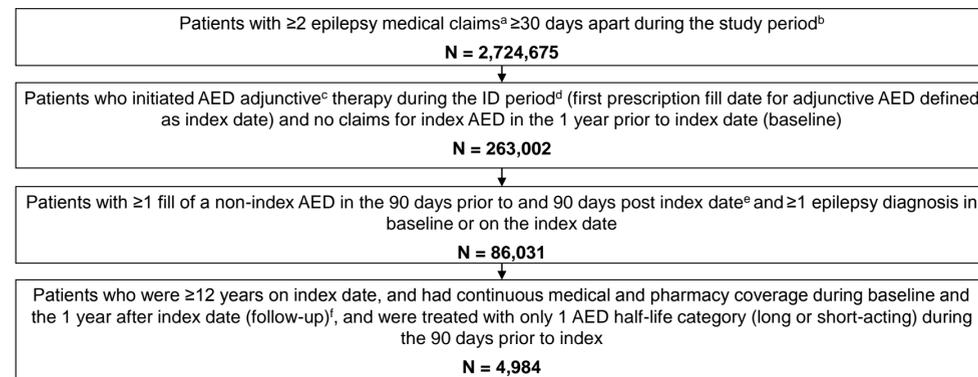
METHODS

Study Design and Data Source

- Retrospective, longitudinal cohort study using the Symphony Health Solution (SHS) Patient Integrated Dataverse (IDV[®]) over the period of 8/1/2012 to 7/31/2017

Patient Selection

Figure 1: Patient Attrition Flowchart



^a ICD-9-CM: 345.xx (epilepsy) or 780.39 (other convulsions); ICD-10-CM: G40.xxx or R56.9. ^b 8/1/2012 to 7/31/2017. ^c Patients must have ≥1 AED different from index AED prior to initiation of adjunctive therapy. Patients with multiple adjunctive AEDs were excluded. ^d 8/1/2013 to 7/31/2016. ^e Must have ≥1 of the same AED in the pre and post 90-day periods and treatment in post 90-day period must overlap with index treatment ≥60 days. ^f Patients were considered continuously covered during the periods between claims no more than 120 days apart.

Study Cohorts

- Two mutually exclusive cohorts (LHL vs. SHL) based on AED half-life (<20 versus >20 hours)
 - Short half-life AEDs included in the study were: Acetazolamide, brivaracetam, diazepam, divalproate, eslicarbazepine, ethosuximide, fosphenytoin, gabapentin, lacosamide, levetiracetam, methsuximide, oxcarbazepine, piracetam, pregabalin, primidone, rufinamide, stiripentol, tiagabine, valproic acid, and vigabatrin.
 - Long half-life AEDs included in the study were: Carbamazepine, clobazam, clonazepam, ethosuximide, felbamate, lamotrigine, perampampanel, phenobarbital, phenytoin, topiramate, and zonisamide.

Study Measures

- Covariates of interest
 - Baseline measures (Table 1)
 - Adherence to any AED during 1-year follow-up period, measured as proportion of days covered (PDC) calculated as number of available days of any AED therapy divided by 365
- Outcome measure
 - Relative risk (RR) of all-cause hospitalization in the 1-year following index

Statistical Analysis

- Chi-square tests for categorical variables and two sample t-tests for continuous variables were performed.
- Poisson regressions with robust error variances³ were performed for the RR of all-cause hospitalization, adjusting for covariates of interest.

RESULTS

Patient Characteristics

- A total of 4,984 epilepsy patients were identified (2,705 SHL and 2,279 LHL) (Figure 1).
- Compared to the SHL cohort, patients in the LHL cohort were significantly younger [mean (SD): 43.9 (18.5) vs. 49.2 (17.2); p<0.001], more female (67.6% vs. 63.7% p=0.003), and had fewer comorbid conditions [mean (SD) CCI: 1.2 (1.8) vs. 1.8 (2.2); p<0.001] (Table 1).⁴
- During the 1-year follow-up period, the LHL cohort had a mean (SD) PDC of any AED of 0.97 (0.07) compared to 0.96 (0.08) in the SHL cohort (p<0.05).

Risk of Hospitalization

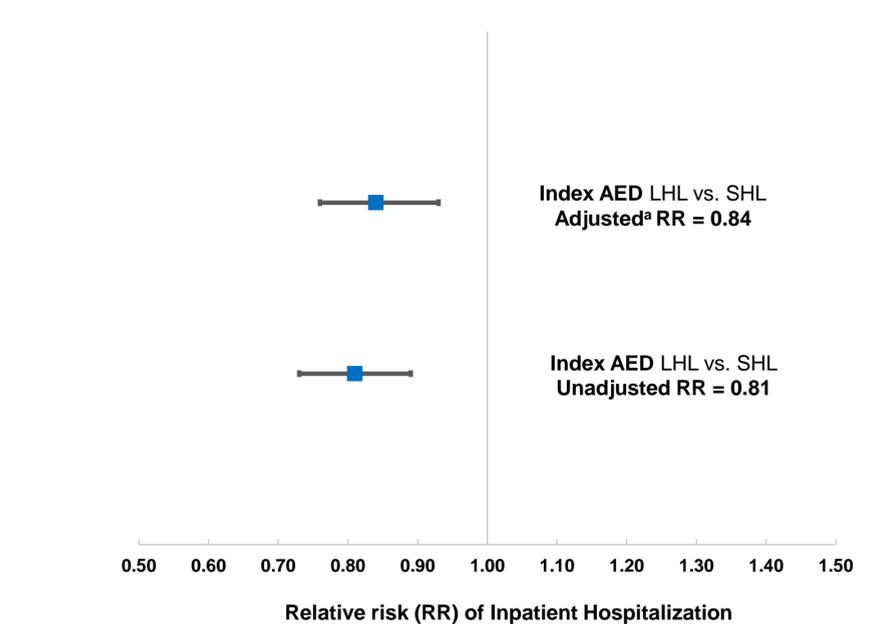
- In the 1-year post-index period, the unadjusted RR of hospitalization was lower in the LHL cohort vs. the SHL cohort [0.81 (95% CI: 0.73 - 0.89); p<0.001].
- After adjusting for group differences, the RR of hospitalization for the LHL cohort was significantly lower vs. the SHL cohort [0.84 (95% CI: 0.76 - 0.93); p=0.0007] (Figure 2).

Table 1: Baseline^a Patient Demographics and Clinical Characteristics

Characteristic	Long (LHL)	Short (SHL)	p value
N	2,279	2,705	
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	1,541 (67.6)	1,722 (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)	1,041 (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	1,513 (66.39)	1,878 (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
Post-traumatic 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)	1,181 (43.66)	<0.001
Hypertension, n (%)	970 (42.56)	1,415 (52.31)	<0.001

^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^{6,7}, number of Healthcare Cost and Utilization Project (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.

Figure 2: Risk of Inpatient Hospitalization During the 1-Year Follow-up



^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, and pre-index AED.

CONCLUSIONS

Conclusions

- In patients with uncontrolled epilepsy who were initiated on an adjunctive AED, the choice of a LHL vs. SHL was associated with a significantly lower risk of hospitalization for LHL medications.
- The benefits of selecting a 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.

Limitations

- The Symphony Health database on includes inpatient data from 30% of hospitals in the U.S.
- We could not differentiate patients who were serviced by the hospitals included in the SHS data set from those with missing data from hospitals outside of the SHS data set to perform the analysis.
- We reported the relative risk of hospitalization instead of absolute rates, assuming that missing data were randomly distributed across the study population.

REFERENCES

- Chen Z, et al. JAMA Neurol. 2018;75(3):279-286.
- Cramer JA, et al. Epilepsy Behav. 2014;32:135-41.
- Zou G. Am J Epidemiol. 2004;159:702-6.
- Charlson ME, et al. J Chronic Dis. 1987;40:373-383.

Funding for this study was provided by Eisai Inc. JAC is a consultant for Eisai Inc. JTY and RT are employees of Partnership for Health Analytic Research, LLC, a health services research consultancy paid by Eisai Inc. to conduct this research. RK, CF, MM, and JC are employees of Eisai Inc.