Epilepsy & Behavior 44 (2015) 40–46

Contents lists available at ScienceDirect

Epilepsy & Behavior

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

Health-care costs and utilization related to long- or short-acting antiepileptic monotherapy use☆

Joyce A. Cramer [a,*], Zhixiao J. Wang [b], Eunice Chang [c], Ronda Copher [b], Dasha Cherepanov [c], Michael S. Broder [c]

[a] 49 Briar Hollow Lane, #1804, Houston, TX 77027, USA
[b] Eisai, Inc., 100 Tice Boulevard, Woodcliff Lake, NJ 07677, USA
[c] Partnership for Health Analytic Research, LLC, 280 S. Beverly Drive, Suite 404, Beverly Hills, CA 90212, USA

ARTICLE INFO

Article history:
Received 1 August 2014
Revised 15 December 2014
Accepted 16 December 2014
Available online 27 January 2015

Keywords:
Epilepsy
Seizures
Antiepileptic drugs
Cost analysis
Economics
Medical care
Adherence

ABSTRACT

Purpose: This study aimed to compare health-care utilization and costs in patients treated with long-acting (LA) vs. short-acting (SA) antiepileptic drug (AED) monotherapy.
Methods: We conducted a cross-sectional study of claims from the OptumInsight™ database. Our analysis was restricted to adults diagnosed with epilepsy and who used AED monotherapy. Patients were excluded if they used >1 type of AED, had <9 months of treatment, or had a treatment gap of >60 days. Antiepileptic drugs were classified as LA or SA based on published data and expert opinion. Medical and pharmacy claims were used to estimate health-care utilization and costs, and baseline group differences were adjusted using multivariate analyses.
Results: There were 4058 (49.6%) LA AED users and 4122 (50.4%) SA AED users. Medication possession ratios (MPRs) were not significantly different between LA AED users and SA AED users ($P = 0.125$). Long-acting AED users had lower mean overall health-care costs ($9757 vs. $12,689), lower epilepsy-related costs ($3539 vs. $5279), and lower rate of overall (8.8% vs. 10.9%) and epilepsy-related hospitalizations (5.7% vs. 7.6%) compared with SA AED users (all $P < 0.01$). After adjusting for demographics and clinical characteristics, mean overall costs were lower by $686 and the mean epilepsy-related costs were lower by $894 in LA AED users.
Conclusion: Although MPRs were similar in LA AED and SA AED groups, patients treated with LA monotherapy had a lower economic burden compared with those treated with SA monotherapy, indicating that using AEDs with extended duration of action is associated with decreased health-care use and lower health-care costs.

1. Introduction

Epilepsy affects approximately 2.2 million Americans [1] and accounts for an estimated $15.5 billion in direct and indirect costs in the United States annually [2]. Patients with epilepsy typically require long-term or lifetime pharmacotherapy, and with more than 20 antiepileptic drugs (AEDs) currently available, the decision-making process for treatment is increasingly complex [3]. Suboptimal adherence has been linked to a wide variety of consequences, including increased rates of seizures, head injuries, and hospitalizations, and is associated with increased health-care utilization and costs [4–6].

A long-acting (LA) AED will remain in a patient's systemic circulation longer after the last dose compared with a short-acting (SA) AED. Extended-release drugs are formulated to dissolve and release slowly, allowing for less frequent dosing. This property may make longer half-life or ER drugs more "forgiving" of missed doses, with the reduced serum medication levels more effectively bridged by drugs with longer half-lives. If this is the case, then use of longer half-life or extended-release (ER) formulations might mitigate the impact of imperfect adherence. That is, for a given level of adherence, users of longer half-life or ER drugs might be expected to have better efficacy and lower health-care utilization and costs compared with users of shorter half-life drugs.

To assess whether AEDs with extended half-life or longer duration of action might be associated with improved health and economic outcomes, we used a large commercial health-care claims database to compare the extent of health service utilization and costs in adult patients treated with either LA or SA AED monotherapy.

2. Material and methods

2.1. Study design and data sources

We conducted a cross-sectional study to compare clinical and economic outcomes among adult patients using LA or SA AED monotherapy. Antiepileptic drugs were classified as LA (those with long half-life or

☆ Statistical analyses completed by Eunice Chang, PhD, Partnership for Health Analytic Research, LLC.

* Corresponding author at: 49 Briar Hollow Lane, #1804, Houston, TX 77027-9310, USA. Tel.: +1 713 552 0289.
E-mail addresses: joyce.cramer@gmail.com (J.A. Cramer), Jason_Wang@eisai.com (Z.J. Wang), echang@pharllc.com (E. Chang), Ronda_Copher@eisai.com (R. Copher), dasha@pharllc.com (D. Cherepanov), mbroder@pharllc.com (M.S. Broder).

http://dx.doi.org/10.1016/j.yebeh.2014.12.020
1525-5050/

extended, delayed, or controlled release) based on prescribing information, published data, and expert opinion [7] (see Appendix Table). Long-acting AEDs included phenytoin ER (PHT ER), carbamazepine ER (CBZ ER), topiramate (TPM), divalproex ER (DVP ER), divalproex delayed release (DR) (DVP DR), phenobarbital (PB), levetiracetam ER (LEV ER), and zonisamide (ZNS). Short-acting AEDs included levetiracetam (LEV), lamotrigine (LTG), carbamazepine (CBZ), and oxcarbazepine (OXC).

The study used data from the OptumInsight™ Clinformatics™ Data Mart database, a commercial Health Insurance Portability and Accountability Act (HIPAA)-compliant administrative claims database of roughly 14 million covered lives per year that represents all major regions of the United States. The OptumInsight database contains deidentified adjudicated pharmacy claims (e.g., outpatient prescriptions) and medical claims (e.g., inpatient and outpatient services) submitted for payment by providers, health-care facilities, and pharmacies and includes information on each physician visit, medical procedure, hospitalization, drug dispensed, date of service/prescription, number of days of medication supplied, and tests performed. Drug-related claims are only recorded for the outpatient setting. Pricing data are also included, and these data are adjusted to account for differences in contracting and other variations across health plans. These standardized prices are used as costs in this analysis. Also available are member enrollment and benefit information as well as limited patient, provider, and hospital demographic information.

2.2. Study population and study timeframe

We included commercially insured adults (≥18 years old) who were diagnosed with epilepsy and who were treated with LA or SA AED monotherapy during the 2011 calendar year (study period). Patients were included in the study if they had ≥2 medical claims at least 30 days apart with International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes of 345.xx (epilepsy) or 780.39 (other convulsions) in any diagnosis field. In order to exclude newly diagnosed patients (who might have differed significantly from those receiving ongoing care), one epilepsy claim had to occur during the study period, and another claim had to occur during the year before the study period. In addition, patients were required to have had ≥2 pharmacy claims for one of the listed AEDs, both during the study period.

Patients were excluded from the study if they had more than 1 type of AED filled during the study period; if they were not continuously enrolled during the 12-month study period and for 3 months before the study period (used to determine if AEDs were available at the start of the study period); if they were treated for <9 months or if they had a treatment gap of >60 days between the end of days of supply and the next fill date; or if they did not use one of the top 12 most frequently used AEDs.

2.3. Study measures

Study measures were derived using enrollment files, medical claims, and pharmacy claims. The claim database contains every claim for an individual's period of enrollment. We assumed that there were no missing data because a payment is processed only if a claim exists. We used all medical and pharmacy claims in the 12-month study period to construct the baseline measures, including patient demographics, AED adherence, specialty of the usual care physician, and burden of illness. Medical and pharmacy claims were used to estimate health-care utilization and costs, and baseline differences were adjusted using multivariate analysis.

Enrollment records were used to identify patient demographic information (age, sex, and US census region). Antiepileptic drug adherence was estimated by the medication possession ratio (MPR), defined as the total days of therapy available in the study period divided by 365 days. Considering this definition, that MPR summarizes medication fills and not actual medication-taking behavior. To calculate the MPR, we truncated days of supply to exclude AEDs available before, or AED claims extending after, the study period. Specialty of the usual physician was defined as the physician specialty with the largest plurality of office visits with evaluation and management (E&M) service codes during the review period [8]. 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.

Severity of illness was captured by three measures: the Charlson Comorbidity Index, the number of chronic conditions, and the epilepsy-specific comorbidities, all of which were measured during the study period (2011 calendar year). The Charlson Comorbidity Index, initially developed as predictor of in-hospital mortality, has been widely adapted and used to measure overall burden-of-illness in the general population [9,10]. We used the validated Healthcare Cost and Utilization Project (HCUP) Chronic Condition Indicator [11,12], which categorizes ICD-9-CM diagnosis codes as chronic or not chronic, to count the number of chronic conditions. A chronic condition is defined as a condition 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 [12]. Finally, we identified epilepsy-specific comorbidities that may have complicated the management of epilepsy or could have caused the disease: head injury, brain tumor, cerebrovascular disease/stroke, meningitis/vasculitides, tuberous sclerosis, and depression and other mood disorders.

The main outcome measures were annual health-care utilization and costs, both overall and epilepsy-related. Measures of health-care utilization included the number of inpatient hospitalizations, the number of emergency department (ED) visits, and the number of physician office visits. Epilepsy-related utilization was defined as AED prescription fills, medical services associated with claims with an epilepsy diagnosis in any diagnosis field, and epilepsy-related tests (AED levels, electroencephalography [EEG], and brain imaging studies such as computed tomography, magnetic resonance imaging, positron emission tomography, and single-photon emission computed tomography). Epilepsy-related costs were defined similarly.

2.4. Statistical analysis

Descriptive statistics, including mean, standard deviation (SD), and percentage, were reported for all measures, stratified by treatment cohort. The chi-square test and Student's *t*-test were used for dichotomous and continuous variables, respectively. All tests were two-sided with a significance level of 0.05.

We conducted several regression models to study the association between treatment half-life and outcomes. These included multivariate models for annual overall and epilepsy-related costs and logistic regression models for the occurrence of inpatient hospitalization (both overall and epilepsy-related). All models were adjusted for patient and clinical characteristics as appropriate, including age, sex, US census region, usual physician specialty, Charlson Comorbidity Index, chronic conditions, and epilepsy-specific comorbidities. Data transformations and statistical analyses were performed using SAS® version 9.3 (SAS Institute, Cary, NC).

3. Results

We initially identified 32,705 patients with ≥2 epilepsy claims (1 in 2010 and 1 in 2011) from the OptumInsight database. Of these, we excluded 5736 patients who filled <2 AED claims in 2011, 4131 who were not continuously enrolled between 10/1/2010 and 12/31/2011, 4488 who were <18 years old, and 7653 who were treated with more than one AED. We also excluded 2087 patients who were treated for <9 months or who had a treatment gap of >60 days and 429 patients

who were not receiving one of the top 12 AED regimens. The final analytic sample included 8180 adult AED users, of whom 4058 (49.6%) used LA AEDs and 4122 (50.4%) used SA AEDs.

Table 1 describes patient and physician characteristics of the study cohort. Long-acting AED users were older and had a lower Charlson Comorbidity Index score, fewer chronic conditions, and fewer epilepsy-specific comorbidities compared with their SA AED counterparts, while SA AED users were more commonly female. Long-acting AED and SA AED users both received their care most frequently from primary care physicians (52.4% vs. 39.6%, respectively), followed by neurologists (28.9% vs. 39.5%), and other specialists (18.7% vs. 20.9%). There was no statistically significant difference in AED adherence between LA AED users and SA AED users, with a mean MPR of 0.899 (SD: 0.13) in LA AED users compared with an MPR of 0.903 (SD: 0.13) in SA AED users ($P = 0.125$) (Table 2).

In univariate comparisons of health-care utilization in the study period (Table 3), 8.8% of LA AED users had ≥1 inpatient hospitalization compared with 10.9% of SA AED users ($P = 0.003$), while 5.7% of LA AED users had ≥1 epilepsy-related hospitalization compared with 7.6% of SA AED users ($P = 0.005$). Long-acting AED users also had significantly fewer overall annual ED visits and fewer overall and epilepsy-related physician office visits compared with SA AED users. There was no difference in the number of epilepsy-related ED visits between LA AED users and SA AED users ($P = 0.343$). Long-acting AED users did have a significantly higher rate of testing for AED levels compared with SA AED users (22.8% of LA AED users were tested ≥1 times vs. 12.7% of SA AED users; $P < 0.001$), but the percentage of patients who had ≥1 electroencephalographic (7.4% vs. 12.6%) or brain imaging study (11.2% vs. 18.0%) was lower in LA AED users than in SA AED users (all $P < 0.001$).

Table 4 displays unadjusted costs associated with the treatment of adult patients with epilepsy. Annual health-care costs were significantly lower in LA AED users ($9757; SD: $21,634) than in SA AED users per patient-year ($12,689; SD: $25,358; $P < 0.001$), a difference of $2932 reflected by $1586 less in medical costs and $1346 less in pharmacy costs annually (both $P \leq 0.001$). Epilepsy-related annual health-care costs were similarly lower (a difference of $1740) in LA AED users than in SA AED users ($3539 [SD: 11,077] vs. $5279 [SD: 17,157]; $P < 0.001$), including $842 less in epilepsy-related medical costs ($2355 for LA vs. $3197 for SA; $P = 0.008$) and $898 less in AED costs ($1184 for LA vs. $2082 for SA; $P < 0.001$).

After adjusting for baseline demographics, region, usual care physician specialty, and clinical characteristics, we found that the mean overall costs were $686 less (standard error [SE]: $460; $P = 0.137$) and that the mean epilepsy-related costs were $894 less (SE: $319; $P = 0.005$) in LA AED users than in SA AED users (Table 5). The risk of inpatient hospitalization (odds ratio [OR]: 1.02; 95% confidence interval [CI]: 0.87–1.21) and epilepsy-related inpatient hospitalization (OR: 0.94; 95% CI: 0.78–1.13) were not statistically significantly different for patients who received SA AED monotherapy than for patients who received LA AED monotherapy. Adjusted costs were greater in SA AED users than in LA AED users, but this difference was only statistically significant for epilepsy-related costs.

4. Discussion

Suboptimal adherence to medications is a serious problem in chronic illness management. Medication adherence is a complex behavior and affected by many factors. A recent systematic review identified hundreds of factors contributing to medication adherence or lack thereof, two of which include dosing frequency and duration of action [13]. Prior medical claims studies have suggested that suboptimal medication adherence in epilepsy has been a particularly critical problem [4,14]. Lack of adherence to AEDs has been linked to increased burden of illness, and previous studies have examined the impact of nonadherence to AEDs on health-care utilization and costs [4–6]. Moreover, educational and behavioral interventions to improve adherence to AEDs in patients with epilepsy have had only mixed results [15]. The lack of

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

	Long-acting AED monotherapy n = 4058; 49.6%	Short-acting AED monotherapy n = 4122; 50.4%	All N = 8180	*P* value[a]
Age, year, mean (SD)	47.7 (14.5)	45.1 (16.0)	46.4 (15.3)	<0.001
Age group, year, n (%)				<0.001
18–34	811 (20.0)	1185 (28.7)	1996 (24.4)	
35–44	762 (18.8)	820 (19.9)	1582 (19.3)	
45–54	1084 (26.7)	902 (21.9)	1986 (24.3)	
55+	1401 (34.5)	1215 (29.5)	2616 (32.0)	
Female, n (%)	1931 (47.6)	2349 (57.0)	4280 (52.3)	<0.001
Region, n (%)				0.829
Midwest	1208 (29.8)	1212 (29.4)	2420 (29.6)	
Northeast	411 (10.1)	443 (10.7)	854 (10.4)	
South	1866 (46.0)	1883 (45.7)	3749 (45.8)	
West	573 (14.1)	584 (14.2)	1157 (14.1)	
Usual physician specialty, n (%)				<0.001
Neurology	1174 (28.9)	1628 (39.5)	2802 (34.3)	
Primary care[b]	2127 (52.4)	1632 (39.6)	3759 (46.0)	
Other[c]/unknown[d]	757 (18.7)	862 (20.9)	1619 (19.8)	
Charlson Comorbidity Index, mean (SD)	0.7 (1.5)	0.8 (1.6)	0.7 (1.6)	<0.001
Number of chronic conditions, mean (SD)	2.9 (1.8)	3.1 (2.0)	3.0 (1.9)	<0.001
Any epilepsy-specific comorbidities,[e] n (%)	772 (19.0)	1031 (25.0)	1803 (22.0)	<0.001
Head injury	16 (0.4)	32 (0.8)	48 (0.6)	0.024
Brain tumor	93 (2.3)	236 (5.7)	329 (4.0)	<0.001
Cerebrovascular disease/stroke	287 (7.1)	399 (9.7)	686 (8.4)	<0.001
Depression and other mood disorders	429 (10.6)	496 (12.0)	925 (11.3)	0.037
Meningitis/vasculitides	15 (0.4)	14 (0.3)	29 (0.4)	0.819
Tuberous sclerosis	8 (0.2)	10 (0.2)	18 (0.2)	0.661

AED, antiepileptic drug; E&M, evaluation and management; SD, standard deviation.
[a] Long-acting vs. short-acting AED monotherapy.
[b] Including family practice, internal medicine, and pediatrics.
[c] All individual specialties in "Other" are <2%.
[d] 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.
[e] Patients could have more than one comorbidity.

Table 2
Antiepileptic drug use and medication possession ratio (MPR).

Long-acting AED monotherapy n = 4058; 49.6%					Short-acting AED monotherapy n = 4122; 50.4%				
AED	No. (%)	MPR (0–1)			AED	No. (%)	MPR (0–1)		
		Mean	(SD)	[Median]			Mean	(SD)	[Median]
All	4058 (100.0)	0.899[a]	(0.13)	[0.953]	All	4122 (100.0)	0.903[a]	(0.13)	[0.959]
PHT ER	1604 (39.5)	0.902	(0.12)	[0.951]	LEV	1667 (40.4)	0.902	(0.13)	[0.956]
CBZ ER	661 (16.3)	0.908	(0.13)	[0.964]	LTG	1351 (32.8)	0.910	(0.13)	[0.967]
TPM	449 (11.1)	0.877	(0.14)	[0.937]	CBZ	593 (14.4)	0.898	(0.14)	[0.962]
DVP ER	407 (10.0)	0.885	(0.14)	[0.942]	OXC	511 (12.4)	0.895	(0.14)	[0.948]
DVP DR	321 (7.9)	0.879	(0.14)	[0.932]					
PB	273 (6.7)	0.920	(0.11)	[0.973]					
LEV ER	191 (4.7)	0.921	(0.11)	[0.964]					
ZNS	152 (3.7)	0.907	(0.13)	[0.967]					

AED, antiepileptic drug; ER, extended release; DR, delayed release.
LA AEDs: phenytoin ER (PHT ER); carbamazepine ER (CBZ ER); topiramate (TPM); divalproex ER (DVP ER); divalproex DR (DVP DR); phenobarbital (PB); levetiracetam ER (LEV ER); zonisamide (ZNS); SA AEDs: levetiracetam (LEV); lamotrigine (LTG); carbamazepine (CBZ); oxcarbazepine (OXC).
[a] MPRs were not significantly different between the two cohorts ($P = 0.125$).

studies that assessed whether AEDs of long half-life or with long duration of action might mitigate the impact of poor adherence on health-care utilization and costs was the impetus for the current study.

A recent study examined economic outcomes between groups of adult patients identified as having stable and uncontrolled epilepsy [16], but, to our knowledge, this is the first study to provide detailed information on health-care utilization and costs incurred by commercially insured patients with epilepsy in the US who were treated with LA or SA AED monotherapy. Using a large administrative claims database, our study demonstrated that for patients with similar adherence rates, those who were treated with LA AED monotherapy incurred a lower economic burden compared with those who were treated with SA monotherapy. This finding suggests that the use of longer half-life drugs might mitigate the impact of imperfect adherence. In addition, LA AED users had a significantly lower rate of hospitalization, a lower mean number of office visits compared with SA AED users, and significantly lower use of EEG and brain imaging. They had fewer overall ED visits, but there was no significant difference in epilepsy-related ED visits. The only aspect of resource utilization that was higher in LA AED users was AED serum level testing. Taken as a whole, these results

Table 3
Annual overall and epilepsy-related health-care utilization in adult patients with epilepsy.

	Long-acting AED monotherapy n = 4058; 49.6%	Short-acting AED monotherapy n = 4122; 50.4%	All N = 8180	*P* value[a]
Annual overall health-care utilization				
Inpatient hospitalizations, n (%)				0.003
0	3704 (91.3)	3676 (89.2)	7380 (90.2)	
1	295 (7.3)	357 (8.7)	652 (8.0)	
2+	59 (1.5)	89 (2.2)	148 (1.8)	
ED visits, n (%)				0.009
0	3735 (92.0)	3724 (90.3)	7459 (91.2)	
1	156 (3.8)	184 (4.5)	340 (4.2)	
2+	167 (4.1)	214 (5.2)	381 (4.7)	
Office visits, mean (SD) [median]	8.8 (9.4)	9.9 (10.0)	9.4 (9.7)	<0.001
Annual epilepsy-related[b] health-care utilization				
Epilepsy-related[b] inpatient hospitalizations, n (%)				0.005
0	3826 (94.3)	3812 (92.5)	7638 (93.4)	
1	208 (5.1)	279 (6.8)	487 (6.0)	
2+	24 (0.6)	31 (0.8)	55 (0.7)	
Epilepsy-related[b] ED visits, n (%)				0.343
0	4037 (99.5)	4094 (99.3)	8131 (99.4)	
1+	21 (0.5)	28 (0.7)	49 (0.6)	
Epilepsy-related[b] office visits, mean (SD)	1.8 (1.5)	2.0 (1.6)	1.9 (1.6)	<0.001
EEG, n (%)				<0.001
0	3760 (92.7)	3602 (87.4)	7362 (90.0)	
1	251 (6.2)	427 (10.4)	678 (8.3)	
2	28 (0.7)	51 (1.2)	79 (1.0)	
3+	19 (0.5)	42 (1.0)	61 (0.7)	
Brain imaging, n (%)				<0.001
0	3605 (88.8)	3378 (82.0)	6983 (85.4)	
1	349 (8.6)	499 (12.1)	848 (10.4)	
2	69 (1.7)	132 (3.2)	201 (2.5)	
3+	35 (0.9)	113 (2.7)	148 (1.8)	
AED levels, n (%)				<0.001
0	3135 (77.3)	3596 (87.2)	6731 (82.3)	
1	685 (16.9)	381 (9.2)	1066 (13.0)	
2	177 (4.4)	107 (2.6)	284 (3.5)	
3+	61 (1.5)	38 (0.9)	99 (1.2)	

AED, antiepileptic drug; ED, emergency department; EEG, electroencephalogram; SD, standard deviation.
[a] Long-acting vs. short-acting AED monotherapy.
[b] Claims with a diagnosis of epilepsy in any diagnosis field or epilepsy-related tests.

Table 4
Annual overall and epilepsy-related health-care costs in adult patients with epilepsy.

	Long-acting AED monotherapy n = 4058; 49.6%		Short-acting AED monotherapy n = 4122; 50.4%		All N = 8180		*P* value[a]
	Mean	(SD)	Mean	(SD)	Mean	(SD)	
Overall health-care costs, $	9757	(21,634)	12,689	(25,358)	11,234	(23,628)	<0.001
Medical cost, $	6745	(19,984)	8331	(23,557)	7544	(21,870)	0.001
Pharmacy cost, $	3012	(4891)	4358	(6042)	3690	(5542)	<0.001
Epilepsy-related overall health-care costs, $	3539	(11,077)	5279	(17,157)	4416	(14,489)	<0.001
Epilepsy-related[b] medical cost, $	2355	(10,896)	3197	(17,002)	2779	(14,308)	0.008
AED cost, $	1184	(1733)	2082	(2412)	1637	(2150)	<0.001
PHT ER (n = 1604)	$444	(208)					
CBZ ER (n = 661)	$1419	(759)					
TPM (n = 449)	$2237	(3563)					
DVP ER (n = 407)	$1594	(1212)					
DVP DR (n = 321)	$1440	(1174)					
PB (n = 273)	$70	(51)					
LEV ER (n = 191)	$4455	(2231)					
ZNS (n = 152)	$1114	(1104)					
LEV (n = 1667)			$2346	(2044)			
LTG (n = 1351)			$2309	(3097)			
CBZ (n = 593)			$424	(581)			
OXC (n = 511)			$2544	(1949)			

AED, antiepileptic drug; ED, emergency department; SD, standard deviation.
[a] Long-acting vs. short-acting AED monotherapy.
[b] Claims with a diagnosis of epilepsy in any position.

may indicate that patients with epilepsy who take SA AEDs could decrease their economic burden and health-care resource utilization by switching to LA AEDs.

Epilepsy-related annual health-care costs remained significantly lower in LA AED users than in SA AED users after adjusting for demographics, usual physician specialty, and comorbidities. The overall health-care cost difference between the LA AED users and the SA AED users became statistically insignificant after adjusting for patient and clinical characteristics; however, the numeric difference points to the direction of potentially better economic outcomes with LA AED use. Those findings are consistent with the finding that LA AED users also had a generally lower rate of resource utilization. Epilepsy-related health-care costs in our study accounted for <40% of total observed health-care costs, which suggests that comorbid conditions may be costly and/or that epilepsy-related health-care utilization was underidentified. Timely surveillance and treatment of comorbid conditions in adults with epilepsy are important because co-occurring conditions can be the cause of seizures (e.g., cerebrovascular disease) or can be exacerbated by epilepsy (e.g., neurodegenerative diseases), and poor control of comorbidities may further complicate the overall management of the disease, leading to an increased economic burden [1,17–20].

4.1. Strengths and limitations

We analyzed a large sample of adult patients with epilepsy identified in a major commercial insurance claims database representing all geographic regions of the United States. The availability of this large dataset allowed us to detect statistically significant group differences in measures of burden-of-illness, health-care utilization, and health-care costs. The breadth of the claims database allowed us to compare adult patients who were treated with either LA or SA AED monotherapy

Table 5
Regression models of overall and epilepsy-related health-care costs and utilization in adult patients with epilepsy.

	Overall health-care costs			Epilepsy-related overall health-care costs			Risk of inpatient hospitalization		Risk of epilepsy-related inpatient hospitalization	
	Coefficient	(SE)	*P*	Coefficient	(SE)	*P*	OR	(95% CI)	OR	(95% CI)
Age group, year										
18–34 vs. 55+	**3476**[a]	(666)	<0.001	**2304**[a]	(461)	<0.001	**1.92**[a]	(1.52–2.43)	**1.84**[a]	(1.41–2.40)
35–44 vs. 55+	**3224**[a]	(685)	<0.001	**2059**[a]	(474)	<0.001	**1.47**[a]	(1.15–1.86)	**1.44**[a]	(1.09–1.90)
45–54 vs. 55+	**1283**[a]	(621)	0.039	**936**[a]	(430)	0.030	**0.79**[a]	(0.63–1.00)	0.89	(0.68–1.15)
Female vs. male	226	(455)	0.620	82	(315)	0.796	**1.22**[a]	(1.04–1.44)	1.07	(0.89–1.29)
Region										
Midwest vs. West	−488	(726)	0.502	124	(503)	0.805	0.99	(0.77–1.27)	1.01	(0.76–1.34)
Northeast vs. West	−**2065**[a]	(918)	0.025	−911	(636)	0.152	**0.62**[a]	(0.45–0.87)	**0.68**[a]	(0.47–1.00)
South vs. West	−107	(684)	0.876	100	(474)	0.834	0.93	(0.74–1.18)	0.89	(0.68–1.17)
Usual physician specialty										
Neurology vs. primary care	**2790**[a]	(541)	<0.001	**1764**[a]	(375)	<0.001	1.13	(0.92–1.39)	1.18	(0.93–1.49)
Other/unknown vs. primary care	**6036**[a]	(610)	<0.001	**1089**[a]	(423)	0.010	**1.33**[a]	(1.09–1.61)	**1.35**[a]	(1.08–1.69)
Charlson Comorbidity Index	**4543**[a]	(173)	<0.001	**943**[a]	(120)	<0.001	**1.19**[a]	(1.14–1.25)	**1.11**[a]	(1.06–1.16)
No. of chronic conditions	**3460**[a]	(156)	<0.001	**1393**[a]	(108)	<0.001	**1.53**[a]	(1.45–1.60)	**1.46**[a]	(1.38–1.54)
Any epilepsy-specific comorbidities[b]	934	(601)	0.121	32	(417)	0.939	**1.27**[a]	(1.06–1.52)	**1.29**[a]	(1.05–1.58)
Long-acting vs. short-acting	−686	(460)	0.137	−**894**[a]	(319)	0.005	1.02	(0.87–1.21)	0.94	(0.78–1.13)

CI, confidence interval; OR, odds ratio; SE, standard error.
[a] Estimate is statistically significantly different from zero.
[b] Head injury, brain tumor cerebrovascular disease/stroke, depression and other mood disorders, meningitis/vasculitides, and tuberous sclerosis.

on a number of key overall and epilepsy-related health-care utilization and cost measures. We were also able to produce age, gender, geographic region, and comorbidity-adjusted estimates of epilepsy cohort differences in health-care utilization and costs.

This study has limitations. Administrative claims databases are designed for payment, not research. Claims data lack clinical detail, do not capture disease severity and duration, and do not include the reasons why certain AEDs were prescribed to a patient. International Classification of Diseases, Ninth Revision, Clinical Modification codes also do not provide information about specific epilepsy syndromes. Hence, there could be a variety of unmeasured AED monotherapy group differences, which we were not able to adjust for in our analyses, but which may impact outcomes of interest. The claims database included only commercially insured patients; thus, the results may not be generalizable to populations without insurance or other types of coverage. The use of this database only allowed us to analyze direct costs, although epilepsy may be associated with considerable social and emotional burden and their associated indirect costs [1,21–25]. Another limitation of our study is that MPR summarizes medication fills, not actual medication-taking behavior. This study was also not designed to assess whether costs changed if a patient switched from a SA AED to a LA AED or vice versa.

Patients who receive LA AED monotherapy accrue lower costs compared with those who receive SA AED monotherapy, indicating that AEDs with extended duration of action are associated with less health-care use and decreased economic burden. The higher pharmacy costs in the SA AED monotherapy patients, however, do not explain the higher overall costs since medical care costs are also higher in the SA AED monotherapy patients than in those with LA AED monotherapy. These findings support our study hypothesis that the LA AEDs are associated with improved health and economic outcomes. This could be the result of reduced peak-to-trough serum AED fluctuations, improved adherence due to the convenience of less frequent administration, or mitigation of imperfect adherence. Future studies should assess the impact of duration of action on outcomes in combination therapy, as many patients with epilepsy require more than one AED to achieve optimal disease control. Patients with uncontrolled epilepsy use more health-care services and incur higher costs compared with those with stable epilepsy [16]. Future research should examine economic impacts between LA and SA AED treatment groups while controlling for epilepsy disease status.

4.2. Conclusion

Commercially insured patients treated with LA monotherapy had a lower economic burden compared with those treated with SA monotherapy, indicating that using AEDs with extended duration of action was associated with decreased health-care use and lower health-care costs.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.yebeh.2014.12.020.

Acknowledgments

The authors thank Gordon H. Sun for critical review of the manuscript.

Funding

Funding for this study was provided by Eisai Inc.

Disclosures

Ms. Cramer is a consultant for Eisai Inc. Dr. Wang and Dr. Copher are employees of Eisai Inc. Dr. Broder, Dr. Chang, and Dr. Cherepanov are employees of Partnership for Health Analytic Research, LLC, a healthb services research company paid by Eisai Inc. to conduct this research.

Authorship contributions

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

References

[1] IOM (Institute of Medicine). Epilepsy across the spectrum: promoting health and understanding. Washington, DC: The National Academy Press; 2012.
[2] Centers for Disease Control and Prevention. Targeting epilepsy: improving the lives of people with one of the nation's most common neurological conditions, at a glance 2011. http://www.cdc.gov/chronicdisease/resources/publications/AAG/epilepsy.htm. [accessed September 12, 2013].
[3] Perucca E, Tomson T. The pharmacological treatment of epilepsy in adults. Lancet–Neurol 2011;10:446–56.
[4] Davis KL, Candrilli SD, Edin HM. Prevalence and cost of nonadherence with antiepileptic drugs in an adult managed care population. Epilepsia 2008;49:446–54.
[5] Ettinger AB, Manjunath R, Candrilli SD, Davis KL. Prevalence and cost of nonadherence to antiepileptic drugs in elderly patients with epilepsy. Epilepsy Behav 2009;14:324–9.
[6] Faught RE, Weiner JR, Guérin A, Cunnington MC, Duh MS. Impact of nonadherence to antiepileptic drugs on health care utilization and costs: findings from the RANSOM study. Epilepsia 2009;50:501–9.
[7] Patsalos PN, Berry DJ, Bourgeois BF, Cloyd JC, Glauser TA, Johannessen SI, et al. Antiepileptic drugs — best practice guidelines for therapeutic drug monitoring: a position paper by the subcommission on therapeutic drug monitoring, ILAE Commission on Therapeutic Strategies. Epilepsia 2008;49:1239–76.
[8] O'Malley A, Pham H, Schrag D, Wu B, Bach P. Potentially avoidable hospitalizations for COPD and pneumonia: the role of physician and practice characteristics. Med Care 2007;45:562–70.
[9] Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40(5):373–83.
[10] Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. J Clin Epidemiol 1992;45(6):613–9.
[11] Hwang W, Heller W, Ireys H, Anderson G. Out-of-pocket medical spending for care of chronic conditions. Health Aff 2001;20(6):267–78.
[12] HCUP chronic condition indicator. Healthcare Cost and Utilization Project (HCUP). Rockville, MD: Agency for Healthcare Research and Quality; 2011[Available at: www.hcup-us.ahrq.gov/toolssoftware/chronic/chronic.jsp. Accessed September 12, 2013].
[13] Kardas P, Lewek P, Matyjaszczyk M. Determinants of patient adherence: a review of systematic reviews. Front Pharmacol 2013;4:91.
[14] Briesacher BA, Andrade SE, Fouayzi H, Chan KA. Comparison of drug adherence rates among patients with seven different medical conditions. Pharmacotherapy 2008:437–43.
[15] Al-Aqeel S, Al-Sabhan J. Strategies for improving adherence to antiepileptic drug treatment in patients in epilepsy. Cochrane Database Syst Rev 2011(1):CD008312.

[16] Cramer JA, Wang ZJ, Chang E, Powers A, Copher R, Cherepanov D, et al. Healthcare utilization and costs in adults with stable and uncontrolled epilepsy. Epilepsy Behav 2014;31:356–62.
[17] Gaitatzis A, Carroll K, Majeed AW, Sander J. The epidemiology of the comorbidity of epilepsy in the general population. Epilepsia 2004;45(12):1613–22.
[18] Strine TW, Kobau R, Chapman DP, Thurman DJ, Price P, Balluz LS. Psychological distress, comorbidities, and health behaviors among U.S. adults with seizures: results from the 2002 National Health Interview Survey. Epilepsia 2005;46:1133–9.
[19] Kobau R, Zahran H, Thurman DJ, Zack MM, Henry TR, Schachter SC, et al. Epilepsy surveillance among adults — 19 states, behavioral risk factor surveillance system. MMWR Surveill Summ 2008;57:1–20.
[20] Seidenberg M, Pulsipher DT, Hermann B. Association of epilepsy and comorbid conditions. Futur Neurol 2009;4:663–8.
[21] Begley CE, Famulari M, Annegers JF, Lairson DR, Reynolds TF, Coan S, et al. The cost of epilepsy in the United States: an estimate from population-based clinical and survey data. Epilepsia 2000;41(3):342–51.
[22] Strzelczyk A, Reese JP, Dodel R, Hamer HM. Cost of epilepsy: a systematic review. Pharmacoeconomics 2008;26(6):463–76.
[23] Ivanova JI, Birnbaum HG, Kidolezi Y, Qiu Y, Mallett D, Caleo S. Economic burden of epilepsy among the privately insured in the US. Pharmacoeconomics 2010;28(8):675–85.
[24] Ivanova JI, Birnbaum HG, Kidolezi Y, Qiu Y, Mallett D, Caleo S. Direct and indirect costs associated with epileptic partial onset seizures among the privately insured in the United States. Epilepsia 2010;51(5):838–44.
[25] Lu B, Elliott JO. Beyond seizures and medications: normal activity limitations, social support, and mental health in epilepsy. Epilepsia 2012;53(2):e25–8.