



# New-onset lesional and nonlesional epilepsy in the US population: Patient characteristics and patterns of antiepileptic drug use

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## ABSTRACT

**Purpose:** Describe treatment patterns in patients from the United States with new-onset epilepsy, comparing those with and without lesional epilepsy.

**Methods:** In this observational study we used Truven Health MarketScan databases derived from commercial health insurance, Medicare and Medicaid claims covering at least 5 years, commencing in 2008. We identified incident epilepsy cases based on International Classification of Diseases, Ninth Revision, Clinical Modification codes indicating epilepsy or recurrent seizures, taking into account antiepileptic drug (AED) claims, consistent with International League Against Epilepsy Commission on Epidemiology recommendations. We identified patients with lesional epilepsy when associated diagnoses indicated central nervous system infection, neoplasm, traumatic brain injury, stroke, senile dementia and static encephalopathy. Lesional and nonlesional cohorts were matched 1:1 on baseline characteristics of age, sex and insurance type for group comparisons.

**Results:** In unmatched cohorts lesional epilepsy patients ( $N = 15,302$ ) were more commonly older (mean age 48.7 years) compared with nonlesional epilepsy patients ( $N = 15,970$ ; mean age 18.5 years). Among lesional patients < 20 years of age, the leading putative etiology was static encephalopathy, while among ages  $\geq 20$  years and older, the leading putative etiology was stroke or cerebrovascular disease. In matched cohorts (7063 patients each), those with lesional epilepsy were significantly less likely to be untreated at 1 year versus those with nonlesional epilepsy (37.2% vs 56.1%). In children and adults among matched cohorts, levetiracetam was the most common AED prescribed for initial AED therapy for the lesional (39.5%) and nonlesional (32.1%) groups. Lesional epilepsy patients on monotherapy were only slightly less likely than nonlesional epilepsy patients to be on the same AED 1 year after treatment initiation (55.6% vs 59.7%).

**Significance:** Compared with patients with lesional epilepsy, a higher proportion of patients with nonlesional epilepsy remain untreated 1 year after diagnosis. There were differences in AED selection by epilepsy etiology; levetiracetam is the most commonly prescribed drug for both cohorts.

## 1. Introduction

Conceptually, epilepsy is a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures (Fisher et al., 2014). It is one of the most common neurological disorders of the brain, affecting approximately 70 million people worldwide (Ngugi et al., 2010). The lifetime risk of developing epilepsy is between 3% and 5%,

with the highest incidence reported in neonates, young children and the elderly (Banerjee et al., 2009). Epilepsy is associated with increased morbidity and mortality and can severely impact patients' quality of life (Quintas et al., 2012).

Within the International League Against Epilepsy classification of epilepsies described by Scheffer et al., 2017; lesional epilepsy would fit with subcategories of focal epilepsy that are attributable to structural

**Abbreviations:** AED, antiepileptic drug; CCMC, commercial claims and medicare; CNS, central nervous system; HIPAA, health Insurance portability and accountability act; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification

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etiologies including hippocampal sclerosis, traumatic brain injury, cerebrovascular disease, brain tumors or central nervous system (CNS) infections (Carter et al., 2004; Senanayake and Roman, 1993; Singh et al., 2006).

Antiepileptic drugs (AEDs) are the mainstay of treatment for the majority of patients with epilepsy, and are intended to eliminate further seizures. More than 20 AEDs are currently available, and single-drug treatment (monotherapy) is recommended first for patients with newly diagnosed epilepsy. Combination therapy may be initiated if seizures are unresponsive to monotherapy (Stephen and Brodie, 2009). Approximately 70% of patients with epilepsy who are treated achieve long-term remission or freedom from seizures, usually within 5 years of diagnosis (Kwan and Sander, 2004). The choice of AEDs is primarily based on evidence of efficacy for the patient's seizure type, safety profile of the drug and patient-specific factors including age, sex, childbearing potential, comorbidities and use of concomitant medications (Perucca and Tomson, 2011).

Multiple studies have examined prescribing patterns using administrative data in patients with epilepsy (Faught et al., 2008, 2018; Hansen et al., 2009; Margolis et al., 2014; Pugh et al., 2008). However, little information is known about how patient characteristics and treatment patterns in patients with lesional epilepsy compare to those with nonlesional epilepsy. The objective of this study is to describe these phenomena in patients in the United States (US), using administrative data from commercial, Medicare and Medicaid insurance databases.

## 2. Methods

### 2.1. Data sources

This retrospective cohort study was conducted using the Truven Health MarketScan Commercial Claims and Medicare (CCMC) database for January 1, 2008 through September 30, 2013 and the Truven Health Multi-state Medicaid database (Medicaid) for January 1, 2008 through December 31, 2012. The pooled databases contain over 100 million covered lives per year. The CCMC database comprises privately insured individuals in all 50 US states under a variety of commercial insurance plans and are deemed to be representative of the US commercially insured population, as well as patients 65 years of age and older with supplemental Medicare coverage. The Medicaid database comprises individuals from 13 states in four census regions in the US.

The databases capture information on hospital inpatient, outpatient, emergency medical care and pharmacy claims (Helmert et al., 2015). The information includes date and place of service, International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis, and dispensed medications, as well as information on age, sex, health insurance payer type and monthly enrollment status. These files are linkable by encrypted patient identification numbers.

### 2.2. Standard protocol approvals, registrations and patient consents

The MarketScan Research Databases are de-identified and fully compliant with the Health Insurance Portability and Accountability Act of 1996 (HIPAA).

### 2.3. Study methods

For each patient, the study encompassed an initial baseline period, an index date and a subsequent follow-up period. The minimum baseline periods were 2 years for patients  $\geq 2$  years of age, and 1 year for those 1 to  $< 2$  years of age. For those less than 1 year of age there was no minimum baseline enrollment period requirement. During the baseline period, patients were required to have continuous medical and pharmacy enrollment in order to ensure complete claims histories.

Epilepsy cases were identified when any of the following criteria

were met within the patient selection period:

- An occurrence of at least two ICD-9-CM codes of 345.xx among separate medical encounters (separate dates in any care venue),
- An occurrence of at least one ICD-9-CM code of 345.xx AND at least one ICD-9-CM code of 780.3x among separate medical encounters,
- An occurrence of one ICD-9-CM code of 345.xx AND code(s) for AED prescription after the 345.xx code,
- An occurrence of at least two ICD codes of 780.39 among separate medical encounters AND code(s) for AED treatment. The code(s) for the AED treatment should occur after the second 780.39 irrespective of the presence or absence of an AED code after the first 780.39 code.
- Patients with ICD-9-CM code 345.3 (status epilepticus) will be required to have an occurrence of at least two ICD-9-CM codes of 345.3 separated by at least 30 days, or an occurrence of the 345.3 code and at least one ICD-9-CM code 780.39 separated by at least 30 days, or at least one ICD-9-CM code 345.3 and at least one ICD-9-CM code 345.xx encounter on separate days.

The epilepsy cases were considered incident (new onset) when no occurrences of ICD-9-CM 345.xx or 780.39, and no AED prescriptions were recorded during the minimum baseline period, as defined above. The time of first occurrence of any of these ICD-9-CM defined the index date.

Patients were required to have a minimum 180-day follow-up period to assess all outcomes. Patients were followed from the index date until the first occurrence of any of the following:

- Date of last enrollment after the index date for patients who were not continuously enrolled through the end of the study period, or
- End date of the study period, for patients who were continuously enrolled through the end of the study period of interest, or
- Date of death.

The authors developed the classification criteria for lesional and nonlesional epilepsy. We identified a lesional epilepsy cohort among patients with a diagnosis of epilepsy if they had at least one diagnosis indicating a brain lesion or disorder such as infection, neoplasm, traumatic brain injury, stroke, senile dementia, static encephalopathy including hypoxic ischemic encephalopathy, perinatal intracranial hemorrhage and congenital infection (Supplement Table 1), occurring either in the baseline period or up to 3 months after the index date. The cohort was further stratified by these etiologic categories. Patients with a diagnosis recorded during the same period indicating CNS conditions of uncertain or low association with epilepsy (Supplement Table 2) were excluded from this cohort and categorized as indeterminate.

We identified a cohort of patients with nonlesional epilepsy in the absence of any brain lesion or disorder associated or possibly associated with epilepsy (Supplement Tables 1 and 2) recorded any time during the study period.

Treatment was classified as monotherapy if a single AED was taken for  $\geq 90$  continuous days, polytherapy if two or more AEDs were taken for  $\geq 90$  days continuous days, undefined if one or more AEDs were taken for  $< 90$  days or the patient did not receive AEDs, or indeterminate if treatment line was started within 90 days of the end of the follow-up period.

### 2.4. Statistical analysis

Descriptive analyses were used and continuous variables were presented using mean and standard deviation (SD), median and quartiles, or range. Categorical variables were presented using frequencies and percentages. Kaplan–Meier survival curves were used to estimate time to AED treatment. Lesional and nonlesional cohorts were matched 1:1 on baseline characteristics of age, sex and insurance type for group

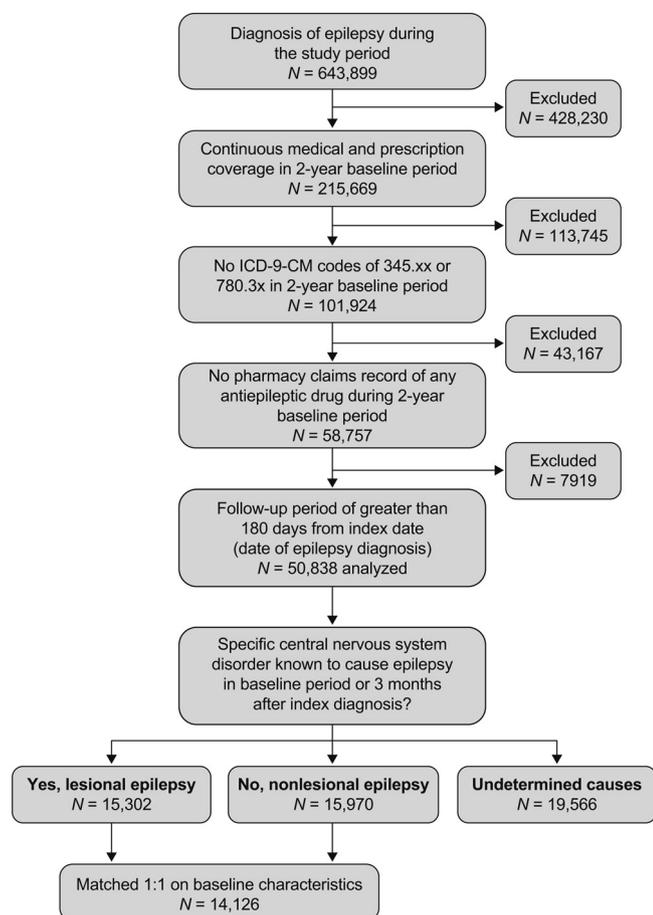


Fig. 1. Patient selection algorithm for incident epilepsy matching.

comparisons. The McNemar's test was used to compare categorical outcomes between the two cohorts.  $P$ -values  $< 0.05$  were considered significant. The analyses were conducted using SAS version 9.3 (SAS Institute Inc., Cary, NC).

### 3. Results

#### 3.1. Study sample

A total of 643,899 patients with epilepsy were identified in the CCMC and Medicaid databases. The final study cohort for the population consisted of 50,838 incident epilepsy patients who met all study criteria (Fig. 1), including 15,302 lesional, 15,970 nonlesional and 19,566 indeterminate cases. Following matching, the lesional and nonlesional epilepsy groups consisted of 7063 patients each.

#### 3.2. Demographic and clinical characteristics

Most patients in the unmatched lesional epilepsy population had an epilepsy etiology of stroke or cerebrovascular disease (Table 1). The mean (SD) age of the unmatched lesional epilepsy population was 48.7 (29.1) years, for the nonlesional epilepsy population it was 18.5 (16.4) years, and 40.4 (25.8) years for indeterminate epilepsy (Table 2). 50.8% ( $n = 25,814$ ) of the total incident cases were female.

In children and adolescents of 0–19 years of age, the leading epilepsy etiologies were static encephalopathies (38.2%), stroke (12.1%), traumatic brain injury (11.4%) and infection (8.6%) (Fig. 2). In adults 20 years of age and older, leading epilepsy etiologies were stroke (39.3%) and 48.1% in patients 20–64 years and  $\geq 65$  years, respectively), dementia (1.8% and 12.2%, respectively), tumors (includes

Table 1

Epilepsy etiology in the lesional epilepsy cohort before matching ( $N = 15,302$ ).

Etiology	Number of patients (%)
Stroke or cerebrovascular disease	5441 (35.6)
Childhood static encephalopathy	1838 (12.0)
Traumatic brain injury	1098 (7.2)
Senile dementias	770 (5.0)
Infection	648 (4.2)
Malignant tumors	535 (3.5)
Other tumors	524 (3.4)
More than one etiology	4448 (29.1)

malignant and other tumors; 11.6% and 3.8%, respectively) and traumatic brain injury (9.0% and 2.3%, respectively). Stroke and cerebrovascular disease was the single most common etiology in adults. Tumors overall (malignant and other) were a higher proportion of etiologies in adults of 20–64 years of age (Fig. 2).

#### 3.3. AED use

The lesional epilepsy group was substantially less likely to remain untreated at 1 year when compared with the nonlesional epilepsy group (Fig. 3; 37.2% vs 56.1%,  $P \leq 0.01$ ). Medicaid-insured patients were only slightly more likely not to have initiated treatment at 1 year (lesional epilepsy 38.8%, nonlesional epilepsy 58.7%) versus those with Medicare and private insurance (lesional epilepsy 36.3%, nonlesional epilepsy 54.6%).

Most patients in the matched cohorts received first-line monotherapy (Fig. 4). Levetiracetam was the most common AED prescribed for initial AED monotherapy in both groups (Fig. 5) and was more commonly prescribed in patients with lesional epilepsy compared with nonlesional epilepsy (39.5% versus 32.1% across all ages). In children and adolescents, the proportion of patients prescribed phenobarbital was higher in patients with lesional than nonlesional epilepsy (12.7% versus 8.2%) whereas the proportions of patients prescribed valproic acid (4.2% versus 7.9%), lamotrigine (2.1% versus 5.3%) and ethosuximide (0.4% versus 5.7%) were lower in patients with lesional versus nonlesional epilepsy. In adults, the proportion of patients prescribed lamotrigine (3.5% versus 8.0%) was lower in patients with lesional versus nonlesional epilepsy.

Lesional epilepsy patients on monotherapy were slightly less likely to remain on the same AED at 1 year than nonlesional epilepsy patients (55.6% vs 59.7%,  $P = 0.006$ ). In patients with initial levetiracetam monotherapy, the median time to second-line treatment was 226 days in lesional epilepsy patients and 240 days in nonlesional epilepsy patients (Table 3). For commonly prescribed AEDs with the highest rates of continuance until censoring (at study end or change in insurance), only small differences in continuance were noted between lesional and nonlesional cases, i.e., oxcarbazepine (lesional 54.1%, nonlesional 58.5%), lamotrigine (lesional 54.3%, nonlesional 56.2%) and levetiracetam (lesional 46.4%, nonlesional 50.5%).

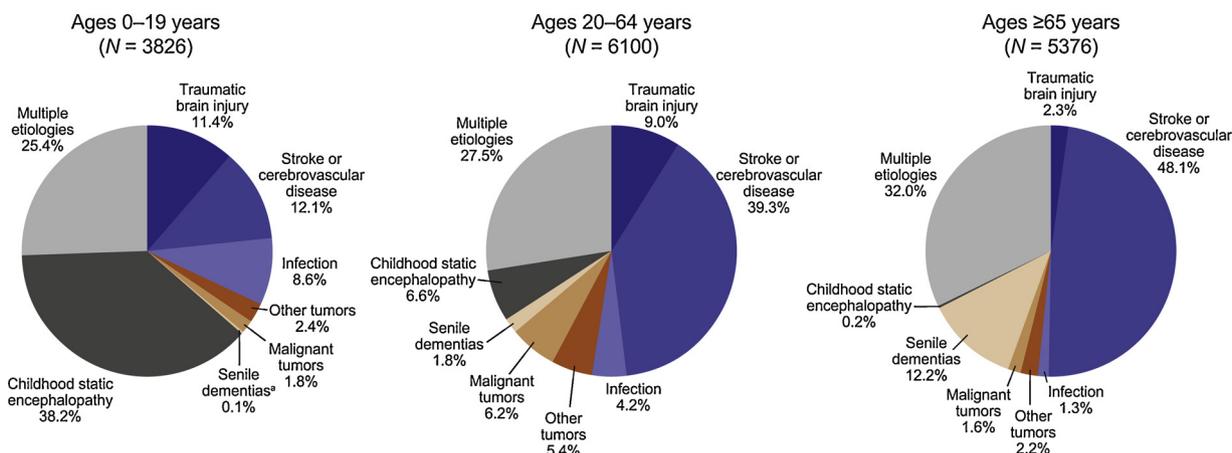
In patients with first-line polytherapy, the most common AED combinations were levetiracetam and phenobarbital in children and adolescents, and levetiracetam in combination with gabapentin or phenytoin in adults (Fig. 5). In all patients with first-line monotherapy who added an AED (second-line polytherapy), the most common AED combinations were levetiracetam combined with either oxcarbazepine (80 patients), lamotrigine (73 patients), topiramate (58 patients), clonazepam (51 patients) or gabapentin (51 patients).

### 4. Discussion

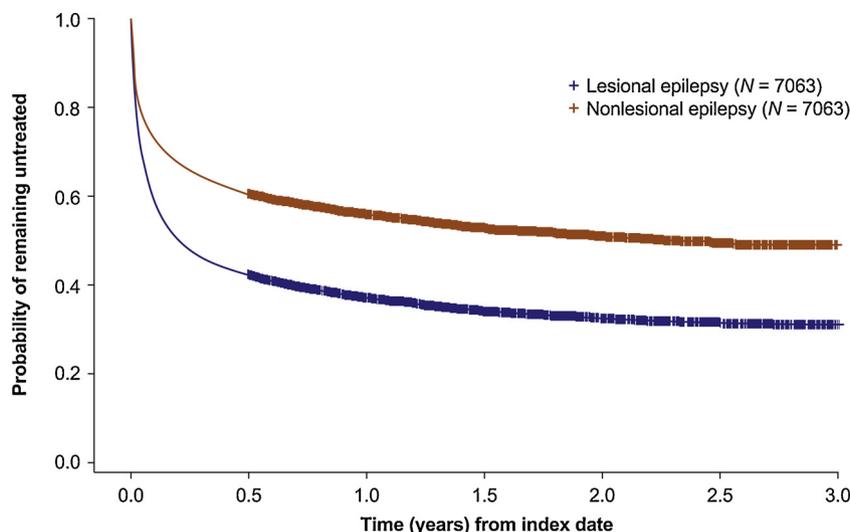
To our knowledge, this is the first published study comparing the characteristics and AED prescribing patterns among patients with epilepsy of lesional or nonlesional origin, using a nationally drawn

**Table 2**  
Baseline patient demographic characteristics.

Variable	Unmatched			Matched	
	Lesional N = 15,302	Nonlesional N = 15,970	Indeterminant N = 19,566	Lesional N = 7063	Nonlesional N = 7063
Age, mean (SD), years	48.7 (29.1)	18.5 (16.4)	40.4 (25.8)	24.5 (21.2)	24.3 (20.9)
Age (years), n (%)					
0–4	1767 (11.5)	2965 (18.6)	1904 (9.7)	1606 (22.7)	1606 (22.7)
5–19	2059 (13.5)	7608 (47.6)	4052 (20.7)	2056 (29.1)	2056 (29.1)
20–64	6100 (39.9)	5209 (32.6)	10,134 (51.8)	3213 (45.5)	3213 (45.5)
65+	5376 (35.1)	188 (1.2)	3476 (17.8)	188 (2.7)	188 (2.7)
Female, n (%)	7357 (48.1)	8380 (52.5)	10,077 (51.5)	3466 (49.1)	3466 (49.1)
Health plan type, n (%)					
CCMC	12,185 (79.6)	10,933 (68.5)	15,556 (79.5)	4547 (64.4)	4547 (64.4)
Medicaid	3117 (20.4)	5037 (31.5)	4010 (20.5)	2516 (35.6)	2516 (35.6)



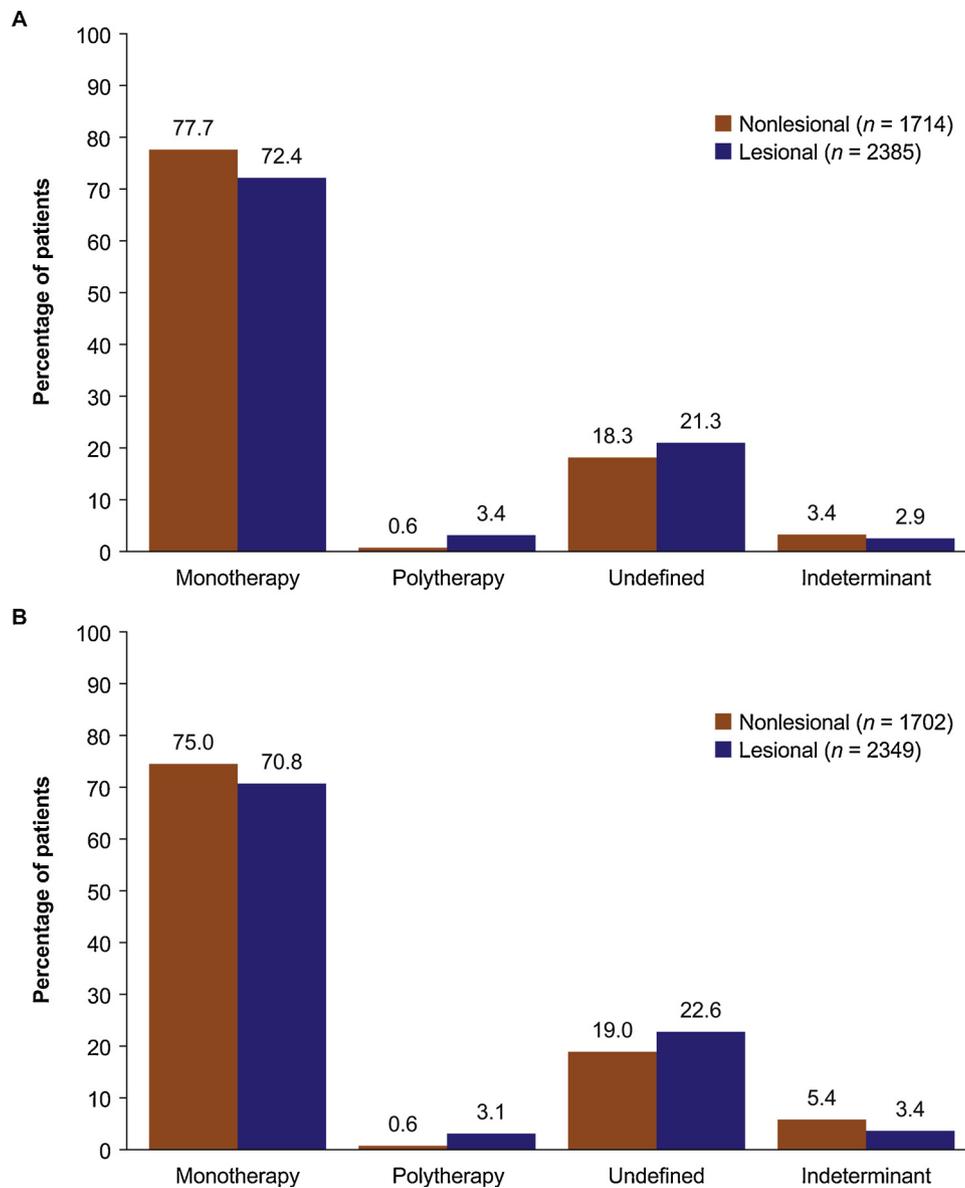
**Fig. 2.** Etiology of lesional epilepsy stratified by age (pre-matching; N = 19,566).  
<sup>a</sup>Four patients aged 0–19 years had an etiological factor of senile dementia because of coding errors.



**Fig. 3.** Probability of not initiating treatment with any AED (incident epilepsy matched cohorts). Patients who were either not treated or who only have intervals of AED exposure lasting < 30 days are considered to be untreated.

database comprising both commercial and government insurance beneficiaries. These data appear broadly representative of the US insured population (Helmert et al., 2015), allowing individual patient information to be linked across inpatient and outpatient care venues and across years, in contrast to most other broad national health care surveys instigated by the US government (National Center for Health Statistics, 2017).

Newly diagnosed lesional and nonlesional epilepsy patients differ substantially by age and by the time within which AED treatment is initiated. Lesional epilepsy more commonly arises in older age categories. As putative etiologies, static encephalopathies such as cerebral palsy and intellectual disability predominate among children, whereas cerebrovascular etiologies predominate among adults. Lesional epilepsy patients are more likely to be treated with AEDs within 1 year and those



**Fig. 4.** Percentage of patients receiving monotherapy or polytherapy, or who were undefined or indeterminant in incident epilepsy matched cohorts stratified by age (A) for ages 0–19 years, (B) for ages  $\geq 20$  years.

Patients were classified as taking monotherapy if a single AED was taken for  $\geq 90$  continuous days, polytherapy if two or more AEDs were taken for  $\geq 90$  continuous days, undefined if one or more AEDs were taken for  $< 90$  days or the patient did not receive AEDs, or indeterminant if treatment line was started within 90 days of the end of the follow-up period.

with monotherapy were slightly less likely to remain on the same AED at 1 year than nonlesional epilepsy patients. At 1 and 3 years following diagnosis, the apparent high proportion of untreated epilepsy patients in both categories is notable, a finding also of a related study that is under further exploration (Faught et al., 2018; Kalilani et al., 2019).

There are several limitations to this study. The information available on each patient is limited to that contained in claims databases. There is potential for misclassification bias, as patient medical records were not available to independently confirm diagnoses of epilepsy or comorbidities. Lastly, the misclassification of prevalent or incident epilepsy is possible given the baseline period of only 2 years, which may not identify prevalent epilepsy among patients who infrequently access medical care.

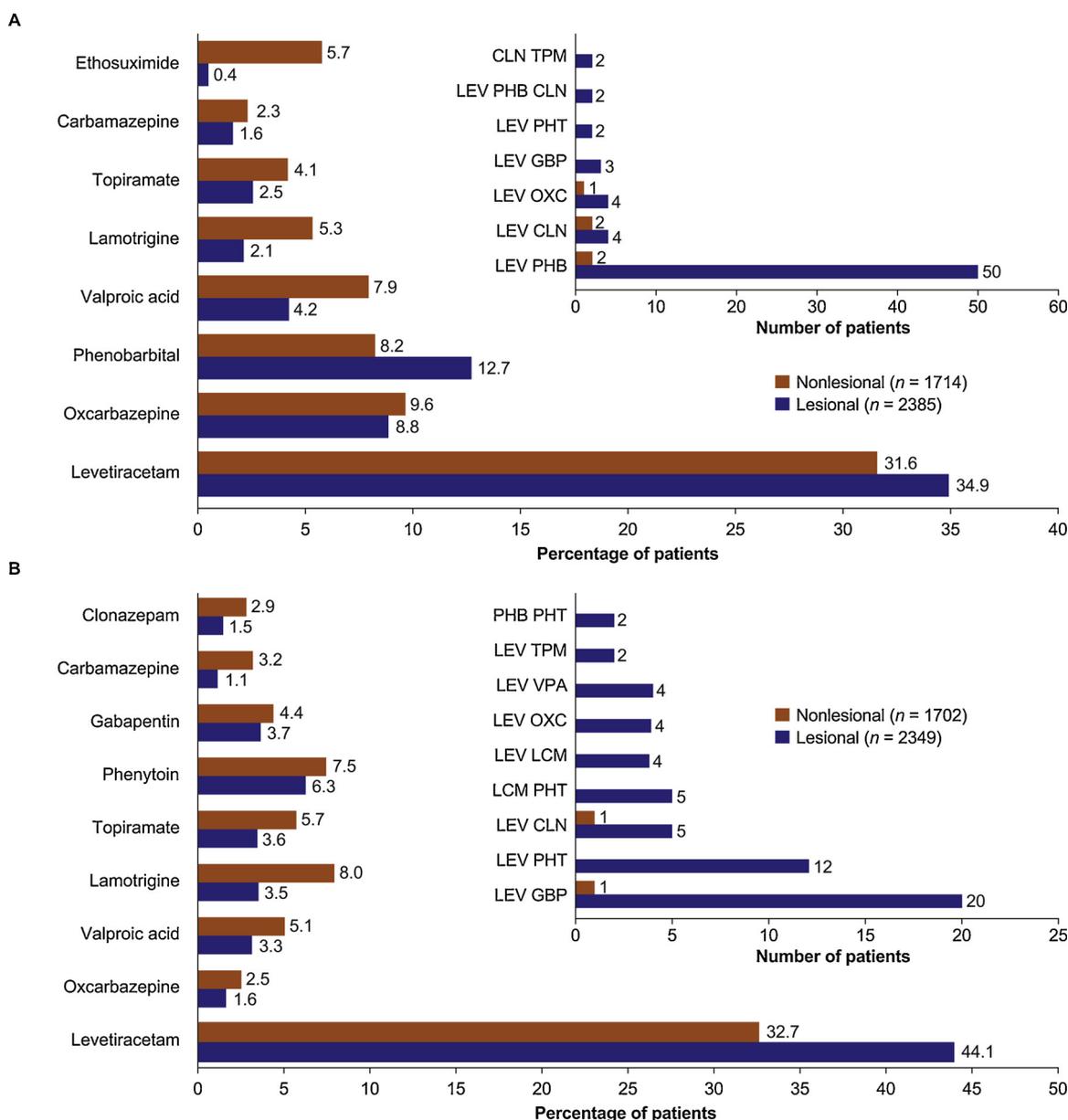
Our findings showed little disparity across insurance types. Patients with Medicaid were only slightly less likely to be started on an AED regardless of type of epilepsy at 6 months and 1 year. Whether greater disparities exist in the use of specific AEDs and specific subpopulations

differentiated by age, sex and seizure type may be a subject for further research.

Administrative databases hold the promise of examining populations with both broad and specific approaches that can further evaluate the differences among these populations without the limits imposed by specific registries or state-sponsored insurance databases.

## 5. Conclusion

There are some differences in AED selection by epilepsy etiology; levetiracetam is the most commonly prescribed drug for both lesional and nonlesional epilepsy. Compared to patients with lesional epilepsy, a higher proportion of patients with nonlesional epilepsy remain untreated 1 year after diagnosis.



**Fig. 5.** First-line AED monotherapy (main figure) and polytherapy (inset) in incident epilepsy matched cohorts stratified by age (A) for ages 0–19 years, (B) for ages ≥ 20 years.

The main figures represent the most common first-line monotherapies (≥ 2% of patients in any group). Insets show the most common first-line polytherapies (more than one patient in any group). CLN, clonazepam; GBP, gabapentin; LCM, lacosamide; LEV, levetiracetam; OXC, oxcarbazepine; PHB, phenobarbital; PHT, phenytoin; TPM, topiramate; VPA, valproic acid.

**Disclosures**

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**Table 3**  
Time to second-line therapy in patients with new-onset lesional or nonlesional epilepsy on initial monotherapy before matching.

Patients on initial monotherapy	Lesional (n = 3390)	Nonlesional (n = 2609)
Time to second-line treatment, median (range), days		
Levetiracetam	226.0 (1, 1089)	240.0 (1, 1092)
Phenobarbital	144.0 (1, 965)	152.0 (14, 692)
Oxcarbazepine	242.5 (3, 1067)	255.5 (4, 1071)
Valproate	200.0 (8, 1060)	200.5 (5, 1056)
Phenytoin	147.5 (2, 1074)	149.0 (1, 1090)
Lamotrigine	233.5 (1, 1001)	255.0 (1, 1012)
Topiramate	161.0 (1, 760)	181.0 (1, 1040)
Gabapentin	147.0 (1, 929)	124.0 (10, 917)
Carbamazepine	221.5 (3, 1060)	198.0 (24, 1042)
Clonazepam	132.5 (6, 984)	162.0 (1, 936)
Ethosuximide	135.0 (54, 517)	310.0 (24, 965)
Zonisamide	223.0 (13, 799)	210.0 (1, 790)
Lacosamide	185.0 (3, 820)	163.0 (13, 624)
Pregabalin	216.0 (14, 648)	97.0 (5, 212)
Primidone	542.0 (46, 672)	250.0 (58, 404)
Vigabatrin	61.0 (7, 343)	154.0 (151, 178)
Clobazam	10.0 (10, 10)	29.0 (22, 40)

## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.eplespsyres.2019.106210>.

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