Healthcare Resource Utilization Among Patients with Focal Seizures Treated with Eslicarbazepine Acetate in the US Long-Term Care Setting: A Retrospective Claims Database Analysis

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ABSTRACT

Introduction: The aim of this study was to compare healthcare resource utilization (HCRU) before and after initiation of eslicarbazepine acetate (ESL) in the long-term care (LTC) setting (rehabilitation center, mental health center, LTC non-skilled nursing facility/assisted-living facility, home health, assisted living, nursing home, other/unknown).

Methods: This retrospective analysis used IQVIA’s New Data Warehouse, which includes deterministically linked LTC, prescription, and professional fee claims data and IQVIA Hospital Charge Data Master database. The study period was 1 April 2013 to 31 December 2019. The index date was the date of ESL initiation in the LTC setting. Inclusion criteria were: (1) ≥ 1 new ESL prescription between 1 April 2014 and 31 December 2018; (2) diagnosis of focal seizure (FS) during the 12 months pre-index date; and (3) no ESL prescription during the 12-month period pre-index. A 12-month pre-post analysis compared epilepsy-specific and all-cause HCRU before and after ESL initiation. Categorical variables were compared with McNemar’s tests.

Results: A total of 307 patients (mean age 52.2 years, 57.7% male) with FS were included, of whom 24.8% were in nursing homes. Patients used a mean of 3.1 antiseizure drugs prior to initiation of ESL, and 87.9% of patients initiated ESL as adjunctive treatment. There were significant reductions in proportion of patients with epilepsy-specific physician office visits, emergency department (ED) visits, hospitalizations, and all-cause physician office visits and hospitalizations in the post-index period compared to the pre-index period (P < 0.05). Similar results were observed in sensitivity (patients with an epilepsy diagnosis) and subgroup analyses [presence or absence of intellectual developmental disorders or age (≥ 65 and < 65 years)].

Conclusion: Proportion of patients with epilepsy-specific physician office visits, ED visits, hospitalizations, and all-cause physician office visits and hospitalizations were significantly reduced following initiation of ESL in patients with FS in LTC.
**Key Summary Points**

**Why carry out this study?**

Eslicarbazepine acetate (ESL), a third-generation antiseizure drug, was approved by the US Food and Drug Administration in 2013 for the treatment of partial-onset seizure [focal seizure (FS)] in patients aged ≥ 4 years.

There are no data that examine healthcare resource utilization (HCRU) after initiation of ESL among patients with FS residing in the long-term care (LTC) setting.

This study compared HCRU before and after initiation of ESL in the LTC setting among patients with FS.

**What was learned from the study?**

Initiation of ESL among patients with FS in LTC was associated with significant reductions in the proportion of epilepsy-specific physician office visits, emergency departments visits, hospitalizations, and all-cause physician office visits and hospitalizations.

Similar results were observed among patients with an epilepsy diagnosis and in subgroups of patients with presence of intellectual developmental disorders or aged ≥ 65 and < 65 years.

This retrospective study showed that ESL treatment in patients with FS residing in a LTC setting was associated with reduced HCRU.

**DIGITAL FEATURES**

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.14216495.

**INTRODUCTION**

In the USA, epilepsy affects 1.2% of individuals, including 3 million adults and 470,000 children, with prevalence highest in the youngest and oldest age groups [1, 2]. Focal seizures (FS), formerly referred to as partial-onset seizures [3], are the most common type of seizures and may account for 60% of all epilepsies [4, 5]. The burden of epilepsy in long-term care (LTC) settings is substantial [6, 7].

Individuals with epilepsy commonly have several comorbid conditions, including stroke, heart disease, depression, or intellectual developmental disorders (IDD) [1]. Intellectual or learning disability is common in patients with epilepsy (occurring in at least 25% of these patients) [8, 9], and epilepsy is also prevalent in people with intellectual disability [10, 11]. The clinical and economic burden of supporting individuals with both epilepsy and IDD is substantial, primarily due to the increased incidence of hospitalizations [8, 12] and social care costs [8] compared to individuals with IDD alone.

Antiseizure drug (ASD) therapy is administered to patients with FS [13] with the overall goal of eliminating seizures and maintaining or improving quality of life. There are three generations of ASDs, with the third-generation drugs typically used in later lines of therapy [13, 14]. Achieving seizure control while avoiding adverse events associated with ASD therapy is a major challenge in the management of epilepsy [14]. Newer ASDs may have fewer side effects than earlier-generation drugs [15, 16].

Eslicarbazepine acetate (ESL) is a third-generation ASD approved by the US Food and Drug Administration in 2013 for the treatment of partial-onset seizure (FS) in patients aged ≥
4 years [17]. Multiple randomized phase III clinical trials have demonstrated the efficacy and safety of ESL in patients with FS [18]. In these clinical trials, ESL was well-tolerated; the most common AEs included dizziness, nausea, headache, and somnolence, and all were generally mild to moderate in intensity [18].

Data describing ASD use in the LTC setting are limited [7, 19]. In the USA, approximately 10–24% of nursing home residents receive ASDs, with phenytoin and gabapentin among the most widely used [7, 20, 21]. Proper selection of ASDs is essential and should be based on severity of epilepsy, type and cause of seizures, and presence of coexisting medical conditions [22]. ASD users in nursing homes have significant comorbidities, including anxiety, depression, and diabetes [21]. In elderly individuals, ASDs may increase the risk of falls, cognitive side effects, and drug interactions [19].

In nursing homes, patients with epilepsy use more services and incur higher costs compared to patients without epilepsy [23]. Among institutionalized Medicare beneficiaries in nursing facilities, an elderly population with epilepsy has significantly higher per-patient per-month costs ($3479 vs. $2381; \( P < 0.001 \)), inpatient admissions (1105 vs. 697 per 1000 beneficiaries; \( P < 0.001 \)), and 30-day readmissions (287 vs. 145 per 1000 beneficiaries; \( P < 0.001 \)) compared to the population without epilepsy [23]. ESL initiation has been associated with reduced healthcare resource utilization (HCRU) and costs among the community-dwelling population in real-world routine clinical practice [24, 25]. To date, no studies have characterized the population of patients using ESL in LTC and there are no data that examine HCRU after initiation of ESL in LTC settings.

The objectives of this study were to (1) describe the baseline demographic and clinical characteristics of patients with FS using ESL either as monotherapy or adjunctive therapy in the LTC setting, and (2) compare epilepsy-specific and all-cause HCRU before and after initiation of ESL in the LTC setting among patients with FS. LTC settings included the following types of facilities: rehabilitation center, mental health center, LTC non-skilled nursing facility (SNF)/assisted-living facility (ALF), home health, assisted living, nursing home, and other/unknown.

A sensitivity analysis including patients with an epilepsy diagnosis was considered, as FS diagnoses are typically under-coded in US LTC settings. Subgroup analyses of patients with FS or an epilepsy diagnosis stratified by the presence or absence of IDD, and of patients with an epilepsy diagnosis stratified by age (\( \geq 65 \) and < 65 years) were performed.

**METHODS**

**Data Source**

The analytical dataset was constructed from IQVIA’s New Data Warehouse, which includes deterministically linked LTC, prescription, and professional fee claims data and IQVIA Hospital Charge Data Master (CDM) database.

IQVIA’s New Data Warehouse (Open Source Claims Data) includes prescriber-/patient-level data for over 1000 independent LTC pharmacies in addition to approximately 165 pharmacies located within the Community Mental Health Center Clinic (LTC pharmacy database); more than 1.6 billion retail or mail-order prescription claims, representing dispensed prescriptions for approximately 90% of all pharmacies (prescription claims); approximately 1 billion professional fee claims per year, representing over 870,000 practitioners per month, and obtained through agreements with electronic claims re-processors (professional fee claims); and records from over 400 hospitals, covering 7 million annual inpatient stays and 60 million annual outpatient visits (CDM). Linkage to CDM was not mandated.

IQVIA data are de-identified in compliance with the Health Insurance Portability and Accountability Act. Therefore, this study did not constitute human subjects research [26], and review by an institutional review board was not required.
**Study Design**

This was a retrospective, observational, 12-month pre-post analysis. The study period was between 1 April 2013 and 31 December 2019. The index date was the date of the first prescription of ESL in the LTC pharmacy database at any time between 1 April 2014 and 31 December 2018 (selection window). The study consisted of a baseline pre-index period, defined as the 12 months prior to the index date, and a follow-up post-index period, defined as a minimum of 12 months following the index date (Fig. 1).

**Patient Population**

Patients were included in the analysis if they met the following criteria: (1) age ≥ 4 years at index date; (2) ≥ 1 prescription of ESL in the LTC pharmacy data at any time between 1 April 2014 and 31 December 2018 (i.e., the selection window); (3) deterministic linking of LTC pharmacy, prescription claims, and professional fee claims data from IQVIA’s New Data Warehouse during the study period; (4) diagnosis of FS in professional fee claims or CDM (International Classification of Diseases, 9th Revision, Clinical Modification [ICD-9-CM] codes: 345.4X, 345.5X; ICD-10-CM codes: G40.0x, G40.1x, G40.2x) [24] during the 12 months prior to the index date (pre-index/baseline period), and including the index date; (5) activity in the 12-month pre- and post-index periods, defined as ≥ 1 professional fee claim and ≥ 1 prescription (LTC pharmacy database or prescription claims) as a proxy for continuous enrollment; (6) pharmacy stability in the LTC pharmacy database or prescription claims in the 12-month pre- and post-index periods, defined as consistent reporting of data from the pharmacy most frequently visited by the patient and ≥ 80% coverage rate for each month in the 12-month pre- and post-index periods.

Patients were excluded from this analysis if they met the following criteria: (1) ESL prescription in prescription claims data in the 12-month pre-index period, excluding the index date; (2) evidence of pregnancy at any time during the study period (ICD-9-CM codes: 630.xx–679.xx, V22–V24; ICD-10-CM codes: O00-O9A, Z33, Z34, Z36, Z3A); or (3) evidence of data quality issues (e.g., invalid year of birth, gender, region).

Sensitivity analyses were conducted to examine patients with an epilepsy diagnosis. Inclusion criteria for the sensitivity analysis were the same as the those for the primary analysis except that patients had a diagnosis of epilepsy in professional fee claims or CDM during the 12-month pre-index period, including the index date, instead of FS.

Subgroup analyses stratified patients with FS and an epilepsy diagnosis by presence or absence of IDD (ICD-9/10-CM codes: 317, 318, 318.0, 318.1, 318.2, 319, F70, F71, F72, F73, F78, F79) [Electronic Supplementary Material (ESM) Table S1] and patients with an epilepsy diagnosis by age (≥ 65 and < 65 years). Subgroup analyses of patients with FS stratified by age were not conducted due to the small sample size.

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**Fig. 1** Study design. ESL Eslicarbazepine acetate, LTC long-term care
Study Measures and Statistical Analyses

Baseline Demographic Characteristics
Baseline demographic characteristics were measured during the 12-month pre-index (baseline) period or on the index date and included age, gender, geographic region (according to US Census Bureau: Northeast, Midwest, South, West), and payer type [cash, Medicaid, Medicare, third party (i.e., commercial, including Medicare Advantage), other/unknown].

Baseline Clinical Characteristics
Baseline clinical characteristics were measured during the 12-month pre-index (baseline) period, including mean number of prior ASDs, Charlson Comorbidity Index (CCI)/Dartmouth-Manitoba adaptation, days in LTC (estimated), and indicators of frailty. Frailty status was defined by the presence of a claim for any of the following: home oxygen use, wheelchair use, walker use, dementia, urinary catheter use, falls and fractures, and a composite of any of these indicators [27]. In addition to the CCI index, conditions that often occur with epilepsy [28, 29], other mental health disorders (e.g., attention-deficit/hyperactivity disorder (ADHD), anxiety, autism, behavioral/emotional disorders (excluding ADHD), bipolar disorder, cognitive impairment, depression, disorders of psychological development (including autism), IDD, mood disorders (excluding depression), schizophrenia, and unspecified developmental delay), and certain other medical comorbidities (e.g., alcohol/drug dependence, atherosclerosis, cancer, central nervous system infections, hypertension, hyponatremia, nervous system neoplasms, Parkinson’s disease, sleep apnea, traumatic brain injury) [25] were reported.

Index Treatment Characteristics
Patients receiving ESL as monotherapy versus as adjunctive therapy (combination or add-on therapy) were identified. Adjunctive therapy was defined as (1) receipt of ESL with another ASD on the same day (ESL index date in LTC pharmacy data); or (2) receipt of ESL with another ASD (from prescription claims or LTC pharmacy data) as add-on therapy, where the two medications were filled on separate days, but had an overlap in days’ supply. For the latter, adjunctive therapy was confirmed if the same ASD was refilled less than 30 days after its supply had run out. All other patients prescribed ESL in the LTC setting but not meeting the criteria for adjunctive therapy were classified as receiving monotherapy.

LTC facility type (rehabilitation center, mental health center, LTC non-SNF/ALF, home health, assisted living, nursing home, other/unknown) was assessed from LTC pharmacy data as of the patient’s index date, if available, as first option or over the 12-month pre-index period.

Healthcare Resource Utilization
Epilepsy-related and all-cause HCRU was measured as the percentage of patients having ≥ 1 HCRU of each category during the 12-months pre- and post-index periods. The following HCRU outcomes were reported: outpatient visits (professional claims/CDM outpatient data), including emergency department (ED) visits and physician office visits; and inpatient hospitalizations (CDM). Epilepsy-specific HCRU was identified with a diagnosis of epilepsy, post-traumatic seizures, or other/unspecified convulsions (ICD-9 codes: 345.xx, 780.33, 780.39; ICD-10 codes: G40.xx, R561, and R569) in the primary diagnosis position associated with that claim [25].

Statistical Analyses
Patient demographics, clinical characteristics, and treatment characteristics were evaluated using frequency (n) and percentage for categorical variables and mean and standard deviation (SD), and median for continuous variables. HCRU was compared pre- (baseline) and post-ESL initiation using McNemar’s test for categorical variables (given matched cohorts). P < 0.05 was considered to be statistically significant. Statistical analyses were conducted using SAS® Release 9.4 (SAS Institute Inc., Cary, NC, USA).
RESULTS

Primary Analysis: Patients with FS

Baseline Characteristics
A total of 2674 patients with ≥ 1 prescription of ESL during the selection window (1 April 2014 to 30 June 2019) were identified in the LTC pharmacy database, of which 307 met the inclusion criteria (Fig. 2).

Baseline demographics of the patients with FS initiating ESL and the subgroups stratified by the presence or absence of IDD are described in Table 1. In the overall patient population, mean (± SD) age was 52.2 (± 16.9) years and 57.7% of patients were male. Most patients (56.4%) were enrolled in Medicare. Among the facility types that could be identified, 24.8% of patients were in nursing homes, 15.6% were in assisted living, and 11.3% were in other facility types, including rehabilitations centers, mental health centers, and LTC non-SNF/ALF. Facility type was unknown for 48.2% of patients but may comprise other facilities, such as intermediate care facilities (ICF).

Clinical characteristics of patients with FS initiating ESL and the subgroups stratified by the presence or absence of IDD are described in Table 2. The overall patient population was frail with a high number of comorbidities (composite of any indicators of frailty status 44.6%; mean CCI score 1.63). Of the conditions that often co-occur with epilepsy, stroke (25.1%) was the most common, IDD (31.3%) and depression (25.4%) were the most common mental health disorders, and hypertension (35.5%) was the most common other medical comorbidity [27]. Patients spent a mean 239.9 days in LTC prior to the index date. The mean number of ASDs prior to ESL initiation was 3.1, and 87.9% of patients initiated ESL as an adjunctive treatment.

Fig. 2 Sample selection. a The date of the first prescription of ESL in the LTC pharmacy data was the patients’ index date. b Patient activity was defined as ≥ 1 office visit (in professional fee claims) and ≥ 1 prescription (in prescription claims or LTC pharmacy data). c Pharmacy stability was defined as consistent reporting of data from the pharmacy most frequently visited by the patient or ≥ 80% coverage rate for each month in the 12-month pre- and post-index periods (prescription claims and LTC pharmacy stability were assessed independently). A patient could fit either definition to meet this criterion. d Codes indicating pregnancy included ICD-9: 630.xx–679.xx, V22–V24; ICD-10: O00-O9A, Z33, Z34, Z36, Z3A. Note: From the final sample, 113 patients had linkage to CDM. CDM Charge Data Master, FS focal seizure, ICD-9/10-CM International Classification of Diseases 9/10th revision, Clinical Modification
**Table 1** Primary analysis: baseline demographics of patients with focal seizure

| Patient characteristic | New users of ESL \((N = 307)\) | Users of ESL with IDD \((N = 96)\) | Users of ESL without IDD \((N = 211)\) |
|------------------------|-------------------------------|--------------------------------|-----------------------------------------|
| Age in years, mean (SD) | 52.2 (16.9)                  | 49.8 (13.8)                   | 53.3 (18.0)                             |
| Age categories, years, n (%) |                               |                                |                                         |
| < 65                   | 236 (76.9)                  | 83 (86.5)                     | 153 (72.5)                              |
| 4–17                   | 4 (1.3)                     | 1 (1.0)                       | 3 (1.4)                                 |
| 18–34                  | 51 (16.6)                   | 15 (15.6)                     | 36 (17.1)                               |
| 35–49                  | 76 (24.8)                   | 30 (31.3)                     | 46 (21.8)                               |
| 50–64                  | 105 (34.2)                  | 37 (38.5)                     | 68 (32.2)                               |
| ≥ 65                   | 71 (23.1)                   | 13 (13.5)                     | 58 (27.5)                               |
| 65–74                  | 41 (13.4)                   | 12 (12.5)                     | 29 (13.7)                               |
| 75–84                  | 14 (4.6)                    | 0 (0.0)                       | 14 (6.6)                                |
| ≥ 85                   | 16 (5.2)                    | 1 (1.0)                       | 15 (7.1)                                |
| Gender\(^a\), n (%)   |                              |                                |                                         |
| Male                   | 177 (57.7)                  | 56 (58.3)                     | 121 (57.3)                              |
| Payer type (in professional claims), n (%) |                             |                                |                                         |
| Medicaid               | 33 (10.7)                   | 11 (11.5)                     | 22 (10.4)                               |
| All Medicare           | 173 (56.4)                  | 58 (60.4)                     | 115 (54.5)                              |
| Third party (i.e., commercial, including Medicare Advantage) | 94 (30.6) | 24 (25.0) | 70 (33.2) |
| Other/unknown          | 7 (2.3)                     | 3 (3.1)                       | 4 (1.9)                                 |
| Facility type\(^b\) (in LTC), n (%) |                             |                                |                                         |
| Nursing home           | 76 (24.8)                   | 15 (15.6)                     | 61 (28.9)                               |
| Assisted living        | 48 (15.6)                   | 22 (22.9)                     | 26 (12.3)                               |
| Rehabilitation center  | 21 (6.8)                    | 4 (4.2)                       | 17 (8.1)                                |
| Mental health center   | 13 (4.2)                    | 3 (3.1)                       | 10 (4.7)                                |
| LTC non-SNF/ALF        | 1 (0.3)                     | 1 (1.0)                       | 0 (0.0)                                 |
| Home health            | 0 (0.0)                     | 0 (0.0)                       | 0 (0.0)                                 |
| Other/unknown          | 148 (48.2)                  | 51 (53.1)                     | 97 (46.0)                               |

\(ALF\) Assisted living facility, ESL eslicarbazepine acetate, IDD intellectual developmental disorders, LTC long-term care, SD standard deviation, SNF skilled nursing facility

\(^a\) Females comprised 42.3% of new users of ESL, 41.7% of users of ESL with IDD and 42.7% of users of ESL without IDD

\(^b\) Assessed from LTC data as of patient’s index date (if available, as first option) or over the 12-month pre-index period
Table 2 Primary analysis: clinical characteristics of patients with focal seizure

| Characteristic                        | New users of ESL (N = 307) | Users of ESL with IDD (N = 96) | Users of ESL without IDD (N = 211) |
|--------------------------------------|-----------------------------|--------------------------------|-----------------------------------|
| CCI, mean (SD)                       | 1.63 (2.17)                 | 1.06 (1.41)                    | 1.89 (2.39)                       |
| **Comorbidities often occurring with epilepsy, n (%)** |                             |                                |                                   |
| Stroke                               | 77 (25.1)                   | 10 (10.4)                      | 67 (31.8)                         |
| Alzheimer’s disease/dementia         | 71 (23.1)                   | 18 (18.8)                      | 53 (25.1)                         |
| Arthritis                            | 42 (13.7)                   | 14 (14.6)                      | 28 (13.3)                         |
| Diabetes                             | 39 (12.7)                   | 9 (9.4)                        | 30 (14.2)                         |
| PVD                                  | 24 (7.8)                    | 5 (5.2)                        | 19 (9.0)                          |
| **Other mental health disorders, n (%)** |                             |                                |                                   |
| IDD                                  | 96 (31.3)                   | 96 (100.0)                     | 0 (0.0)                           |
| Depression                           | 78 (25.4)                   | 23 (24.0)                      | 55 (26.1)                         |
| Anxiety                              | 63 (20.5)                   | 15 (15.6)                      | 48 (22.7)                         |
| Schizophrenia                        | 33 (10.7)                   | 11 (11.5)                      | 22 (10.4)                         |
| Mood disorders (excluding depression and bipolar disorder) | 27 (8.8)                   | 11 (11.5)                      | 16 (7.6)                          |
| Disorders of psychological development (including autism) | 25 (8.1)                   | 12 (12.5)                      | 13 (6.2)                          |
| Bipolar disorder                     | 20 (6.5)                    | 5 (5.2)                        | 15 (7.1)                          |
| Behavioral/emotional disorders (excluding ADHD) | 19 (6.2)                   | 7 (7.3)                        | 12 (5.7)                          |
| Autism                               | 16 (5.2)                    | 8 (8.3)                        | 8 (3.8)                           |
| Cognitive impairment                 | 12 (3.9)                    | 1 (1.0)                        | 11 (5.2)                          |
| **Other medical comorbidities, n (%)** |                             |                                |                                   |
| Hypertension                         | 109 (35.5)                  | 31 (32.3)                      | 78 (37.0)                         |
| Atherosclerosis                      | 35 (11.4)                   | 5 (5.2)                        | 30 (14.2)                         |
| Hyponatremia                         | 31 (10.1)                   | 9 (9.4)                        | 22 (10.4)                         |
| Cancer                               | 30 (9.8)                    | 6 (6.3)                        | 24 (11.4)                         |
| Sleep apnea                          | 25 (8.1)                    | 10 (10.4)                      | 15 (7.1)                          |
| Traumatic brain injury               | 25 (8.1)                    | 3 (3.1)                        | 22 (10.4)                         |
| Parkinson’s disease                  | 11 (3.6)                    | 5 (5.2)                        | 6 (2.8)                           |
| **Indicators of frail health status, n (%)** |                             |                                |                                   |
| Dementia                             | 63 (20.5)                   | 18 (18.8)                      | 45 (21.3)                         |
| Falls                                | 52 (16.9)                   | 15 (15.6)                      | 37 (17.5)                         |
| Fractures                            | 40 (13.0)                   | 15 (15.6)                      | 25 (11.8)                         |
Among the overall patient population, there were 96 patients with and 211 patients without IDD (Tables 1, 2). Patients with and without IDD spent a mean of 291.3 and 216.4 days in LTC prior to index. Compared to patients without IDD, patients with IDD were younger (mean ± SD 49.8 ± 13.8 vs. 53.3 ± 18.0 years), a lower proportion resided in nursing homes (15.6 vs. 28.9%), a higher proportion resided in ALF (22.9 vs. 12.3%), and mean CCI was lower (1.06 vs. 1.89). Among patients with and without IDD, the mean number of ASDs prior to ESL initiation was 3.7 and 2.8, and 89.6 and 87.2% of patients initiated ESL as an adjunctive treatment, respectively.

### Table 2 continued

| Characteristic | New users of ESL (N = 307) | Users of ESL with IDD (N = 96) | Users of ESL without IDD (N = 211) |
|---------------|-----------------------------|-------------------------------|----------------------------------|
| Wheelchair use | 28 (9.1)                    | 14 (14.6)                     | 14 (6.6)                         |
| Urinary catheter use | 13 (4.2)                    | 4 (4.2)                       | 9 (4.3)                          |
| Home oxygen use | 11 (3.6)                    | 4 (4.2)                       | 7 (3.3)                          |
| Walker use | 4 (1.3)                     | 2 (2.1)                       | 2 (0.9)                          |
| Composite of the above (any indicators mentioned above) | 137 (44.6)                  | 48 (50.0)                     | 89 (42.2)                        |
| Number of prior ASDs, mean (SD) | 3.1 (1.7)                  | 3.7 (1.8)                    | 2.8 (1.6)                        |

#### Index treatment characteristics

| Adjunctive therapy | 270 (87.9) | 86 (89.6) | 184 (87.2) |
| Days in LTC prior to index, mean (SD) | 239.85 (145.38) | 291.34 (118.18) | 216.42 (150.71) |

**ADHD** Attention deficit hyperactivity disorder, **ASD** antiseizure drug, **CCI** Charlson Comorbidity Index, **PVD** peripheral vascular disease

- **a** Comorbidities and other mental health disorders with > 5% prevalence are reported in the table.
- **b** All variables were assessed over the pre-index period, not including index date.
- **c** Other mental health disorders included ADHD, reported in 2.0% of new users of ESL, 2.1% of users of ESL with IDD, and 1.9% of users of ESL without IDD; and unspecified developmental delay, reported in 2.6% of new users of ESL, 2.1% of users of ESL with IDD, and 2.8% of users of ESL without IDD.
- **d** Other medical comorbidities included alcohol/drug dependence, reported in 3.9% of new users of ESL, 2.1% of users of ESL with IDD, and 4.7% of users of ESL without IDD; nervous system neoplasms, reported in 2.3% of new users of ESL, 0.0% of users of ESL with IDD, and 3.3% of users of ESL without IDD; and central nervous system infections, reported in 0.7% of new users of ESL, 1.0% of users of ESL with IDD, and 0.5% of users of ESL without IDD.
- **e** Monotherapy was used by 37 (12.1%) of new users of ESL, 10 (10.4%) of users of ESL with IDD and 27 (12.8%) of users of ESL without IDD.
- **f** Defined as days between first pharmacy LTC claim prior to index date over the 12-month pre-index period and index date, inclusive of both boundaries.

Healthcare resource utilization

**Overall population** Epilepsy-specific HCRU for the overall population of patients with FS initiating ESL is shown in Fig. 3. There were statistically significant reductions in the percentage of patients with ≥ 1 physician office visit (59.9 vs. 49.5%; P < 0.001), ED visit (33.2% vs. 26.1%; P = 0.03), or inpatient hospitalization (29.6 vs. 16.6%; P < 0.0001) in the post-index period compared to the pre-index period. All-cause HCRU for the overall population of patients with FS initiating ESL is shown in Fig. 3. There were statistically significant reductions in the percentage of patients with ≥ 1 physician office visit (82.7 vs. 74.9%);
$P < 0.01$) or inpatient hospitalization (45.0 vs. 37.1%; $P = 0.02$) and numerical reductions in the percentage of patients with $\geq 1$ ED visit [59.6 vs. 54.7%; not significant (NS)].

**IDD and non-IDD** Epilepsy-specific HCRU for patients with FS initiating ESL stratified by the presence or absence of IDD is shown in Fig. 4. For patients with FS and IDD, there were statistically significant reductions in the percentage of patients with $\geq 1$ physician office visit (64.6 vs. 53.1%; $P = 0.03$) or inpatient hospitalization (32.3 vs. 16.7%; $P < 0.01$) and numerical reductions in the percentage of patients with $\geq 1$ ED visit (36.5 vs. 29.2%; NS) in the post-index period compared to the pre-index period (Fig. 4a). For patients with FS and no IDD, there were statistically significant reductions in the percentage of patients with $\geq 1$ physician office visit (80.1 vs. 73.0%; $P = 0.02$) and numerical reductions in the percentage of patients with $\geq 1$ ED visit (56.4 vs. 53.6%; NS) or inpatient hospitalization (44.5 vs. 38.4%; NS) (Fig. 4b).

### Sensitivity Analysis: Patients with an Epilepsy Diagnosis

#### Baseline Characteristics

Sensitivity analyses examined a broader definition of epilepsy by selecting the patient population with an epilepsy diagnosis ($N = 998$) (ESM Fig. S1).

Baseline demographics of the patients with an epilepsy diagnosis initiating ESL and the subgroups stratified by the presence or absence of IDD or age ($\geq 65$ and $< 65$ years) are described in ESM Table S2. In the overall patient population, mean (± SD) age was 56.5 (± 16.8) years, 45.9% of patients were female, and most...
(56.7%) patients were enrolled in Medicare. Among the facility types that could be identified, 34.1% of patients were in nursing homes, 11.5% of patients were in ALF, and 12.9% of patients were in other types of living facilities, including rehabilitation centers, mental health centers, and LTC non-SNF/ALF. Facility type was unknown for 41.5% of patients but could comprise other facilities such as ICF.

Clinical characteristics of patients with an epilepsy diagnosis initiating ESL and the subgroups stratified by the presence or absence of IDD or age (≥ 65 and < 65 years) are described in ESM Table S3. The overall patient population was frail, with a high number of comorbidities (composite score for frail status: 47.2%; mean CCI score 1.93). Of the conditions that often co-occur with epilepsy, stroke (29.6%) was the most common, IDD (24.1%) and depression (23.2%) were the most common mental health disorders, and hypertension (45.4%) was the most common other comorbidity [27]. Patients spent a mean 243.3 days in LTC prior to index date. The mean number of ASDs prior to ESL initiation was 2.7, and 81.8% of patients initiated ESL as an adjunctive treatment.

Among the overall patient population, there were 241 patients with and 757 patients...
without IDD (ESM Tables S2, S3). Patients with and without IDD spent a mean of 286.1 and 229.7 days in LTC prior to index, respectively. Compared to patients without IDD, patients with IDD were younger (mean ± SD 50.6 ± 14.3 vs. 58.4 ± 17.1 years), a lower proportion resided in nursing homes (21.6 vs. 38.0%), a higher proportion resided in ALFs (18.7 vs. 9.2%), and mean CCI was lower (1.07 vs. 2.21). Among patients with and without IDD, the mean number of ASDs prior to ESL initiation was 3.22 and 2.53, and 86.3 and 80.3% of patients initiated ESL as an adjunctive regimen, respectively.

Among the overall patient population, there were 331 patients aged ≥ 65 years and 667 patients aged < 65 years (ESM Tables S2, S3). Patients aged ≥ 65 years or < 65 years spent a mean of 255.2 and 219.2 days in LTC prior to index. Compared to patients aged < 65 years, a higher proportion of patients aged ≥ 65 years resided in nursing homes (45.6 vs. 28.3%) or rehabilitation centers (13.0 vs. 6.1%), a lower proportion resided in ALFs (8.5 vs. 13.0%) or mental health centers (0.6 vs. 5.4%), and mean CCI was higher (3.08 vs. 1.36). Among patients aged ≥ 65 and < 65 years, the mean number of ASDs prior to ESL initiation was 2.24 and 2.93, and 72.8 and 86.2% of patients initiated ESL as an adjunctive regimen, respectively.

**Healthcare Resource Utilization**

Epilepsy-specific and all-cause HCRU for the overall population of patients with an epilepsy diagnosis initiating ESL and the subgroups stratified by the presence or absence of IDD are described in Fig. 5.

**Overall population** In the overall population with an epilepsy diagnosis, there were statistically significant reductions in the percentage of patients with ≥ 1 epilepsy-specific ED visit (21.1 vs. 14.5%; P = 0.005) or inpatient hospitalization (27.8 vs. 14.5%; P < 0.0001) in the post-index period compared to the pre-index period. There were statistically significant reductions in the percentage of patients with ≥ 1 all-cause ED visit (66.2 vs. 50.9%; P = 0.0002), or inpatient hospitalization (48.2 vs. 39.6%; P < 0.0001).

**IDD and non-IDD** For patients with an epilepsy diagnosis and IDD, there were statistically significant reductions in the percentage of patients with ≥ 1 epilepsy-specific inpatient hospitalization (21.6 vs. 14.1%; P = 0.02) and numerical reductions in the percentage of patients with ≥ 1 physician office visit (49.4 vs. 44.8%; NS) or ED visit (30.3 vs. 24.9%; NS) in the post-index period compared to the pre-index period. There were statistically significant reductions in the percentage of patients with ≥ 1 all-cause inpatient hospitalization (44.8 vs. 35.3%; P = 0.02), and numerical reductions in the percentage of patients with ≥ 1 physician office visit (77.6 vs. 76.3%; NS) or ED visit (60.2 vs. 56.4%; NS).

For patients with an epilepsy diagnosis and no IDD, there were statistically significant reductions in the percentage of patients with ≥ 1 epilepsy-specific physician office visit (34.9 vs. 31.2%; P = 0.007), ED visit (27.2 vs. 20.2%; P < 0.0001), or inpatient hospitalization (23.0 vs. 14.7%; P < 0.0001) in the post-index period compared to the pre-index period. There were statistically significant reductions in the percentage of patients with ≥ 1 all-cause physician office visit (67.9 vs. 63.0%; P < 0.002), ED visit (60.0 vs. 54.6%; P = 0.002), or inpatient hospitalization (48.2 vs. 39.6%; P < 0.0001).

**Elderly and non-elderly** Epilepsy-specific and all-cause HCRU for the overall population of patients with an epilepsy diagnosis stratified by age (≥ 65 and < 65 years) are described in Fig. 6. For patients with an epilepsy diagnosis aged ≥ 65 years, there were statistically significant reductions in the percentage of patients with ≥ 1 epilepsy-specific ED visit (21.1 vs. 14.5%; P = 0.005) or inpatient hospitalization (27.8 vs. 14.5%; P < 0.0001) and numerical reductions in the percentage of patients with ≥ 1 physician office visit (23.9 vs. 19.3%; NS) in the post-index period compared to the pre-index period. There were statistically significant reductions in the percentage of patients with ≥ 1 all-cause physician office visit (64.9 vs. 58.8%; P = 0.001), ED visit (60.0 vs. 54.0%; P = 0.004), or inpatient hospitalization (49.3 vs. 41.0%; P = 0.0001).
or inpatient hospitalization (61.9 vs. 47.1%; \( P \leq 0.0001 \)).

For patients with an epilepsy diagnosis aged \( \geq 65 \) years, there were statistically significant reductions in the percentage of patients with \( \geq 1 \) epilepsy-specific ED visit (30.9% vs. 23.1%; \( P = 0.0001 \)) or inpatient hospitalization (20.7% vs. 14.8%; \( P = 0.002 \)) and numerical reductions in the percentage of patients with \( \geq 1 \) all-cause inpatient hospitalization (41.4% vs. 35.8%; \( P = 0.02 \)) and numerical reductions in the percentage of patients with \( \geq 1 \) all-cause inpatient hospitalization (41.4% vs. 35.8%; \( P = 0.02 \)) and numerical reductions in the percentage of patients with \( \geq 1 \) physician office visit (40.3% vs. 37.0%; NS) in the post-index period compared to the pre-index period. There were statistically significant reductions in the percentage of patients with \( \geq 1 \) all-cause inpatient hospitalization (41.4% vs. 35.8%; \( P = 0.02 \)) and numerical reductions in the percentage of patients with \( \geq 1 \) physician office visit (69.6% vs. 68.1%; NS) or ED visit (58.3% vs. 54.4%; NS).

**Fig. 5** Sensitivity analysis: HCRU in patients with an epilepsy diagnosis stratified by the presence or absence of IDD. a New users of ESL \( (N = 998) \), b IDD \( (N = 241) \), c No-IDD \( (N = 757) \). Asterisk denotes a significant difference in results at \( P < 0.05 \).

**Fig. 6** Sensitivity analysis: patients with an epilepsy diagnosis stratified by age \( \geq 65 \) years (a) or \(< 65 \) years (b). a \( \geq 65 \) years \( (N = 331) \), b \(< 65 \) years \( (N = 667) \). Asterisk denotes a significant difference in results at \( P < 0.05 \).
DISCUSSION

The results from this retrospective real-world study of administrative claims data suggest that ESL initiation was associated with statistically significant reductions in epilepsy-specific and all-cause physician office visits and inpatient hospitalizations and epilepsy-specific ED visits in patients with FS in LTC. Subgroup analyses demonstrated statistically significant reductions in epilepsy-specific and all-cause physician office visits and epilepsy-specific inpatient hospitalizations in patients with FS, with or without IDD. Reductions in HCRU were comparable for both patient subgroups, which is consistent with data showing similar clinical effectiveness of ESL in patients with FS alone and patients with FS and psychiatric comorbidities and intellectual disability [30, 31]. The sensitivity analysis in patients with an epilepsy diagnosis supported the findings from the primary analysis. For patients aged ≥ 65 years, there were statistically significant reductions in epilepsy-specific and all-cause ED visits and inpatient hospitalizations and all-cause physician office visits. For patients aged < 65 years, there were statistically significant reductions in epilepsy-specific ED visits and inpatient hospitalizations and all-cause inpatient hospitalizations. The reductions in epilepsy-specific and all-cause HCRU following ESL initiation in these patients may be driven by the clinical efficacy, safety, and tolerability of ESL. ESL was shown to be well-tolerated, causing few side effects, and few discontinuations were reported in clinical trials and observational studies [18, 32–34].

To the authors’ knowledge, this is the first study to characterize a population of individuals with FS in LTC facilities, including younger age groups and an elderly population, and to report economic outcomes in patients taking third-generation ASDs such as ESL. The type of LTC facility was unknown for the majority of patients in this study. Based on stratified analyses, we assume these include patients residing in intermediate care facilities; however, this could not be fully ascertained due to limitations associated with data. Patients with FS were frail, as shown by indicators of frailty and high levels of comorbidities, including hypertension, IDD, depression, and stroke. The prevalence of hypertension and stroke was also high in patients with FS stratified by the presence or absence of IDD, patients with an epilepsy diagnosis, and patients with an epilepsy diagnosis stratified by the presence or absence of IDD or age (≥ 65 or > 65 years). Most patients in this study received at least two ASDs prior to initiating ESL, suggesting that they had uncontrolled seizures before ESL was added to the therapeutic regimen as adjunctive [35]. Similar findings were reported in adult and pediatric patients in non-LTC settings, where the majority of patients received approximately two ASDs prior to initiating ESL [24, 25].

Previous studies describing epilepsy in LTC have focused on elderly patients in nursing home populations. In five cross-sectional cohorts of all residents aged ≥ 65 years in any Medicare/Medicaid-certified nursing home in the USA (2003–2007), scores for activities of daily living, frailty, and cognition were worse in individuals with epilepsy and seizure than in those without this diagnosis [6]. In a cross-sectional study among long-stay older residents who enrolled in fee-for-service Medicare and lived in nursing homes in the USA in 2016, comorbidities among ASD users included depression, cognitive impairment, Alzheimer’s disease or dementia, diabetes, anxiety, or stroke [21]. Stroke in particular has a strong association with epilepsy/seizure risk, as individuals with stroke have 2.1-fold higher risk for epilepsy/seizure than those without stroke, and there is a strong decreasing association with age (65- to 74-year-olds had higher odds than those aged 85+ years in those with and without stroke) [6]. In our study population, 50.5% of patients with an epilepsy diagnosis aged ≥ 65 years had a history of stroke.

In the present study, 45% of patients with FS in LTC had at least one all-cause inpatient hospitalization during the 12-month pre-index period, suggesting that patients with FS in the LTC setting impose a heavy burden on healthcare system resources. Consistent with this, a cross-sectional analysis of the institutionalized Medicare population with and without epilepsy using Medicare 5% sample claims data from...
2013 and 2014 reported higher inpatient admission rates in the institutionalized population with epilepsy than in those without epilepsy (1105 per 1000 beneficiaries vs. 697 per 1000 beneficiaries; \( P < 0.001 \)) [23]. The inpatient costs accounted for 37% of the total costs for institutionalized patients with epilepsy [23]. Our findings suggest that treatment with ESL may reduce the burden of inpatient admission and help alleviate some of the economic burden associated with FS in LTC settings.

In the USA, epilepsy is an important public health problem among Medicare beneficiaries and older adults [36]. Epilepsy is sevenfold more prevalent among LTC residents than elderly residing in the community [6, 7]. With the aging of the US population, the prevalence of epilepsy in those aged \( \geq 60 \) years is increasing and is expected to rise even further [37]. The impacts of this increasing prevalence of epilepsy to the US healthcare system are substantial, as more patients with epilepsy will need permanent in-home assistance or care in a LTC setting [8, 37]. Model projections for institutionalized Medicare beneficiaries with epilepsy suggest an 18% increase in population size and a 72% increase in cost between 2017 and 2027 [23].

Patients who can better manage their seizures and associated comorbidities are likely to incur less HCRU and associated medical costs. Data from the present study imply that ESL may provide a beneficial treatment option in patients with FS or an epilepsy diagnosis, including those aged \( \geq 65 \) years in the LTC setting.

This study has several strengths. It used real-world data to characterize a patient population with FS from a LTC setting, and is likely more representative than patients evaluated in a controlled trial setting. The source of LTC data includes data from large group provider organizations and other multiple independent pharmacies. Hence, the data coverage may be representative of the LTC marketplace. However, there were several limitations to the study. The professional fee claims/prescription claims/CDM/LTC pharmacy data sources used for the study are open-source databases and do not capture healthcare activity/consumption at nonparticipating pharmacies, offices, and hospitals. LTC settings differ in the way residents access care. Physicians may visit residents in nursing homes or an ICF for individuals with IDD, while residents in an ALF may have an outpatient office visit to see their physician. Proxies implemented for continuous enrollment may not completely capture continuous eligibility. Linkage to CDM was not mandated as patients in the CDM database have \( \geq 1 \) hospital visit. Inclusion of patients from prescription and professional fee claims and CDM may have introduced strong selection bias towards patients having \( \geq 1 \) hospitalization. Comparison data describing HCRU in patients who initiated ASDs other than ESL, or who continued a prior regimen, were not included as a part of current study objective, but these patients represent an area of future research. The single group pre/post study design does not address history and/or maturation bias associated with time spent in LTC and other time-varying factors, such as ageing, changes in severity, and therapy over time. Time in LTC was captured using a proxy by measuring days between first and last LTC pharmacy claim and index date for pre-index and post-index periods, respectively. This may not capture time spent out of the LTC setting, such as when a patient was discharged and then readmitted to the LTC setting within the pre- and post-index periods. Some diagnoses, such as cognitive impairment, mental health disorders, and alcohol/drug dependence, are likely underreported or miscoded in claims data sources. The results from the current study could be augmented in future studies by supplementing claims data with data from electronic medical records or patient charts, which could provide information on reasons for initiating ESL and baseline seizure frequency. Future studies could also identify causative factors (e.g., efficacy, adherence, complexity of dosing regimen [15, 16, 38–42]) associated with the reduction in HCRU.

CONCLUSIONS

In conclusion, this real-world study of patients with FS demonstrates that initiation of ESL in a LTC setting was associated with statistically
significant reductions in epilepsy-related physician visits, ED visits, inpatient hospitalizations, and all-cause physician visits and inpatient hospitalizations. ESL treatment in a LTC setting may lead to reductions in HCRU and associated costs over 1 year among this population.

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Compliance with Ethics Guidelines. IQVIA’s New Data Warehouse data are de-identified in compliance with the Health Insurance Portability and Accountability Act; therefore, this study did not constitute Human Subjects Research, and review by an institutional review board was not required (US Department of Health and Human Services).

Data Availability. The datasets generated and/or analyzed during the current study are not publicly available due to a licensing agreement with IQVIA’s New Data Warehouse.

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