

Treatment patterns in patients with a new diagnosis of epilepsy and psychiatric comorbidities

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ABSTRACT

Objective: The objective of this study was to describe antiepileptic drug (AED) treatment patterns in patients with epilepsy, with and without psychiatric comorbidities.

Methods: This was a retrospective claims-based cohort study using Truven Health MarketScan databases (Commercial and supplemental Medicare, calendar years 2012–2017; Medicaid, 2012–2016). Persons met epilepsy diagnostic criteria, had an index date (first epilepsy diagnosis) with a preceding 2-year baseline (<1 year for persons of 1 to <2 years of age; none for persons <1 year), and continuous medical and pharmacy enrolment without epilepsy/seizure diagnosis or AED prescription during baseline. Based on presence/absence of psychiatric diagnosis codes in the baseline period, persons were classified into two cohorts: with or without psychiatric comorbidities. Outcomes included percentage of treated persons (AED prescription), type, duration, and outcome of first-line AED treatment.

Results: There were 18,062 persons in each cohort with and without psychiatric comorbidities, matched by age, sex, and insurance type, who met selection (or inclusion) criteria. More patients with psychiatric comorbidities were prescribed an AED after diagnosis (57.6% vs. 52.8%), and had at least two AEDs prescribed during follow-up (16.7% vs. 11.4%) than patients without psychiatric comorbidities. Most patients with and without psychiatric comorbidities prescribed AED monotherapy as first-line treatment (73.0% vs. 78.7%). Levetiracetam was the most common AED prescribed less frequently in patients with than without psychiatric comorbidities (40.8% vs. 56.7%). More patients with psychiatric comorbidities changed first-line AED treatment than patients without psychiatric comorbidities.

Conclusion: The presence of psychiatric comorbidities may impact treatment decisions in newly diagnosed persons with epilepsy to optimize patient outcomes.

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1. Introduction

Epilepsy is a condition characterized by at least two unprovoked (or reflex) seizures occurring greater than 24 h apart or one unprovoked (or reflex) seizure and a probability of further seizures [1], affecting approximately 45.6 million people worldwide [2]. Epilepsy is associated with increased morbidity and mortality, and can severely impact quality of life [3].

The association between epilepsy and psychiatric disorders is complex, hence the management of patients with epilepsy and psychiatric

disorders is challenging. Epilepsy increases the risk for developing psychiatric conditions [4–6]. Conversely, studies have reported an increased risk for developing epilepsy in patients with psychiatric disorders [7,8]. Additionally, patients with epilepsy may experience psychiatric symptoms around the ictus [9]. Furthermore, while certain antiepileptic drugs (AEDs) are used for treating psychiatric disorders, some AEDs induce psychiatric adverse events [10]. Studies have also reported that patients with psychiatric disorders have an increased tendency for developing drug-resistant epilepsy [11].

Consequently, the choice of AEDs in patient with epilepsy and comorbid psychiatric conditions should not only be based on the evidence of efficacy/effectiveness for the patient's seizure type, but also consideration for potential interactions between the two conditions. There are limited published data on the effect of psychiatric comorbidities on AED treatment decisions in patients with epilepsy. This evidence is important to inform the current management practices of patients with epilepsy and psychiatric comorbidities. The objective of the study was

Abbreviations: AED, antiepileptic drug; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; ICD-10, International Classification of Diseases, Tenth Revision; SD, standard deviation.

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to describe and compare AED treatment patterns in newly diagnosed patients with epilepsy, with and without psychiatric comorbidities.

2. Study methods

2.1. Data source

This was a retrospective cohort study conducted using the United States-based Truven Health MarketScan claims databases (Commercial Claims and Medicare database and Medicare Supplemental and Coordination of Benefits [CCMC 2017 v0.3] covering the period from January 1, 2012 to December 31, 2017, and Medicaid databases [MDCD 2016 v1.0] covering the period from January 1, 2012 to December 31, 2016). The databases consist of data from > 100 million individuals from the United States including commercially insured individuals (i.e., working age adults and their dependents), patients aged 65 years and older with Medicare coverage plus employer-paid commercial plans, and individuals with limited resources whose insurance is paid by the state, respectively. The databases capture information on medical (inpatient, outpatient, and emergency care) and pharmacy claims for medication filled at outpatient pharmacies, as well as enrolment history. These databases are compliant with the Health Insurance Portability and Accountability Act (HIPAA) of 1996.

2.2. Study design

The study included incident cases of epilepsy identified between January 1, 2014 and June 30, 2017 for the Commercial/Medicare database, and between January 1, 2014 and June 30, 2016 for the Medicaid database. The index date was the first date that the patient fulfilled the diagnosis criteria for epilepsy. Patients were required to have a 2-year baseline period with continuous enrolment with medical and insurance coverage, and no diagnosis for epilepsy or AED medication before the index date (<1 year for those of 1 to <2 years of age; none for those <1 year of age). Patients were defined as having an epilepsy diagnosis if they fulfilled any of the following criteria:

- An occurrence of at least two International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) or International Classification of Diseases, Tenth Revision (ICD-10) codes of 345.xx or G40.x among separate medical encounters (separate dates in any care venue)
- An occurrence of at least one ICD-9-CM or ICD-10 code of 345.xx or G40.x and at least one ICD-9-CM or ICD-10 code of 780.39 or R56.9 among separate medical encounters
- An occurrence of one ICD-9-CM or ICD-10 code of 345.xx or G40.x and code(s) for AED prescription after the 345.xx or G40.x codes
- An occurrence of at least two ICD-9-CM or ICD-10 codes of 780.39 or R56.9 among separate medical encounters and code(s) for AED treatment. The code(s) for the AED treatment should occur after the second 780.39 or R56.9 code irrespective of the presence or absence of an AED code after the first 780.39 or R56.9 codes
- Patients with ICD-9-CM or ICD-10 code 345.3, G40.301, or G40.311 were required to have an occurrence of at least two ICD-9-CM or ICD-10 codes of 345.3, G40.301, or G40.311 separated by at least 30 days, or an occurrence of the 345.3, G40.301, or G40.311 codes and at least one ICD-9-CM or ICD-10 code 780.39, R56.9 separated by at least 30 days, or at least one ICD-9-CM or ICD-10 code 345.3, G40.301, or G40.311 and at least one ICD-9-CM or ICD-10 code 345.xx, G40.xx encountered on separate days.

Patients were classified as having a psychiatric comorbidity if they had at least one inpatient or outpatient diagnostic claim listed in Table 1 as a principal or second diagnosis. Patients were classified as not having psychiatric comorbidities if they did not have a diagnostic code for

Table 1
ICD-9-CM and ICD-10 codes for defining psychiatric comorbidities.

Category	ICD-9-CM and ICD-10 codes
Mood disorders	293.83; 296.xx; 311, F32, F33
Anxiety and dissociative disorders	293.84; 300.xx; 308.xx; 300.2, F40, F41
Adjustment disorders	309.xx, F43.2
Delusional disorders	293.0; 293.1; 297.xx, F22
Personality disorders	301.xx, F60
Schizophrenia and other psychotic disorders	293.81; 293.82; 295.xx; 298.xx, F20, F21, F23, F24, F25, F28, F29
Other childhood disorders	313.xx (minus 313.83); 314.xx, F93 (minus F93.8), F90

ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; ICD-10, International Classification of Diseases, Tenth Revision.

any of the psychiatric comorbidities at any time during the study period. Patients were required to have a minimum follow-up period of 180 days, and were followed from the index date until the first occurrence of any of the following: date of last enrolment, end of the study period, or date of death.

2.3. Study outcomes

The type, duration, and outcome of the first-line AED regimen prescribed following the diagnosis of epilepsy were described for patients with and without psychiatric comorbidities. The AEDs evaluated included brivaracetam, carbamazepine, clobazam, clonazepam, ethosuximide, felbamate, gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, peramppanel, phenobarbital, phenytoin, pregabalin, primidone, rufinamide, tiagabine, topiramate, valproic acid/valproate sodium, vigabatrin, and zonisamide. Treatment was classified as monotherapy (prescription claims for one AED for ≥ 90 days), polytherapy (simultaneous prescription claims for at least two AEDs for ≥ 90 continuous days), or undetermined (either AED claims for <90 days or AED claims started within 90 days of the end of the follow-up period). A treatment line was defined as a period during which the patient was treated with a constant AED regimen. The first-line treatment commenced upon prescription of the first AED on or after the index date. Antiepileptic drug treatment outcomes were defined as continued (no treatment change until end of follow-up), augmented (addition of at least one AED to an existing AED regimen), switched (current treatment line contained at least one AED not in the next line, and next line contained at least one AED not present in the current line), or discontinued (no prescription for the AED after the last prescription of >90 days). The patient characteristics including age, sex, region of residence, and type of health coverage were defined at index date.

2.4. Statistical analysis

Descriptive analyses were used with continuous variables presented using means and standard deviations (SDs), and frequency and proportions for categorical variables. Kaplan–Meier survival curves were used to estimate time from diagnosis to treatment, and time to changing first-line AED treatment. The cohorts of patients with and without psychiatric comorbidities were matched by age, sex, and insurance type. The analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC).

3. Study results

3.1. Study participant characteristics

Of the 751,561 persons who had at least one diagnosis code of epilepsy or seizures during the study period, 64,642 persons fulfilled the criteria for a new diagnosis of epilepsy. Of the eligible patients, 20,204

Table 2
Characteristics of the study participants.

Characteristic	Unmatched cohorts		Matched cohorts	
	Patients with epilepsy and preexisting psychiatric comorbidities (n = 20,204)	Patients with epilepsy without psychiatric comorbidities (n = 31,256)	Patients with epilepsy and preexisting psychiatric comorbidities (n = 18,062)	Patients with epilepsy without psychiatric comorbidities (n = 18,062)
Age (years)				
Mean (SD)	38.7 (24.7)	29.3 (27.2)	38.4 (25.1)	38.3 (25.2)
Sex, n (%)				
Male	8864 (43.9)	16,655 (53.3)	8497 (47.0)	8497 (47.0)
Female	11,340 (56.1)	14,601 (46.7)	9565 (53.0)	9565 (53.0)
Region of residence, n (%)				
North central	4037 (20.0)	5033 (18.3)	3781 (20.9)	3192 (17.7)
Northeast	2951 (14.6)	4550 (14.8)	2832 (15.7)	2909 (16.1)
South	5371 (26.6)	8928 (28.6)	5132 (28.4)	5514 (30.5)
West	1861 (9.2)	3087 (9.9)	1778 (9.8)	1891 (10.5)
Other or unknown	50 (0.2)	108 (0.3)	47 (0.3)	64 (0.4)
Health plan type, n (%)				
Commercial/Medicare	14,270 (70.6)	21,706 (69.4)	13,570 (75.1)	13,570 (75.1)
Medicaid	5934 (29.4)	9550 (30.6)	4492 (24.9)	4492 (24.9)

SD, standard deviation.

had a psychiatric comorbidity diagnosis before the index date, and 31,256 had no psychiatric comorbidities during the study period. After matching on age, sex, and insurance type, the number of patients in each cohort with or without psychiatric comorbidities was 18,062. The characteristics of the study participants are provided in Table 2. Overall, the median follow-up time was 579 days (range: 180–1461 days), and was similar between the two cohorts. The average age for the matched cohorts was 38.4 years (SD: 25.1 years), and 53.0% were female. The Commercial/Medicare population was older than the Medicaid population. The proportion of patients <20 years of age in the Commercial/Medicare vs. Medicaid database was 22.3% vs. 68.5%, respectively.

3.2. First-line treatment

There were 9545 (52.8%) patients without psychiatric comorbidities, and 10,404 (57.6%) patients with psychiatric comorbidities who received AED treatment after the epilepsy diagnosis. The remaining patients did not have documented AED treatment at any time during the follow-up period. The percentage of untreated patients was slightly higher in patients without psychiatric comorbidities than in patients with psychiatric comorbidities (47.2% vs. 42.4%, respectively). Kaplan–Meier estimates of the percentage of patients who were treated with

an AED at 6 months, 1, 2, and 3 years after the diagnosis of epilepsy (without vs. with psychiatric comorbidities) were 44.0% vs. 44.2%, 48.3% vs. 50.4%, 52.8% vs. 57.8%, and 55.8% vs. 62.2%, respectively.

Most patients (without and with psychiatric comorbidities) were prescribed monotherapy as the first-line AED treatment regimen (78.7% vs. 73.0%). Only a few patients were prescribed polytherapy as first-line AED treatment (1.0% vs. 1.3%). The type of AED first-line regimen in the remaining patients was undetermined (20.2% vs. 25.7%) as they had AED prescriptions for <90 days.

3.3. Most common AEDs used for first-line treatment

Levetiracetam was the most common first-line AED prescribed for both cohorts. However, the percentage of patients who were prescribed levetiracetam was higher in patients without than in patients with psychiatric comorbidities (56.7% vs. 40.8%). Other commonly prescribed AEDs comprising >5% of the study population listed in decreasing order were gabapentin, lamotrigine, valproate, topiramate, and oxcarbazepine (Fig. 1). In contrast to levetiracetam, the percentage of patients who were prescribed the other AEDs was higher in patients with psychiatric than in patients without psychiatric comorbidities.

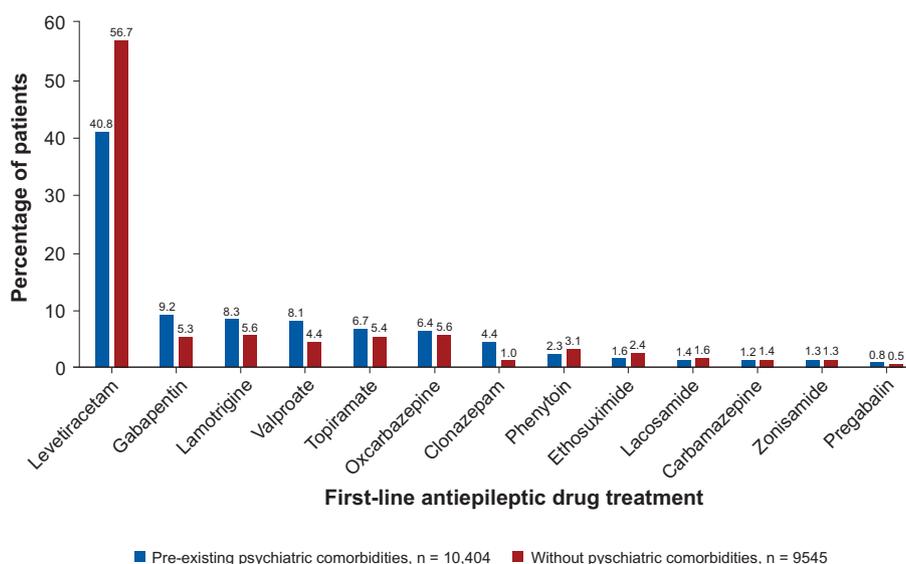


Fig. 1. First-line antiepileptic drugs prescribed in patients with epilepsy with or without psychiatric comorbidities.

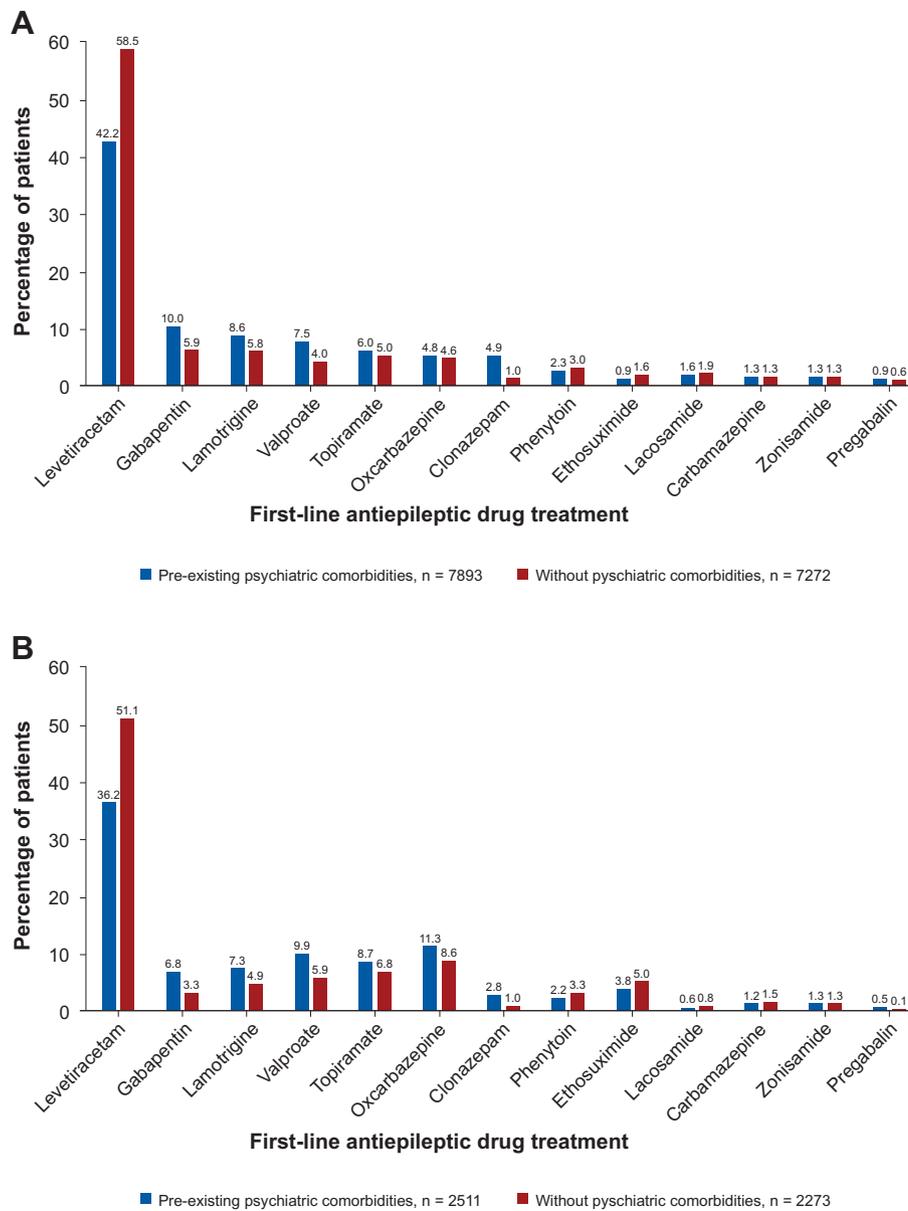


Fig. 2. First-line antiepileptic drug prescriptions stratified by insurance type. (A) Commercial/Medicare database, and (B) Medicaid database.

Similar prescription patterns were found when the analysis was stratified by insurance type (Fig. 2).

3.4. Total number of AEDs prescribed and persistence of initial treatment

The total number of AEDs prescribed during the follow-up period was lower in patients without psychiatric comorbidities than in patients with psychiatric comorbidities; 11.4% vs. 16.7% were treated with at least two AEDs during the follow-up period, respectively. The probability of remaining on the first-line AED monotherapy was higher in patients without than in patients with psychiatric comorbidities as follows: 0.5 year, 82.0% vs. 78.8%; 1 year, 65.8% vs. 58.8%; 2 years, 50.3% vs. 41.0%; and 3 years, 38.8% vs. 30.8%, respectively. The percentage of patients who switched or augmented the first-line AED monotherapy treatment was lower in patients without than in patients with psychiatric comorbidities (Table 3). For patients who had polytherapy as first-line AED treatment, the probability of remaining on the first-line treatment was higher for patients with psychiatric

comorbidities (without vs. with psychiatric comorbidities) as follows: 0.5 year, 61.9% vs. 63.9%; 1 year, 40.8% vs. 40.1%; and 2 years, 19.7% vs. 22.6%.

4. Discussion

This study described treatment patterns in newly diagnosed patients with epilepsy, with and without psychiatric comorbidities. We found that more patients with epilepsy and psychiatric comorbidities were prescribed AED treatment, had a higher number of AEDs, and were more likely to change the first-line AED treatment compared with patients without psychiatric comorbidities. Additionally, there were differences in the type of AEDs prescribed, with patients with epilepsy and psychiatric comorbidities being less likely to be prescribed levetiracetam as first-line AED treatment.

Treatment guidelines recommend AEDs for patients diagnosed with epilepsy to prevent recurrence of seizures [12]. Most patients in the study received AED monotherapy as first-line treatment as per

Table 3
Treatment outcomes of the most common* first-line antiepileptic drug treatments.

Antiepileptic drug	Psychiatric comorbidity	Continued ^a	Switched ^b	Augmented ^c	Indeterminate ^d
Levetiracetam	Present (n = 4240)	74.2	11.2	12.4	2.2
	Absent (n = 5413)	82.3	7.6	8.6	1.6
Gabapentin	Present (n = 961)	83.0	5.7	8.8	2.5
	Absent (n = 505)	88.5	3.8	6.1	1.6
Lamotrigine	Present (n = 862)	77.9	9.2	10.1	2.9
	Absent (n = 533)	81.3	7.9	8.8	2.1
Valproate	Present (n = 842)	78.1	11.0	8.4	2.4
	Absent (n = 424)	76.0	12.3	9.0	2.8
Topiramate	Present (n = 695)	79.0	11.4	6.9	2.7
	Absent (n = 520)	83.3	8.1	6.0	2.7
Oxcarbazepine	Present (n = 664)	73.8	11.0	11.4	3.8
	Absent (n = 534)	79.1	11.2	7.9	1.9

* Antiepileptic drugs prescribed in $\geq 5\%$ of the overall population.

^a Continued indicates no treatment change until end of follow-up period for the patient, or no prescription for another AED for at least 90 days after the last prescription of the first-line treatment.

^b Switched indicates discontinuation of the first-line AED treatment and start of another AED regimen.

^c Augmented indicates the addition of at least one AED to the first-line AED regimen.

^d Indeterminate represents patients who received another AED treatment for <90 days and therefore could not be classified.

treatment guidelines. To our knowledge, this is the first study that has described treatment patterns in newly diagnosed patients with epilepsy and psychiatric comorbidities. Previous studies have evaluated treatment including incident and prevalent cases of epilepsy and psychiatric comorbidities. One study also found that most patients with epilepsy and psychiatric comorbidities were treated with AED monotherapy [13]. More patients with epilepsy and psychiatric comorbidities were prescribed AEDs than patients without psychiatric comorbidities. This could be because patients with epilepsy and psychiatric comorbidities have a higher risk for developing refractory epilepsy [14].

Overall, levetiracetam was the most commonly prescribed AED. However, more patients without psychiatric comorbidities were prescribed levetiracetam than patients with psychiatric comorbidities (56.7% vs. 40.8%). Levetiracetam treatment in patients with epilepsy has been associated with an increased risk for psychiatric adverse events such as anxiety [15] and psychosis [16]. Physicians may choose to prescribe AEDs that do not increase the risk for psychiatric adverse events. Alternatively, they may opt to prescribe AEDs that also have a therapeutic effect for psychiatric comorbidities. We found that more patients with psychiatric comorbidities were prescribed gabapentin, lamotrigine, valproate, topiramate, and oxcarbazepine than patients without psychiatric comorbidities. Lamotrigine, oxcarbazepine, and valproate have positive psychotropic effects, and gabapentin has anxiolytic properties [17].

We also found that during the follow-up period, the total number of AEDs prescribed in patients with epilepsy and psychiatric comorbidities was higher than in patients without psychiatric comorbidities. Additionally, patients with psychiatric comorbidities were more likely to change the first-line treatment than patients without psychiatric comorbidities. Changes made in the treatment could be because of lack of effectiveness. Previous studies have found that patients with epilepsy and psychiatric comorbidities have a higher risk for developing refractory epilepsy [14]. Changes in the first-line AED treatment could have also been made because of the occurrence of adverse events. Patients with psychiatric comorbidities have been reported to have an increased risk for adverse events when treated with AEDs because of pharmacokinetic interactions between AEDs and psychotropic drugs [18]. As a consequence of the limitations of the database, we were unable to evaluate the reason for medication changes. Further studies are needed to evaluate factors that affect treatment changes in this patient population.

This study had several limitations. The study population only included patients with commercial, Medicare supplemental, or Medicaid insurance, and therefore, results may not be representative of the entire United States population. There might be missing information,

miscoding, or underreporting of disorders in the claims data. Insurance claims are financial records in which the diagnosis is the justification for the medical service. Tentative, rule-out diagnoses can be difficult to distinguish from confirmed diagnoses in claims data.

5. Conclusions

This study evaluated how psychiatric comorbidities may affect AED treatment in newly diagnosed patients with epilepsy, and found differences in treatment patterns in patients with vs. without psychiatric comorbidities. To obtain optimal outcomes, treatment of patients with epilepsy should consider the presence of psychiatric comorbidities. Further studies are needed to confirm our findings.

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Data statement

The authors do not have permission to share data.

Declaration of Competing Interest

L. Kalilani is an employee of UCB Pharma. D. Friesen (Friesen Limited) and P. Murray (FTP Software Consultants Ltd.) were paid consultants for UCB Pharma on this study.

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References

- [1] Fisher RS, Cross JH, French JA, Higurashi N, Hirsch E, Jansen FE, et al. Operational classification of seizure types by the International League Against Epilepsy: Position

- Paper of the ILAE Commission for Classification and Terminology. *Epilepsia* 2017;58:522–30 <https://onlinelibrary.wiley.com/doi/full/10.1111/epi.13670>.
- [2] GBD 2016 Epilepsy Collaborators Global, regional, and national burden of epilepsy, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol* 2019;18:357–75.
- [3] Quintas R, Raggi A, Giovannetti AM, Pagani M, Sabariego C, Cieza A, et al. Psychosocial difficulties in people with epilepsy: a systematic review of literature from 2005 until 2010. *Epilepsy Behav* 2012;25:60–7.
- [4] Gaitatzis A, Trimble MR, Sander JW. The psychiatric comorbidity of epilepsy. *Acta Neurol Scand* 2004;110:207–20.
- [5] Swinkels WA, Kuyk J, van Dyck R, Spinhoven P. Psychiatric comorbidity in epilepsy. *Epilepsy Behav* 2005;7:37–50.
- [6] Tellez-Zenteno JF, Patten SB, Jetté N, Williams J, Wiebe S. Psychiatric comorbidity in epilepsy: a population-based analysis. *Epilepsia* 2007;48:2336–44.
- [7] Hesdorffer DC, Ishihara L, Mynepalli L, Webb DJ, Weil J, Hauser WA. Epilepsy, suicidality, and psychiatric disorders: a bidirectional association. *Ann Neurol* 2012;72:184–91.
- [8] Mula M. Epilepsy: bidirectional link between epilepsy and psychiatric disorders. *Nat Rev Neurol* 2012;8:252–3.
- [9] Mula M, Monaco F. Ictal and peri-ictal psychopathology. *Behav Neurol* 2011;24:21–5.
- [10] Dussaule C, Boulleret V. Psychiatric effects of antiepileptic drugs in adults. *Geriatr Psychol Neuropsychiatr Vieil* 2018;16:181–8.
- [11] Kanner AM. Do psychiatric comorbidities have a negative impact on the course and treatment of seizure disorders? *Curr Opin Neurol* 2013;26:208–13.
- [12] Glauser T, Ben-Menachem E, Bourgeois B, Cnaan A, Guerreiro C, Kälviäinen R, et al. Updated ILAE evidence review of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes. *Epilepsia* 2013;54:551–63.
- [13] Bosak M, Cyranka K, Dudek D, Kowalik M, Molek P, Słowik A. Psychiatric comedication in patients with epilepsy. *Epilepsy Behav* 2018;83:207–11.
- [14] Petrovski S, Szoeki CE, Jones NC, Salzberg MR, Sheffield LJ, Huggins RM, et al. Neuropsychiatric symptomatology predicts seizure recurrence in newly treated patients. *Neurology* 2010;75:1015–21.
- [15] Knudsen-Baas KM, Johannesen TB, Myklebust TÅ, Aarseth JH, Owe JF, Gilhus NE, et al. Antiepileptic and psychiatric medication in a nationwide cohort of patients with glioma WHO grade II–IV. *J Neurooncol* 2018;140:739–48.
- [16] Chen Z, Lusicic A, O'Brien TJ, Velakoulis D, Adams SJ, Kwan P. Psychotic disorders induced by antiepileptic drugs in people with epilepsy. *Brain* 2016;139:2668–78.
- [17] Pisani LR, Nikanorova M, Landmark CJ, Johannessen SI, Pisani F. Specific patient features affect antiepileptic drug therapy decisions: focus on gender, age, and psychiatric comorbidities. *Curr Pharm Des* 2017;23:5639–48.
- [18] Perucca P, Jacoby A, Marson AG, Baker GA, Lane S, Benn EK, et al. Adverse antiepileptic drug effects in new-onset seizures: a case-control study. *Neurology* 2011;76:273–9.