Real-world impact of antiepileptic drug combinations with versus without perampanel on healthcare resource utilization in patients with epilepsy in the United States

François Laliberté a, Mei Sheng Duh b, Victoria Barghout c, Guillaume Germain a,*, Feride Frech d, Craig Plauschinat d, Dominique Lejeune a, Manoj Malhotra d, Edward Faught e

a Groupe d'analyse, Liée, Montréal, QC, Canada
b Analysis Group, Inc., Boston, MA, USA
c VEB HealthCare LLC, Morristown, NJ, USA
d Eisai Inc., Woodcliff Lake, NJ, USA
e Emory University School of Medicine, Atlanta, GA, USA

ABSTRACT

Objectives: Combination regimens of antiepileptic drugs (AEDs) with various mechanisms of action (MOA) are commonly used in patients with refractory epilepsy. However, outcomes related to combination AEDs with novel MOA, such as perampanel (PER), are not well described. This study compared healthcare resource utilization (HRU) among recipients of PER-based combinations versus recipients of other non-PER-based combinations.

Methods: This retrospective study used claims data from the Symphony Health's IDV® (Integrated Dataverse) database (August 2012 to July 2018). Patients were aged ≥12 years with epilepsy or non-febrile convulsions, were treated with AED combinations, and had ≥12 and ≥6 months pre- and post-index date, respectively (date of initiation of the second AED in the combination). AEDs were categorized based on MOA: selective non-competitive antagonist of AMPA receptors (i.e., PER), sodium channel blocker (SC), synaptic vesicle protein 2A binding (SV2), and gamma-aminobutyric acid analog (G). Patients were then classified into MOA-based cohorts: PER + SC, PER + SV2, PER + G, SC + SC, SC + SV2, SC + G, SV2 + G, and G + G. HRU outcomes were evaluated during follow-up and compared between PER-based cohorts and non-PER-based cohorts.

Results: On average, patients in the PER + SC (N = 3,592), PER + SV2 (N = 2,200), and PER + G (N = 1,313) cohorts were younger and had a lower Quan-Charlson comorbidity index than those in non-PER-based cohorts. PER + SC and PER + SV2 users had significantly fewer all-cause hospitalizations than non-PER-based users (adjusted RR range: 0.66–0.89, all P < 0.05), while PER + G recipients had fewer all-cause hospitalizations than recipients of SV2 + G and G + G (adjusted RR range: 0.92–0.94). Similar trends were observed for epilepsy-related hospitalizations. Across all comparisons, PER-based combinations were associated with significantly lower rates of all-cause clinic/office/outpatient visits relative to non-PER-based combinations (adjusted RR range: 0.69–0.86, all P < 0.05).

Significance: Results showed that patients treated with PER-based combinations had fewer all-cause and epilepsy-related hospitalizations, and fewer all-cause clinic/office/outpatient visits compared with patients treated with most other non-PER-based combinations.

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1. Introduction

Epilepsy is a chronic and debilitating neurological disorder affecting an estimated 3.4 million people in the United States (US), including three million adults and 470 thousand children [1]. The disease is characterized by recurrent, unprovoked seizures commonly categorized as partial-onset (focal) seizures (POS) or...
generalized seizures, with primary generalized tonic-clonic seizures (PGTCS) as the most common type of generalized seizure [2,3]. Patients with epilepsy are prone to comorbid psychiatric conditions [4], mortality [5], and negative economic outcomes, ranging from reduced lifetime income to increased healthcare resource utilization (HRU) [6,7].

The primary goal of treatment in epilepsy is the control of seizures, with antiepileptic drugs (AEDs) serving as the cornerstone of therapy [8]. Despite a wide range of available treatment options, more than 30% of patients do not achieve adequate control of seizures with AED therapy [9]. Consequently, these patients often undergo multiple rounds of treatment switching or adding-on treatment until an effective AED regimen has been identified [10,11]. Prolonged or recurrent seizures are known to exacerbate comorbidities such as cognitive impairments, leading to further reductions in quality of life [12]. Additionally, the likelihood of becoming seizure-free decreases with each unsuccessful AED regimen [13], underscoring the need for novel therapies.

Perampanel (PER) is a first-in-class noncompetitive AMPA glutamate receptor antagonist approved by the US Food and Drug Administration (FDA) as an adjunctive therapy for POS and PGTCS [14,15]. In phase III clinical trials and real-world studies, PER was associated with a significant reduction in seizure frequency among patients with refractory POS and PGTCS [16–24]. The American Academy of Neurology (AAN) guidelines recommend the use of PER in adults with refractory focal epilepsy due to its established efficacy in this population [25].

Although AED monotherapy remains the gold standard first-line treatment for epilepsy, patients with refractory epilepsy may benefit from AED combination therapy [26]. The results of a real-world, retrospective study from Margolis et al. [27] suggest that combinations of AEDs with different mechanisms of action (MOAs) are associated with improved treatment persistence, lower rates of inpatient admissions, and lower rates of emergency room (ER) visits relative to combinations of AEDs with similar MOAs. Combinations of AEDs with different approach, termed rational polypharmacy, aims to optimize outcomes associated with the use of AED combinations [28]. However, it remains unclear whether specific AED combinations – such as PER-based combinations – may confer benefits. The present study sought to compare HRU among patients who received PER-based AED combinations relative to those who received other non-PER-based combinations.

2. Methods

2.1. Data source

Health insurance claims from the Symphony Health’s IDV® (Integrated Dataverse; August 2012 to July 2018) were used. This large, nationally representative provider-based claims database covers about three fourths of the US population (280 million lives) annually. It includes longitudinal patient data capturing adjudicated claims for prescription, hospital, and physician practices. The Symphony Health’s IDV® database covers all payment types, including commercial plans, Medicare Part D (pharmacy claims), cash, out-of-pocket, assistance programs, and Medicaid. The data were provided in compliance with the Health Insurance Portability and Accountability Act (HIPAA) as the data collected were anonymized and not traceable back to the individual subjects (i.e., no patient identifiers were collected). Therefore, no Institutional Review Board approval or informed consent was required.

2.2. Study design and population

A retrospective cohort design was used. AED combination therapies were identified based on an overlap of ≥90 consecutive days in the supply of ≥2 AEDs following the initiation of the second AED. The index date was defined as the date of initiation of the second AED in the combination. Patient characteristics were measured during the baseline period, defined as the 12 months of continuous clinical activity (i.e., consecutive quarters with ≥1 pharmacy claim) prior to the index date. Outcomes were measured during the observation period, which spanned from the index date up to the earliest among 12 months, end of treatment combination (i.e., gap of >30 days in the dispensing days of supply for ≥1 AED in the combination), end of data availability, or end of clinical activity.

Patients were included in the study if they were ≥12 years of age at the index date, had ≥1 visit with a diagnosis of epilepsy (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM]: 345.xx; ICD-10-CM: G40.xxx) or non-febrile convulsions (ICD-9-CM: 780.39; ICD-10-CM: R56.9) during the baseline or follow-up periods, ≥1 pharmacy dispensing for ≥2 different oral AEDs, ≥90 days of continuous treatment with PER (i.e., at least one prescription claim for PER within the previous 12 months) during the index period. Subsequently, non-PER users were identified, and their selection was mutually exclusive from PER users. Patients who used more than one combination (e.g., SC + SC and SC + SV2) were included in more than one cohort.

| MOA | AEDs |
| --- | --- |
| Selective non-competitive antagonist of AMPA receptors | Perampanel |
| Sodium channel blocker | Ethotoin, fosphenytoin, lacosamide, lamotrigine, oxcarbazepine, phenytoin |
| Synaptic vesicle protein 2A binding | Brivaracetam, levetiracetam |
| Gamma-aminobutyric acid analog | Clonazepam, diazepam, phenobarbital, pregabalin, primidone, tiagabine, vigabatrin |
| Multiple, broad, or other mechanisms | Divalproex sodium, felbamate, gabapentin, topiramate, valproate sodium, valproic acid, zonisamide |

Abbreviations: AEDs = antiepileptic drugs; MOA = mechanisms of action.
2.3. Study outcomes

HRU outcomes included all-cause hospitalizations and all-cause clinic/office/outpatient visits. Epilepsy-related hospitalizations and epilepsy-related clinic/office/outpatient visits were also reported. HRU was considered epilepsy-related if a diagnosis for epilepsy or non-febrile convulsions was documented.

2.4. Analysis

Rates of HRU were calculated as the frequency of HRU events divided by the number of person-years of follow-up for each cohort. Rates were compared between each PER-based cohort and non-PER-based cohort using rate ratios (RRs) with corresponding 95% confidence intervals (CIs) and p-values calculated from a Poisson regression model. More specifically, cohorts were compared using RRs from multivariable Poisson regression models adjusting for the following baseline covariates: age, gender, region, insurance type, type of epilepsy and status epilepticus at baseline, all-cause and epilepsy-related hospitalizations and outpatient visits, combinations and number of unique AEDs used at baseline (0, 1, 2, or 3 vs. 4 + AEDs), number of concomitant AEDs at index date, and baseline comorbidities (with a prevalence ≥10% per comparison).

Patient baseline demographics and clinical characteristics were described using means and standard deviations for continuous variables, and frequencies and proportions for categorical variables.

3. Results

3.1. Patient characteristics

The sample sizes of each cohort are presented in Table 2a-b. On average, patients in PER-based cohorts were qualitatively younger than those in other non-PER-based cohorts (mean age range [years]: PER-based = 35.1–36.0, non-PER-based = 42.4–49.5); patients who received a G-based combination (without PER) appeared older (mean age range [years]: 45.7–49.5). The distribution of patients across the four US census regions was similar across cohorts (e.g., % in South: PER-based = 42.6%–44.5%, non-PER-based = 39.5%–47.3%). Patients were also covered by similar types of health insurance plans across cohorts (i.e., commercial: ~60%, Medicare: ~20%, Medicaid: ~20%). Patients in PER-based cohorts had a qualitatively lower Quan-CCI than those in non-PER-based cohorts (mean range: PER-based = 0.40–0.58, non-PER-based = 0.67–1.06); recipients of G-based combinations (without PER) had a particularly high Quan-CCI (mean range: 0.75–1.06). Patients who received an SV2 + SV2 combination were not evaluated due to the low sample size of the resulting cohort (N = 240).

More recipients of PER-based combinations had status epilepticus at baseline compared with recipients of non-PER-based combinations (range: PER-based = 11.7%–16.0%, non-PER-based = 3.2%–9.2%; Tables 2a-b). The proportion of patients with ≥1 all-cause hospitalization (range: PER-based = 24.1%–30.0%, non-PER-based = 32.3%–41.9%), but not that of patients with ≥1 epilepsy-related hospitalization (range: PER-based = 20.2%–24.7%, non-PER-based = 14.3%–27.8%), was lower among users of PER-based combinations than users of non-PER-based combinations. Relative to patients in non-PER-based cohorts, those in PER-based cohorts used a higher number of unique AEDs during the baseline period (mean range: PER-based = 3.3–4.0, non-PER-based = 2.2–2.7) and at the index date (mean range: PER-based = 3.4–3.9, non-PER-based = 2.5–2.8).

Patients’ HRU outcomes were observed over a median duration of 246, 226, and 209 days for patients in the PER + SC, PER + SV2, and PER + G cohorts, respectively. Patients in the SC + SC and SC + SV2 cohorts were observed over a median of 209 and 216 days, respectively; those in the SC + G, SV2 + G, and G + G cohorts were observed over 184, 184, and 169 days, respectively.

3.2. Healthcare resource use – all-cause and epilepsy-related hospitalization

During follow-up, patients in the PER + SC cohort had 15% lower rates of all-cause hospitalizations than those in the SC + SC cohort; this figure was 17% versus patients in the SC + SV2 cohort, 18% versus those in the SC + G cohort, 26% versus those in the SV2 + G cohort, and 34% versus those in the G + G cohort (all P < 0.05; Fig. 1). Similar results were obtained when using patients in the PER + SV2 cohort as comparator. All-cause hospitalization rates were 6% and 8% lower among patients in the PER + G cohort relative to those in the SV2 + G and G + G cohorts, respectively. All-cause hospitalization rates did not significantly differ between the PER + G cohort versus all cohorts. With regard to epilepsy-related hospitalizations, trends were similar to those observed for all-cause hospitalizations, although differences were less pronounced (Fig. 2). The most common diagnoses associated with non-epilepsy-related hospitalizations are shown in supplemental material (Tables S1–S3).

3.3. Healthcare resource use – all-cause and epilepsy-related clinic/office/outpatient visits

Regardless of the AED combinations being compared, PER-based combinations were associated with significantly lower rates of all-cause clinic/office/outpatient visits than non-PER-based combinations (adjusted RR range: 0.69–0.86, all P < 0.05; Table 3). Differences in the rates of all-cause clinic/office/outpatient visits were highest between PER-based combinations versus G + G (adjusted RR range: 0.69–0.77), and lowest between PER-based combinations versus SC + SC (adjusted RR range: 0.82–0.86); yet, all were statistically significant (all P < 0.05). PER-based combinations were associated with significantly reduced rates of epilepsy-related clinic/office/outpatient visits relative to any non-PER-based combination, except for comparisons with G + G (Table 4).

4. Discussion

This retrospective study based on real-world claims data showed that the use of PER-based AED combinations was associated with reductions in HRU. For the majority of AED combinations evaluated, patients who received a PER-based combination experienced significantly fewer all-cause and epilepsy-related hospitalizations. Similarly, PER-based combinations were associated with significantly reduced rates of all-cause clinic/office/outpatient visits. To our knowledge, this is the first study evaluating HRU patterns following the initiation of a PER-based combination therapy compared to other AED combination therapies among patients with epilepsy in the US.

The majority of patients included in the current study had used ≥2 different AEDs at baseline. Therefore, our study population mostly consisted of patients with refractory epilepsy. A 2013 study by Chen et al. found that patients with refractory epilepsy incurred healthcare costs that were nearly twice as high as those of patients with non-refractory disease [10], highlighting the high burden of these patients on healthcare systems. The present results suggest that the majority of PER-based combinations are more effective than other AED combinations to reduce hospitalizations and
### Table 2a
Demographic and clinical characteristics of AED combination1,2 cohorts.

| PER + | SC (N = 3,592) | SV2 (N = 2,200) | G (N = 1,313) |
|-------|----------------|-----------------|---------------|
| **Demographics** | | | |
| Age, years, mean [median] (SD) | 35.4 [33] (15.8) | 36.0 [34] (16.1) | 35.1 [33] (16.2) |
| Gender, female, n (%) | 1,906 (53.1) | 1,179 (53.6) | 719 (54.8) |
| Region3, n (%) | | | |
| South | 1,530 (42.6) | 951 (43.2) | 584 (44.5) |
| West | 607 (16.9) | 387 (17.6) | 212 (16.1) |
| Midwest | 760 (21.2) | 445 (20.2) | 258 (19.6) |
| Northeast | 684 (19.0) | 408 (18.5) | 253 (19.3) |
| Unknown | 11 (0.3) | 9 (0.4) | 6 (0.5) |
| **Insurance plan type3,4, n (%)** | | | |
| Commercial | 2,224 (61.9) | 1,378 (62.6) | 769 (58.6) |
| Medicare | 612 (17.0) | 354 (16.1) | 232 (17.7) |
| Medicaid | 681 (19.0) | 413 (18.8) | 279 (21.2) |
| Government | 40 (1.1) | 26 (1.2) | 14 (1.1) |
| Unknown | 35 (1.0) | 29 (1.3) | 19 (1.4) |
| **Year of index date3, n (%)** | | | |
| 2013 | - | - | - |
| 2014 | 768 (21.4) | 394 (17.9) | 270 (20.6) |
| 2015 | 854 (23.8) | 474 (21.5) | 303 (23.1) |
| 2016 | 871 (24.2) | 577 (26.2) | 316 (24.1) |
| 2017 | 866 (24.1) | 581 (26.4) | 330 (25.1) |
| 2018 | 233 (6.5) | 174 (7.9) | 94 (7.2) |
| **Clinical characteristics** | | | |
| Type of epilepsy prior to the index date, n (%) | | | |
| POS | 1,356 (37.8) | 769 (35.0) | 444 (33.8) |
| GTCS | 732 (20.4) | 537 (24.4) | 305 (23.2) |
| Other | 192 (5.3) | 129 (5.9) | 86 (6.5) |
| Unspecified | 563 (15.7) | 339 (15.4) | 196 (14.9) |
| No diagnosis | 992 (27.6) | 592 (26.9) | 365 (27.8) |
| Status epilepticus at baseline, n (%) | | | |
| 419 (11.7) | 320 (14.5) | 210 (16.0) |
| Prior frequency of status epilepticus, episodes, mean [median] (SD) | 0.36 [0] (2.1) | 0.48 [0] (2.7) | 0.49 [0] (2.0) |
| **Quan-Charlson comorbidity index5, mean [median] (SD)** | 0.40 [0] (0.9) | 0.47 [0] (1.0) | 0.58 [0] (1.1) |
| **Comorbidities5, n (%)** | | | |
| CNS-specific comorbidities | | | |
| Depression | 323 (9.0) | 195 (8.9) | 142 (10.8) |
| Mental retardation | 280 (7.8) | 188 (8.5) | 161 (12.3) |
| Cerebrovascular disease6 | 138 (3.8) | 106 (4.8) | 69 (5.3) |
| Bipolar disorder | 116 (3.2) | 59 (2.7) | 58 (4.4) |
| Brain tumor | 77 (2.1) | 53 (2.4) | 24 (1.8) |
| Tuberous sclerosis | 43 (1.2) | 18 (0.8) | 11 (0.8) |
| Alzheimer's disease | 4 (0.1) | 2 (0.1) | 0 (0.0) |
| Meningitis | 7 (0.2) | 3 (0.1) | 2 (0.2) |
| Other comorbidities | | | |
| Cardiovascular disease2 | 545 (15.2) | 420 (19.1) | 242 (18.4) |
| Intestinal problems | 257 (7.2) | 178 (8.1) | 128 (9.7) |
| Asthma/pulmonary disease6 | 256 (7.1) | 192 (8.7) | 140 (10.7) |
| Gastric reflux | 237 (6.6) | 158 (7.2) | 115 (8.8) |
| Anemia | 139 (3.9) | 108 (4.9) | 63 (4.8) |
| Diabetic | 142 (4.0) | 113 (5.1) | 65 (5.0) |
| Peptic ulcer | 62 (1.7) | 41 (1.9) | 30 (2.3) |
| **AED treatment** | | | |
| Medications at baseline5 | | | |
| Used AED combinations, n (%) | 2,751 (76.6) | 1,675 (76.1) | 1,089 (82.9) |
| Number of unique AEDs used, mean [median] (SD) | 3.33 [3] (1.3) | 3.46 [3] (1.4) | 4.00 [4] (1.3) |
| **N (%)** | | | |
| 0 AED | 1 (0.0) | 1 (0.0) | 0 (0.0) |
| 1 AED | 159 (4.4) | 89 (4.0) | 22 (1.7) |
| 2 AEDs | 835 (23.2) | 474 (21.5) | 119 (9.1) |
| 3 AEDs | 1,137 (31.7) | 649 (29.5) | 358 (27.3) |
| ≥4 AEDs | 1,460 (40.6) | 987 (44.9) | 814 (62.0) |
| **Medications at index date3** | | | |
| Number of concomitant AEDs, mean [median] (SD) | 3.36 [3] (1.0) | 3.49 [3] (1.0) | 3.89 [4] (1.0) |
| **Baseline healthcare resource utilization2, mean [median] (SD)** | | | |
| **All-cause** | | | |
| Hospitalizations | 0.46 [0] (1.2) | 0.58 [0] (1.4) | 0.68 [0] (1.5) |
| ≥ 1 episode, n (%) | 867 (24.1) | 580 (26.4) | 394 (30.0) |
| Outpatient visits | 13.0 [5] (31.9) | 14.5 [6] (34.9) | 18.4 [7] (43.0) |
| Clinic/office/outpatient | 7.2 [4] (10.4) | 7.3 [4] (9.9) | 8.3 [4] (12.4) |
| Other | 5.9 [0] (30.5) | 7.4 [0] (34.0) | 10.7 [0] (42.3) |
| Unknown | 0.1 [0] (0.8) | 0.1 [0] (1.7) | 0.1 [0] (0.8) |
| **Epilepsy-related** | | | |

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Table 2a (continued)

|                  | PER +                          | SC (N = 3,592) | SV2 (N = 2,200) | G (N = 1,313) |
|------------------|--------------------------------|---------------|----------------|---------------|
| Hospitalizations| 0.34 [0] (0.9)                 | 0.41 [0] (1.1) | 0.48 [0] (1.2)  |
| ≥ 1 episode, n (%) | 727 [20.2]                    | 486 [22.1]    | 324 [24.7]     |
|                  | 4.3 [2] (8.6)                  | 4.9 [3] (8.7)  | 5.5 [3] (12.3)  |
|                  | Clinic/office/outpatient       | 3.2 [2] (4.1)  | 3.3 [2] (4.5)   | 3.3 [2] (4.5)  |
|                  | Other                          | 1.3 [0] (7.7)  | 1.8 [0] (7.6)   | 2.4 [0] (11.6) |
|                  | Unknown                        | 0.0 [0] (0.3)  | 0.0 [0] (1.0)   | 0.0 [0] (0.2)  |

Abbreviations: AED = antiepileptic drug; CNS = central nervous system; G = gamma-aminobutyric acid analog; GTCS = generalized tonic-clonic seizure; PER = perampanel; POS = partial-onset seizure; SC = sodium channel blocker; SD = standard deviation; SV2 = synaptic vesicle protein 2A binding.

Notes: 1. AED combinations were identified by an overlap in the days of supply of the AEDs for a minimum of 90 continuous days following initiation of the second AED. Use of each AED in the combination was considered continuous if no gap of >30 days between days of supply or the last dispensing and the end of clinical activity occurred. Discontinuation of ≥1 AED in the combination (i.e., gap of >30 days) was termed the treatment combination end date. See Table 1 for categorization of AEDs by MOA.
2. AED combinations are not mutually exclusive.
3. Evaluated at the index date.
4. General insurance plan type categories (commercial, Medicare, etc.) only. Government includes Veteran’s Administration and Medical Military (TRICARE).
5. Evaluated during the 12-month baseline period.
6. Includes hemorrhagic stroke, ischemic stroke, and transient ischemic attack.
7. Includes hypertension, myocardial infarction, and other heart diseases.
8. Includes asthma, bronchitis, and chronic obstructive pulmonary disease.
9. Refers to the percentage of patients who used an AED combination during the 12-month baseline period, defined as at least 30 days of overlap in the days of supply of two AEDs.
10. Resources and costs were defined as epilepsy-related if a diagnosis for epilepsy (ICD-9-CM: 345.xx or ICD-10-CM: G40.xxx) or non-febrile convulsions (ICD-9-CM: 780.39 or ICD-10-CM: R56.9) was present during the episode.

The present study is subject to a number of limitations. More specifically, important factors, such as the severity of epilepsy or duration of epilepsy, are not captured in the Symphony database. The authors had access to information about the seizure type in some patients (i.e., focal seizure or GTCS). However, this information was lacking for a significant number of patients. As all observational studies, analyses could not control for unmeasured confounding variables. Some unmeasured confounding variables may impact patient selection; however, we see that the proportion of patients with commercial, Medicare, and Medicaid coverage is fairly comparable between PER and non-PER-based cohorts, and the same was observed for region of residence. The relatively similar distribution in these insurance plan types/region for patients using PER and non-PER-based combinations suggests that the use of PER was not channeled toward a specific population that would

PER has a particularly long half-life and a convenient once-daily dosing schedule [13]; this property may underlie part of the observed reduction in HRU among users of PER-based combinations. Indeed, a previous study showed that AEDs with longer half-lives are associated with significantly lower rates of all-cause and epilepsy-related hospitalizations [34]. The long half-life (105 h) possibly provides an extended protection, and the once-daily dosing schedule may increase the likelihood that patients will adhere to treatment as opposed to a twice-daily regimen where a dose can be more easily missed. Moreover, a study by Gidal et al. reported that missing a dose of PER and supplementing later on may not cause significant changes in the drug’s plasma concentration, compared to what would be anticipated for a drug with a shorter half-life [35]. Further research is warranted to better understand potential agent-specific factors behind the observed lower HRU associated with PER-based combinations.

More generally, since this study provides the first evidence that patients treated with PER-based AED combination therapy experience improved HRU outcomes compared to those treated with non-PER-based AED combinations, further research evaluating AED combinations is also warranted to build on this real-world evidence. Considering the paucity of research of this type and the lack of such comparisons, our study contributes toward rational decision making regarding the optimal choice of treatment for epilepsy.

Hence, the present study is subject to a number of limitations. More specifically, important factors, such as the severity of epilepsy or duration of epilepsy, are not captured in the Symphony database. The authors had access to information about the seizure type in some patients (i.e., focal seizure or GTCS). However, this information was lacking for a significant number of patients. As all observational studies, analyses could not control for unmeasured confounding variables. Some unmeasured confounding variables may impact patient selection; however, we see that the proportion of patients with commercial, Medicare, and Medicaid coverage is fairly comparable between PER and non-PER-based cohorts, and the same was observed for region of residence. The relatively similar distribution in these insurance plan types/region for patients using PER and non-PER-based combinations suggests that the use of PER was not channeled toward a specific population that would
### Table 2b
Demographic and clinical characteristics of AED combination\(^1,2\) cohorts.

| Characteristics                  | SC + G | G + G |
|----------------------------------|--------|-------|
| **Demographics\(^3\)**           |        |       |
| Age, years, mean [median] (SD)    | 42.4 (17.5) | 46.1 (18.5) |
| Gender, female, n (%)            | 12,692 (53.3) | 37,210 (54.5) |
| Region\(^4\), n (%)               |         |       |
| South                            | 18,798 (45.9) | 6,277 (47.3) |
| West                             | 2,221 (13.7)  | 3,046 (11.8)  |
| Midwest                          | 7,262 (16.4)  | 7,720 (16.6)  |
| Northeast                        | 6,548 (15.7)  | 6,633 (15.7)  |
| Unknown                          | 192 (0.5) | 71 (0.5) |
| **Insurance plan type\(^3,4\), n (%)** |         |       |
| Commercial                       | 23,527 (57.5) | 7,372 (55.5) |
| Medicare                         | 10,464 (25.6) | 3,482 (26.2) |
| Medicaid                         | 6,270 (15.3) | 2,186 (16.5) |
| Government                       | 373 (0.9) | 126 (0.9) |
| Unknown                          | 315 (0.8) | 107 (0.8) |
| **Clinical characteristics\(^5\)** |        |       |
| **Type of epilepsy prior to the index date, n (%)** |        |       |
| POS                              | 5,733 (14.0) | 1,153 (8.7) |
| GTCS                             | 4,829 (11.8) | 997 (7.5) |
| Other                            | 2,342 (5.7) | 529 (4.0) |
| Unspecified                      | 9,492 (12.2) | 2,291 (17.3) |
| No diagnosis                     | 18,852 (46.0) | 8,311 (62.6) |
| Status epilepticus at baseline, n (%) | 1,623 (4.0) | 330 (2.5) |
| Prior frequency of status epilepticus, episodes, mean [median] (SD) | 0.10 [0.0] | 0.10 [0.0] |
| Quan-Charlson comorbidity index\(^3\), mean [median] (SD) | 0.07 [0.0] | 0.07 [0.0] |
| **Comorbidities\(^3\), n (%)**   |        |       |
| CNS-specific comorbidities       |        |       |
| Depression                       | 2,124 (46.0) | 483 (10.0) |
| Mental retardation               | 2,124 (46.0) | 483 (10.0) |
| Cerebrovascular disease\(^6\)     | 18,367 (44.9) | 5,839 (44.0) |
| Bipolar disorder                 | 3,730 (9.1) | 1,889 (14.2) |
| Brain tumor                      | 1,676 (4.1) | 189 (1.4) |
| Tuberous sclerosis               | 60 (0.1) | 29 (0.2) |
| Alzheimer's disease              | 337 (0.7) | 48 (0.3) |
| Meningitis                       | 189 (0.5) | 42 (0.3) |
| Other comorbidities              |        |       |
| Cardiovascular disease\(^7\)      | 18,367 (44.9) | 5,839 (44.0) |
| Intestinal problems              | 6,567 (13.8) | 2,283 (17.2) |
| Asthma/pulmonary disease\(^8\)   | 3,730 (9.1) | 1,889 (14.2) |
| Gastric reflux                   | 6,276 (15.3) | 2,552 (19.2) |
| Anemia                           | 4,490 (11.0) | 1,420 (10.7) |
| Diabetes                         | 6,883 (16.8) | 2,445 (18.4) |
| Peptic ulcer                     | 2,226 (5.4) | 980 (7.4) |
| **AED treatment**                |        |       |
| Medications at baseline\(^9\)    |        |       |
| Used AED combinations, n (%)     | 16,253 (68.2) | 36,526 (53.5) |
| Number of unique AEDs used, mean [median] (SD) | 2.68 (1.2) | 2.17 (1.2) |
| N (%)                            | 0 AED 204 (0.9) | 1,632 (2.4) |
| 1 AED                            | 3,666 (15.4) | 19,989 (29.3) |
| 2 AEDs                           | 7,783 (32.7) | 23,944 (35.1) |
| 3 AEDs                           | 6,689 (28.1) | 14,244 (20.9) |
| ≥4 AEDs                          | 5,488 (23.0) | 8,469 (12.4) |
| Medications at index date\(^9\)   |        |       |
| Number of concomitant AEDs, mean [median] (SD) | 2.83 [1.0] | 2.49 [2.0] |
| Baseline healthcare resource utilization\(^7\), mean [median] (SD) |        |        |

\(^{1}\) All-cause

\(^{2}\) Epilepsy-related
we found that the use of PER-based combinations was associated with increased care monitoring, could have an impact on HRU; however, part of the differences in epilepsy severity. Other factors, such as the number of prior AEDs used, which may account for confounding associated with a wide range of observed covariates, had resulted in a potential patient selection bias. Nevertheless, baseline (0, 1, 2, or 3 vs. 4+ AEDs), number of concomitant AEDs at index date, and baseline comorbidities (with a prevalence of at least 5% level). 1. Unadjusted rate ratios and confidence intervals were estimated using univariate Poisson models. 2. Adjusted rate ratios and confidence intervals were estimated using multivariate Poisson models. Covariates included the following: age, gender, region, insurance type, year of index date, Quan-Charlson comorbidity index, type of epilepsy and status epilepticus at baseline, all-cause and epilepsy-related hospitalizations and outpatient visits, combinations and number of unique AEDs used at baseline (0, 1, 2, or 3 vs. 4+ AEDs), number of concomitant AEDs at index date, and baseline comorbidities (with a prevalence ≥10% per comparison).

have resulted in a potential patient selection bias. Nevertheless, multivariable analyses were conducted to minimize the potential confounding associated with a wide range of observed covariates, including the number of prior AEDs used, which may account for part of the differences in epilepsy severity. Other factors, such as increased care monitoring, could have an impact on HRU; however, we found that the use of PER-based combinations was associated with lower rates of all-cause and epilepsy-related clinic/office/outpatient visits relative to patients using other AED combinations, which does not suggest that users of PER-based combinations had an advantage in that regard. Furthermore, except for a limited number of specific AEDs (e.g., felbamate or vigabatrin), there is no existing evidence that a certain class of AED requires increased care monitoring. Epilepsy-related HRU may be underreported since the existing evidence that a certain class of AED requires increased care monitoring. Epilepsy-related HRU may be underreported since...
Higher rate for PER-based combination

All-cause clinic/office/outpatient visits of patients receiving perampanel-based combinations versus other types of combinations.

Abbreviations: CI = confidence interval; G = gamma-aminobutyric acid analog; PER = perampanel; RR = rate ratio; SC = sodium channel blockers; SV2 = synaptic vesicle 2A binding. Notes:*: statistically significant at the 5% level.

### Table 3

| Number of clinic/office/outpatient visits | Total person-years | Rate (per person-year) | RR (95% CI) |
|------------------------------------------|--------------------|------------------------|-------------|
| [A]                                      | [B]                | [A]/[B]                | Unadjusted1 | Adjusted2 |
| **PER + SC (N = 3,592) vs.** | 15,583 | 2,445 | 6.5 | 0.73 (0.72–0.74)* | 0.84 (0.83–0.86)* |
| SC + SC (N = 23,830) | 134,526 | 15,032 | 8.9 | 0.75 (0.73–0.76)* | 0.82 (0.81–0.84)* |
| SC + SV2 (N = 68,278) | 395,580 | 43,873 | 9.0 | 0.73 (0.71–0.74)* | 0.82 (0.81–0.84)* |
| SC + G (N = 48,072) | 311,809 | 28,433 | 11.0 | 0.60 (0.59–0.61)* | 0.75 (0.74–0.76)* |
| SV2 + G (N = 40,949) | 265,157 | 24,161 | 11.0 | 0.60 (0.59–0.61)* | 0.75 (0.74–0.76)* |
| G + G (N = 13,273) | 97,135 | 7,372 | 13.2 | 0.50 (0.49–0.50)* | 0.69 (0.67–0.70)* |
| **PER + SV2 (N = 2,200) vs.** | 9,660 | 1,448 | 6.7 | 0.75 (0.73–0.76)* | 0.82 (0.81–0.84)* |
| SC + SC (N = 23,830) | 134,526 | 15,032 | 8.9 | 0.75 (0.73–0.76)* | 0.82 (0.81–0.84)* |
| SC + SV2 (N = 68,278) | 395,580 | 43,873 | 9.0 | 0.74 (0.73–0.75)* | 0.80 (0.78–0.81)* |
| SC + G (N = 48,072) | 311,809 | 28,433 | 11.0 | 0.61 (0.60–0.62)* | 0.74 (0.72–0.75)* |
| SV2 + G (N = 40,949) | 265,157 | 24,161 | 11.0 | 0.61 (0.60–0.62)* | 0.74 (0.73–0.76)* |
| G + G (N = 13,273) | 97,135 | 7,372 | 13.2 | 0.51 (0.50–0.52)* | 0.71 (0.69–0.72)* |
| **PER + G (N = 1,313) vs.** | 7,702 | 840 | 7.7 | 0.87 (0.84–0.89)* | 0.86 (0.84–0.89)* |
| SC + SC (N = 23,830) | 134,526 | 15,032 | 8.9 | 0.86 (0.84–0.88)* | 0.84 (0.82–0.86)* |
| SC + SV2 (N = 68,278) | 395,580 | 43,873 | 9.0 | 0.86 (0.84–0.88)* | 0.84 (0.82–0.86)* |
| SC + G (N = 48,072) | 311,809 | 28,433 | 11.0 | 0.71 (0.69–0.72)* | 0.70 (0.67–0.74)* |
| SV2 + G (N = 40,949) | 265,157 | 24,161 | 11.0 | 0.71 (0.69–0.72)* | 0.70 (0.67–0.74)* |
| G + G (N = 13,273) | 97,135 | 7,372 | 13.2 | 0.59 (0.57–0.60)* | 0.66 (0.63–0.70)* |

Abbreviations: CI = confidence interval; G = gamma-aminobutyric acid analog; PER = perampanel; RR = rate ratio; SC = sodium channel blockers; SV2 = synaptic vesicle protein 2A binding. Notes:*: statistically significant at the 5% level.

1. Unadjusted rate ratios and confidence intervals were estimated using univariate Poisson models.
2. Adjusted rate ratios and confidence intervals were estimated using multivariate Poisson models. Covariates included the following: age, gender, region, insurance type, year of index date, Quan-Charlson comorbidity index, type of epilepsy and status epilepticus at baseline, all-cause and epilepsy-related hospitalizations and outpatient visits, combinations and number of unique AEDs used at baseline (0, 1, 2, or 3 vs. 4+ AEDs), number of concomitant AEDs at index date, and baseline comorbidities (with a prevalence ≥10% per comparison).
epilepsy may have been a secondary factor in other encounters and this may particularly impact patients with a high comorbidity burden. Symphony Health is a provider-based database, which may not have captured all eligible patients. Impact of PER use on outcomes was present during the episode. Unadjusted rate ratios and confidence intervals were estimated using univariate Poisson models. Adjusted rate ratios and confidence intervals were estimated using multivariate Poisson models. Covariates included the following: age, gender, region, insurance type, year of index date, Quan-Charlson comorbidity index, type of epilepsy and status epilepticus at baseline, all-cause and epilepsy-related hospitalizations and outpatient visits, combinations and number of unique AEDs used at baseline (0, 1, 2, or 3 vs. 4+ AEDs), number of concomitant AEDs at index date, and baseline comorbidities (with a prevalence ≥10% per comparison).

5. Conclusions

The present retrospective study provides the first evidence that the use of a PER-based AED combination is associated with improved HRU outcomes compared with non-PER-based AED combinations. More specifically, patients with epilepsy who received PER-based AED combinations were found to have lower rates of all-cause and epilepsy-related hospitalizations, as well as fewer all-cause clinic/office/outpatient visits compared with the majority of patients treated with non-PER based combinations.

Ethical Publication Statement

We confirm that we have reviewed the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Table 4

Epilepsy-related clinic/office/outpatient visits of patients receiving perampanel-based combinations versus other types of combinations.

| Combination | Number of clinic/office/outpatient visits | Total person-years | Rate (per person-year) RR (95% CI) |
|-------------|------------------------------------------|--------------------|-----------------------------------|
| PER + G (N = 48,072) vs. SC + G (N = 13,273) | 1,488 | 1,077 | 1.41 | 0.95 (0.92–0.98)* 0.89 (0.86–0.92)* |
| PER + SC (N = 23,830) vs. SC + SC (N = 23,830) | 4,460 | 840 | 5.3 | 1.02 (1.00–1.04) 0.91 (0.88–0.94)* |
| PER + SV2 (N = 4,460) vs. G + G (N = 13,273) | 1,077 | 1,077 | 1.00 | 1.00 (1.00–1.00) 0.99 (0.98–1.00)* |

Abbreviations: CI = confidence interval; G = gamma-aminobutyric acid analog; PER = perampanel; RR = rate ratio; SC = sodium channel blockers; SV2 = synaptic vesicle protein 2A binding.

Notes:

*: statistically significant at the 5% level.

1. Visits were considered epilepsy-related if a diagnosis for epilepsy (ICD-9-CM: 345.xx or ICD-10-CM: G40.xxx) or non-febrile convulsions (ICD-9-CM: 780.39 or ICD-10-CM: R56.9) was present during the episode.

2. Unadjusted rate ratios and confidence intervals were estimated using univariate Poisson models.

3. Adjusted rate ratios and confidence intervals were estimated using multivariate Poisson models. Covariates included the following: age, gender, region, insurance type, year of index date, Quan-Charlson comorbidity index, type of epilepsy and status epilepticus at baseline, all-cause and epilepsy-related hospitalizations and outpatient visits, combinations and number of unique AEDs used at baseline (0, 1, 2, or 3 vs. 4+ AEDs), number of concomitant AEDs at index date, and baseline comorbidities (with a prevalence ≥10% per comparison).

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Declaration of Competing Interest

FL, MSD, GG, and DL are employees of Analysis Group, Inc. a company that provided paid consulting services to Eisai Co., Ltd. for the conduct of this study. MM, FF, and CP are employees of Eisai Co., Ltd. EF is employed by Emory University School of Medicine and has received research funding from Eisai Co., Ltd. VB is employed by VEB HealthCare LLC and has received research funding from Eisai Co., Ltd.

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References

[1] Centers for Disease Control and Prevention. Epilepsy Data and Statistics. 2019. Accessed on January 16 2020. Available from: https://www.cdc.gov/epilepsy/data/index.html.

[2] Epilepsy Foundation. Generalized Seizures. 2016. Accessed on January 16 2020. Available from: https://www.epilepsy.org/epilepsy/seizure-types/generalized-seizures/.

[3] Goldenberg MM. Overview of drugs used for epilepsy and seizures: etiology, diagnosis, and treatment. P T 2010;35(7):392–415.

[4] Forsgren L, Hauser WA, Olafsson E, Sander JW, Sillanpaa M, Tomson T. Mortality of epilepsy in developed countries: a review. Epilepsia 2005;46 (Suppl. 11):18–27.

[5] Faught E, Laliberte F, Wang Z, Bargas H, Haider B, Lejeune D, et al. Health care resource utilization before and after perampanel initiation among patients with epilepsy in the United States. Epilepsia 2017;58(10):1742–8.

[6] Center for Disease Control and Prevention. Epilepsy: One of the Nation’s Most Common Neurological Conditions 2017. Accessed on January 16 2020.
Krauss GL, Perucca E, Kwan P, Ben-Menachem E, Wang XF, Shih JJ, et al. Final analysis of adjunctive perampanel: an open-label extension (OLEX) of a Phase III study in patients with drug-resistant primary generalized tonic-clonic (PCTC) seizures in idiopathic generalized epilepsy (IGE) [PS. 233]. Neurology. 2017;88(16 Supplement):P5.233.

[22] Rinaldi F, De Maria C. Safety and efficacy of perampanel as adjunctive therapy in patients with refractory focal epilepsy over 12 months: clinical experience in a real-world setting. Int J Epilepsy 2018;5:75–9.

[23] Rohlacher A, Kales G, Lettinger M, Granbichler C, Deak I, Dobesberger J, et al. Two-year real-world experience with perampanel in patients with refractory focal epilepsy: Austrian data. Ther Adv Neurol Disord 2016;9(6):445–53.

[24] Strzelczyk A, Knake S, Kalviainen R, Santamarina E, Toledo M, Willig S, et al. Perampanel for treatment of status epilepticus in Austria, Finland, Germany, and Spain. Acta Neurol Scand 2019;139(4):369–76.

[25] Kanner AM, Ashman E, Gloss D, Harden C, Bourgeois B, Bautista JF, et al. Practice guideline update summary: efficacy and tolerability of the new antiepileptic drugs II: treatment-resistant epilepsy: report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Epilepsy Society. Neurology 2018;91(2):82–90.

[26] Park RM, Kim SE, Lee BI. Antiepileptic drug therapy in patients with drug-resistant epilepsy. J Epilepsy Res 2019;9(1):14–26.

[27] Willems LM, Bauer S, Rosenow F, Strzelczyk A. Recent advances in the pharmacotherapy of epilepsy: brivaracetam and perampanel as broad-spectrum antiseizure drugs for the treatment of epilepsies and status epilepticus. Expert Opin Pharmacother 2019;20(14):1755–65.

[28] Brodie MJ, Sills GJ. Combining antiepileptic drugs-rational polytherapy? Seizure 2011;20(5):369–75.

[29] Faulkner MA. Spotlight on perampanel in the management of seizures: design, development and an update on place in therapy. Drug Des Devel Ther 2017;11:2921–30.

[30] Villanueva V, Montoya J, Castillo A, Mauri-Llerda JÁ, Giner P, López-González FJ, et al. Perampanel in routine clinical use in idiopathic generalized epilepsy: the 12-month GENERAL study. Epilepsia 2018;59(9):1740–52.

[31] Jette N, Meador KJ, Kwon CS. Readmitted after a seizure-related hospitalization: Deja vu. Neurology 2019;92(5):213–4.

[32] Blank LJ, Crispo JAC, Thibault DP, Davis KA, Litt B, Willis AW. Readmission after seizure discharge in a nationally representative sample. Neurology 2018;92(5):e429–42.

[33] de Zelicourt M, de Toffol B, Vespiignani H, Laurendeau C, Béty-Bachelot L, Murat C, et al. Management of focal epilepsy in adults treated with polytherapy in France: the direct cost of drug resistance (ESPERA study). Seizure 2014;23(5):349–56.

[34] Cramer JA, Yan T, Tieu R, Knoth RL, Fincher C, Malhotra M, et al. Risk of hospitalization among patients with epilepsy using long versus short half-life adjunctive antiepileptic drugs. Epilepsy Behav 2020;102:106634.

[35] Gidal BE, Majid O, Ferry J, Hussein Z, Yang H, Zhu J, et al. The practical impact of altered dosing on perampanel plasma concentrations: pharmacokinetic modeling from clinical studies. Epilepsy Behav 2014;35:6–12.