Evaluation of persistence and healthcare utilization in patients treated with anti-seizure medications as add-on therapy: A nationwide cohort study in South Korea

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A R T I C L E   I N F O
Article history:
Received 5 August 2021
Revised 12 November 2021
Accepted 21 November 2021
Available online 10 December 2021

Keywords:
Anti-seizure medication
Epilepsy
Add-on therapy
Adherence
Persistence
Healthcare utilization

A B S T R A C T
Objective: To compare medication adherence and healthcare utilization among patients who were treated with anti-seizure medications (ASMs) as first add-on to monotherapy for epilepsy using the national health insurance claims data.

Methods: A retrospective observational cohort study was conducted using the Korean National Health Insurance claims data. Patients who received ASM as first add-on to monotherapy during January 2017 to February 2018 were included. The selected patients were followed up for 12 months to evaluate persistence, adherence, and healthcare resource utilization.

Results: In total, 4277 patients who received ASM as first add-on to monotherapy for epilepsy were enrolled. The mean treatment duration of add-on ASM was 296.6 ± 108.6 days during the 1-year follow-up period and 64.3% of the total population were persistent on the add-on ASM at 365 days from the index date. The mean medication possession ratio (MPR) was 90.3 ± 23.7 and the proportion of adherent patients with ≥80% MPR was 79.3%. Lamotrigine (LTG), levetiracetam (LEV), oxcarbazepine (OXC), and perampanel (PER) groups showed significantly higher persistence and adherence than carbamazepine (CBZ), topiramate (TPM), and valproate (VAL) groups during the 1-year follow-up period. Significant differences in length of stays, total hospitalization cost, outpatient visit cost, and emergency cost were shown between ASM groups and LTG, LEV, OXC, and PER showed relatively low utilization and cost.

Conclusions: Better adherence was observed in LTG, LEV, OXC, and PER groups than in CBZ, TPM, and VAL groups. Healthcare utilization and related costs showed significant difference between ASM groups.

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1. Introduction

In 2016, approximately 50 million people worldwide had epilepsy and more than 13 million disability-adjusted life-years (DALYs) were lost to epilepsy, accounting for 0.5% of the total disease burden in global population [1]. About half of the global population reside in Asian countries and epilepsy has been estimated to affect about 23 million people in Asian population. The prevalence of epilepsy was 700 per 100,000 globally and the rates in Asia were reported to be ranged between 1.5 and 14.0 per 1000 [2].

According to the International League Against Epilepsy (ILAE), epilepsy is one of the medical conditions that cannot be cured but can be managed with the appropriate use of anti-seizure medications (ASMs) for at least 2 years [3]. Therefore, it is important to choose therapeutic treatments that allows the best seizure control and has fewer adverse effects for individual patient [4].

In general, ASM monotherapy is used as the first line of treatment for epilepsy; however, full seizure control may be achieved in about 70% of the newly diagnosed patients. The remaining patients either switch to alternative monotherapy or add ASM along with their monotherapy [3]. Despite the benefit of the add-on therapy, the use of ASM combination therapy is reported to be associated with non-adherence which increases the risk of poor seizure control and eventually leads to increased risk of morbidity, lowered quality of life, and economic burden in adult patients with...
epilepsy [1,5–7]. However, lack of studies evaluated the adherence of add-on therapy for the general population with epilepsy. Although the good efficacy of initial monotherapy is well known, combination therapy is inevitable to control epilepsy in some patients [8,9]. Since there have been many new ASMs developed over the last few decades, it is important to identify effective and tolerable add-on therapy scheme. Therefore, the present study aimed to compare medication adherence and healthcare utilizations among patients who were treated with ASMs as first add-on to monotherapy for epilepsy using the national health insurance claims data. In this study, carbamazepine (CBZ), lamotrigine (LTG), levetiracetam (LEV), oxcarbazepine (OXC), perampanel (PER), topiramate (TPM), and valproate (VAL) were considered as the target ASMs as these are the most commonly prescribed ASMs as add-on therapy in Korea [10].

2. Material and methods

2.1. Data sources

A retrospective observational cohort study was conducted using the Korean National Health Insurance claims data retrieved from the Health Insurance Review and Assessment (HIRA) database. The Health Insurance Review and Assessment (HIRA) database contains socio-demographic and medical information such as treatments, drug prescriptions, procedures, and diagnosis for approximately 50 million beneficiaries. Since 98% of citizens in South Korea are covered by the National health insurance scheme, the HIRA data represent the entire Korean population [11]. Diagnoses were coded using the Korean Standard Classification of Diseases, 7th revision (KCD-7) codes, which are based on the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) codes. Treatment and surgical procedures were coded using the HIRA procedure codes whereas pharmaceutical prescriptions were coded using the HIRA drug codes. Ethics approval for this study was waived by the Seoul National University Hospital (E-1905-082-1034) as it did not require direct contact of the study participants. In addition, this study was approved by the HIRA review committee (M20191111139).

2.2. Study population

Patients who received ASM added to monotherapy from 01 January 2017 to 28 February 2018 were included. Add-on to monotherapy was determined as one of 7 target ASMs was added to a single ASM and overlapped ≥84 days from the index date with a grace period of 15 days. Among them, those who were treated with ASM monotherapy for at least 14 days, diagnosed with epilepsy, and were on ASM treatments for at least 120 days during the baseline period (12 months before the index date) were selected. Patients who were below 12 years of age and received non-targeted ASMs for add-on therapy at the index date were excluded. The details of the patient selection process are presented in Fig. 1 and Supplementary Table 1. The selected patients were followed up for 12 months to evaluate persistence, adherence, and healthcare resource utilization.

2.3. Study outcomes

Persistence was measured as the proportion of patients persistent on the index add-on ASM from the index date which was defined as the first prescription date of the targeted ASM prescribed for the add-on to monotherapy. Patients were considered persistent on their add-on treatment if they renewed their index add-on ASM within a defined grace period of 50% of days' supply of the previous index add-on ASM. Time on treatment was defined as the number of days from initiation of add-on ASM to discontinuation during the follow-up period. Treatment adherence was evaluated using the medication possession ratio (MPR). Adherent group was defined as having MPR of 80% or greater whereas those with less than 80% were defined to be non-adherent. MPR was calculated as the percentage of the total number of days' supply of a prescribed index add-on ASM during the follow-up period. Healthcare resource utilization and cost were assessed by hospitalizations, outpatient and emergency visits within 12 months from the index date for all-cause and epilepsy-related cases separately. The epilepsy-related utilization was defined as a medical service with a primary diagnosis of epilepsy. The cost was converted to USD from KRW with the average foreign exchange rate in the year of 2017 (1 US Dollar = 1178.585 South Korean Won) [12]. The healthcare utilization and cost were assessed among users of each

![Fig. 1. Flow chart of patient selection. ASM, anti-seizure medication.](image-url)
healthcare service. Relevant diagnosis and procedure codes used to measure the outcome events are listed in Supplementary Table 2.

2.4. Statistical analysis

A descriptive analysis was performed to evaluate all outcomes including baseline characteristics. Patients’ demographic characteristics and comorbidities were ascertained from the Korean HIRA database and the detailed definitions of comorbidities are presented in Supplementary Table 3. Continuous variables were presented using mean and standard deviation (SD). Categorical variables were presented using frequencies and percentages (%). Chi-square test and Kruskal Wallis test were conducted to compare categorical and continuous variables, respectively. Using the Kaplan–Meier estimate, the probability of ASM continuation was measured for each ASM group during 1-year follow-up period. The continuation probability between ASM groups were compared using log-rank test.

For healthcare utilizations, the average number of admissions, outpatient and emergency department visits were calculated per patient. Also, the average length of stay per admission was calculated. Incidence per person-year was calculated using the number of events during the follow-up period divided by person-year at risk of each healthcare utilization. The differences in the incidence rates of healthcare resource utilization per 1 person-year by ASM group was compared using poison regression model.

All statistical tests were conducted using two-sided tests with a significance level of 0.05 and performed using SAS 9.3 software (SAS Institute, North Carolina, US) via SAS Enterprise Guide version 6.1.

3. Results

3.1. Baseline characteristics

In total, 4277 patients who received ASM as add-on to monotherapy for epilepsy during the period from January 2017 to February 2018 were eligible for analysis. Of 4277 eligible patients, 372 patients, 502 patients, 1115 patients, 306 patients, 276 patients, 505 patients, and 1201 patients received CBZ, LTG, LEV, OXC, PER, TPM, and VAL as add-on to monotherapy at the index date, respectively. The mean age of the total study population was 41.1 ± 19.7 years. LTG, LEV, OXC, and PER groups were younger, had less comorbidities including neurological diseases, and had higher proportion of patients with the medical aid coverage than CBZ, TPM, and VAL. Further, the add-on therapy with LTG, LEV, OXC, and PER were mainly prescribed at tertiary hospitals whereas CBZ, TPM, and VAL add-on therapy were prescribed at clinics (Table 1).

3.2. Persistence and adherence

The mean treatment duration of ASMs add-on to monotherapy was 296.6 ± 108.6 days during the 12 months of follow-up period and 64.3% of the total population were persistent on their index ASM add-on at 365 days from the index date. The treatment durations were significantly longer in LTG, LEV, OXC, and PER groups than in CBZ, TPM, and VAL groups (p < 0.0001). Similarly, the persistence rate was significantly higher in LTG, LEV, OXC, and PER groups than in CBZ, TPM, and VAL groups (p < 0.0001) (Fig. 2). In addition, similar trend of persistence rate was observed in LTG, LEV, OXC, and PER group (categorized as Group 1) and in CBZ, TPM, and VAL groups (categorized as Group 2). The trend of persistence rate was significantly different between Group 1 and Group 2 during the 12 months of follow-up period (p < 0.001) (Supplementary Fig. 1). Until the 90th day from the index date, the persistence rates for all add-on ASM groups were above 90%, whereas the rates were decreased to 80% or below at 180 days. The mean MPR was 90.31 ± 23.7 and the proportion of adherent patients with ≥80% MPR was 79.3%. The trends in the proportion of adherent patients between the add-on ASM groups were somewhat similar to the trends observed for persistence where LTG, LEV, OXC, and PER groups showed significantly higher adherence than those in CBZ, TPM, and VAL groups (p < 0.0001) (Table 2).

3.3. Healthcare utilization and cost

Of 4277 patients, 37.6% and 10.2% experienced ≥1 all-cause and epilepsy-related admissions during the following period, respectively. The mean number of admissions (per person) and length of stay (per admission) was 2.3 and 31.4 days for all-cause and 1.4 and 20.3 days for epilepsy-related cases. The mean total cost was 7546 USD for all-cause and 3588 USD for epilepsy-related admissions. The significant differences in the length of stay (p < 0.0001) and total admission costs (p < 0.0001) were observed between the add-on ASM groups. The lowest length of stay was observed in LTG for all-cause and epilepsy-related admissions. PER and LEV had the lowest cost for all-cause and epilepsy-related admissions, respectively (Table 3).

The mean number of outpatient visit was 28.1 and 6.4 for all-cause and epilepsy-related visits during the 12 months of follow-up period. The mean total cost (per person) was 1281 USD for all-cause and 272 USD for epilepsy-related outpatient visits. Regardless of the cause of visits, the outpatient visit costs were significantly different between study groups. The lowest cost was observed in PER for all-cause and LTG for epilepsy-related outpatient visits (Table 3).

Of the total population, 29.8% and 7.2% had ≥1 emergency department visits. On average, patients had 2.2 all-cause and 1.4 epilepsy-related emergency visits during the follow-up period. The costs for all-cause emergency department visits differed significantly across the study groups, with the lowest cost observed in PER (p < 0.0001) (Table 3).

4. Discussion

4.1. Discussion

In our study better adherence was observed in LTG, LEV, OXC, and PER groups than in CBZ, TPM, and VAL groups. Better adherence in LTG, LEV, OXC, and PER are consistent with the findings observed from previous studies. A recent retrospective cohort study using the private insurance claims databases in the United States reported relatively high ASM persistence in patients who received LTG, OXC, and LEV than those who received phenytoin (PHT) and valproic acid (VAL) as initial ASM monotherapy [13]. The SANAD study, an unblinded randomized controlled trial conducted in United Kingdom, found that patients treated with LTG had 0.78 and 0.65 times significantly lower risk of discontinuation compared to those who had CBZ and gabapentin (GPN), respectively. Meanwhile, the risk of discontinuation did not differ between patient who received TPM, CBZ, and GPN [14]. In Korea, a retrospective medical record-based study reported 3-year retention rate of 81.2%, 78.3% and 54.7% for patients who received LEV, TPM, and OXC, respectively. Similar to our study, LEV showed a higher retention rate, however, the rate for OXC was significantly lower than for TPM, showing an opposite trend from our study [15].

In addition, findings from our study showed higher persistence and adherence rates than previous retrospective studies that were conducted using claims or medical records data. Faught et al. found
Comorbidities such as mCCI score and neurological comorbidities were measured during the baseline period (1 year before the index date). Demographic and socioeconomic characteristics such as age, sex, and insurance type, hospital type, and epilepsy type were measured at the index date. All values are presented as percentages or mean and standard deviation. P-value was derived from the individual chi-square test or Kruskal–Wallis test.

ASM indicates Anti-seizure medication; Mono: Monotherapy; LTG: Lamotrigine; LEV: Levetiracetam; OXC: Oxcarbazepine; PER: Perampanel; CBZ: Carbamazepine; TPM: Topiramate; VAL: Valproate; mCCI: modified Charlson Comorbidity Index; SD: Standard Deviation.

Table 1
Baseline characteristics of study population by index add-on anti-seizure medication (ASM).

| Variables                      | Overall (N = 4277) | Mono + LTG (N = 502) | Mono + LEV (N = 1115) | Mono + OXC (N = 306) | Mono + PER (N = 276) | Mono + CBZ (N = 372) | Mono + TPM (N = 505) | Mono + VAL (N = 1201) | p-Value |
|--------------------------------|--------------------|----------------------|-----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|---------|
| Age, years (mean ± SD)         | 41.4 ± 19.7        | 34.6 ± 18.3          | 41.3 ± 20.3           | 39.2 ± 20.2          | 35.8 ± 16.2          | 50.3 ± 17.6          | 40.0 ± 18.3          | 43.9 ± 20.0          | <0.0001 |
| Sex                            |                    |                      |                       |                      |                      |                      |                      |                      |         |
| Female                         | 45.7               | 53.2                 | 45.5                  | 43.8                 | 52.5                 | 48.4                 | 52.3                 | 38.1                 | <0.0001 |
| Male                           | 54.3               | 46.8                 | 54.5                 | 56.2                 | 47.5                 | 51.6                 | 47.7                 | 62.0                 |         |
| Insurance type                 |                    |                      |                       |                      |                      |                      |                      |                      |         |
| Medical aid                    | 19.3               | 10.2                 | 16.4                 | 13.7                 | 12.3                 | 28.8                 | 19.2                 | 25.9                 | <0.0001 |
| Health insurance               | 80.7               | 89.8                 | 83.6                 | 86.3                 | 87.7                 | 71.2                 | 80.8                 | 74.1                 |         |
| mCCI, Score (mean ± SD)        | 1.3 ± 1.8          | 1.0 ± 1.6            | 1.3 ± 2.0            | 1.2 ± 1.6            | 0.7 ± 1.2            | 1.5 ± 1.9            | 1.2 ± 1.8            | 1.4 ± 1.9            | <0.0001 |
| Neurological comorbidity       |                    |                      |                       |                      |                      |                      |                      |                      |         |
| Depression                     | 24.3               | 22.5                 | 16.8                 | 19.6                 | 15.9                 | 30.1                 | 27.7                 | 31.8                 | <0.0001 |
| Anxiety disorders              | 29.3               | 27.5                 | 23.7                 | 25.8                 | 19.2                 | 35.2                 | 34.1                 | 34.6                 | <0.0001 |
| Bipolar disorder               | 12.4               | 15.9                 | 6.7                  | 4.9                  | 2.5                  | 13.2                 | 14.1                 | 19.2                 | <0.0001 |
| Schizophrenia                  | 8.4                | 8.2                  | 4.4                  | 3.9                  | 2.2                  | 12.1                 | 9.7                  | 13.2                 | <0.0001 |
| Mental retardation             | 6.7                | 6.2                  | 4.1                  | 6.2                  | 4.0                  | 8.6                  | 6.7                  | 9.6                  | <0.0001 |
| Hospital type                  |                    |                      |                       |                      |                      |                      |                      |                      |         |
| Clinic                         | 8.3                | 4.2                  | 4.5                  | 5.9                  | 1.1                  | 18.0                 | 10.9                 | 11.7                 | <0.0001 |
| Hospital                       | 9.4                | 3.6                  | 6.1                  | 2.0                  | 0.4                  | 17.7                 | 8.9                  | 16.5                 |         |
| General hospital               | 32.9               | 27.3                 | 38.0                 | 29.7                 | 24.6                 | 27.7                 | 35.8                 | 33.6                 |         |
| Tertiary hospital              | 49.4               | 64.9                 | 51.4                 | 62.4                 | 73.9                 | 36.6                 | 44.4                 | 38.1                 |         |
| Types of epilepsy              |                    |                      |                       |                      |                      |                      |                      |                      |         |
| Partial seizure                | 15.3               | 16.7                 | 17.0                 | 19.3                 | 25.7                 | 10.8                 | 16.2                 | 10.8                 | <0.0001 |
| Generalized seizure            | 7.8                | 11.6                 | 9.6                  | 4.6                  | 4.0                  | 4.8                  | 7.5                  | 7.2                  |         |
| Unspecified seizure            | 39.3               | 44.6                 | 43.1                 | 47.1                 | 58.7                 | 29.6                 | 35.1                 | 31.9                 |         |
| Others                         | 37.6               | 27.1                 | 30.4                 | 29.1                 | 11.6                 | 55.1                 | 41.2                 | 50.0                 |         |

Overall persistence rate of 61.4%, 36.5%, and 24.2% at 6 months, 1 year, and 2 years, respectively, for ASM monotherapy. At 1 year from the initial polytherapy, between 26.8% and 44.3% of patients remained on the initial treatment [13]. In Korea, retrospective studies that assessed persistence of PER as an add-on therapy using medical records reported retention rates between 37.5% and 61.0% [16,17]. Another study that used the U.S. private health insurance claims database to assess the adherence of ASMs among patients diagnosed with epilepsy found 60.72% of overall adherence rate with mean MPR of 78% [18]. In contrast to our study, a retrospective study assessing the adherence of pediatric patients with epilepsy in Korea reported 91.64%, 88.99%, and 87.29% of the adherence rate at 1, 2, and 3 years, respectively [19]. However, most studies were conducted using small sample sizes with various study designs applied. The study population and therapeutic approach (monotherapy vs. add-on therapy) varied across studies, thus direct comparison with our study findings may not be appropriate.

We found that the overall persistence rates by ASM groups were relatively similar until the 90th day of initiation of the add-on ASM; however, the rates began to show difference from the 90th day. This finding was consistent with a retrospective electronic medical record-based study that evaluated the retention rates and long-term tolerability of new antiepileptic drugs. Most of the discontinuation of ASM happened within 6 months from the initiation of the prescribed ASM [20].

Healthcare cost and utilizations can be used as one of the indications of seizure control. We found significant differences in length of stays, total hospitalization cost, outpatient visit cost, and emergency cost across ASMs and LTG, LEV, OXC, and PER showed relatively low utilization and cost. It might suggest that better adherence of LTG, LEV, OXC, and PER could contribute to the control of epilepsy and consequently it may lead to potential alleviation of disease burdens of epilepsy. However, limited studies are available on the utilization and cost associated with add-on ASMs and previous findings on healthcare service utilization cannot be directly compared with this study. A claims-based study that assessed healthcare utilization and costs among patients with epilepsy found significant reductions in epilepsy-related hospitalizations and emergency department visits in patients who received levetiracetam as an add-on therapy [21]. Previous studies comparing healthcare utilization and cost of patients with well-controlled and uncontrolled seizure reported that the cost and healthcare utilization were higher in...
uncontrolled epilepsy group than those whose seizures were well-controlled [22,23]. In addition, the healthcare utilization and costs of epilepsy could be affected by patients’ socio-demographics including gender, age, and comorbidity [24–28]. According to Jung et al., the economic burden of epilepsy was higher in male compared to female and the age group of 40–49 showed the highest economic burden. Several studies reported that the presence of comorbidity was associated with the economic burden of epilepsy. A retrospective study using claims database reported that the odds of hospitalization was 3.7 times higher in patients with CCI 1 compared to those without comorbidities and depression was the costly comorbidity. Similarly, Wilner et al. reported that the healthcare cost was 3 times higher in patients with 1 comorbidity compared to those who did not have any comorbidities. However, the impacts of the adherence and socio-demographics on the healthcare cost have not been investigated in this study and further studies could be considered to demonstrate the association of the adherence and socio-demographics with the healthcare utilization and cost in patients with epilepsy.

Table 2: Persistence and adherence of index add-on anti-seizure medication (ASM).

| Persistence & adherence | Overall | Type of Index ASM | p-value |
|-------------------------|---------|-------------------|---------|
|                         | (N = 4277) | Mono + LTG (N = 502) | Mono + LEV (N = 1115) | Mono + OXC (N = 306) | Mono + PER (N = 276) | Mono + CBZ (N = 372) | Mono + TPM (N = 505) | Mono + VAL (N = 1201) |
| Persistence             |         |                   |         |                   |         |                   |                   |                   |
| Time on treatment (days; mean ± SD) | 296.6 ± 108.6 | 297.9 ± 116.6 | 309.1 ± 101.7 | 308.5 ± 102.7 | 308.8 ± 99.4 | 287.1 ± 108.4 | 285.3 ± 110.7 | 286.2 ± 112.1 |
| Cumulative persistence rate (%) | <0.0001 |                   |         |                   |         |                   |                   |                   |
| 30 days                 | 95.3    | 91.8              | 95.8    | 95.8              | 97.5    | 96.2              | 96.6              | 94.8              |
| 60 days                 | 94.1    | 90.6              | 95.0    | 94.8              | 95.7    | 94.4              | 95.0              | 93.7              |
| 90 days                 | 93.4    | 89.6              | 94.7    | 94.1              | 95.3    | 93.3              | 94.5              | 92.8              |
| 180 days                | 80.3    | 80.3              | 84.0    | 85.0              | 83.3    | 79.0              | 75.8              | 77.4              |
| 270 days                | 71.7    | 74.5              | 77.0    | 77.1              | 75.4    | 66.4              | 65.7              | 67.4              |
| 365 days                | 64.3    | 67.7              | 70.3    | 69.6              | 70.3    | 57.0              | 58.4              | 59.1              |
| Adherence               |         |                   |         |                   |         |                   |                   |                   |
| MPR (mean ± SD)         | 90.31 ± 23.7 | 94.07 ± 19.3 | 93.43 ± 22.0 | 93.08 ± 22.9 | 91.71 ± 24.3 | 85.53 ± 24.5 | 84.75 ± 27.1 | 88.64 ± 24.5 |
| Adherence rate (%)      | <0.0001 |                   |         |                   |         |                   |                   |                   |
| Adherent (MPR > 80%)    | 79.3    | 85.1              | 84.1    | 83.0              | 82.6    | 71.0              | 70.7              | 76.9              |
| Non-adherent (MPR <80%) | 20.7    | 14.9              | 15.9    | 17.0              | 17.4    | 29.0              | 29.3              | 23.1              |

ASM indicates Anti-seizure medication; MPR: Medication possession ratio; Mono: Monotherapy; LTG: Lamotrigine; LEV: Levetiracetam; OXC: Oxcarbazepine; PER: Perampanel; CBZ: Carbamazepine; TPM: Topiramate; VAL: Valproate; MPR: Medication possession ratio; SD: Standard Deviation.

P-value was derived from the individual chi-square test or Kruskal–Wallis test for time on treatment and medication adherence. P-value for cumulative persistence rate was derived from log-rank test.
Table 3
Healthcare utilization and cost by index add-on anti-seizure medication (ASM).

| Healthcare utilization | Overall | Type of Index ASM | p-value |
|-----------------------|---------|-------------------|---------|
|                       | (N = 4277) | Mono + LTC (N = 502) | Mono + LEV (N = 1115) | Mono + OXC (N = 306) | Mono + PER (N = 276) | Mono + CBZ (N = 372) | Mono + TPM (N = 505) | Mono + VAL (N = 1201) |
| All-cause HCRU        |         |                   |         |                   |                   |                   |                   |                   |
| Hospitalization       |         |                   |         |                   |                   |                   |                   |                   |
| Patients ≥1 admission (%) | 1608(37.6) | 146(29.1) | 428(38.4) | 116(37.9) | 141(45.1) | 172(34.1) | 518(43.1) | <0.0001 |
| Incidence rate (per PYs) | 0.52 | 0.05 | 0.54 | 0.52 | 0.33 | 0.44 | 0.65 | 0.59 |
| Number of admissions (per person) | 2.3 ± 3.2 | 2.6 ± 4.2 | 2.4 ± 3.0 | 2.6 ± 5.5 | 1.9 ± 1.8 | 2.4 ± 2.3 | 2.0 ± 1.9 | 2.3 ± 3.1 | 0.39 |
| Length of stay (per admission) | 31.4 ± 70.7 | 10.3 ± 65.5 | 30.2 ± 65.5 | 13.2 ± 34.2 | 14.3 ± 41.9 | 42.7 ± 78.4 | 27.3 ± 62.8 | 43.8 ± 88.4 | <0.0001 |
| Total hospitalization cost (USD) | 7546 ± 11897.9 | 7772 ± 8783.8 | 5539 ± 13183.2 | 8883 ± 14359.2 | 4906 ± 9118.0 | 6096 ± 10234.4 | 6324 ± 10320.9 | 8054 ± 11090.0 | <0.0001 |
| Out-patient visit      |         |                   |         |                   |                   |                   |                   |                   |
| Patients ≥1 visit (%)  | 4233(99.0) | 501(99.8) | 1103(98.9) | 306(100.0) | 275(99.6) | 368(98.9) | 502(99.4) | 1178(98.1) | <0.0001 |
| Incidence rate (per PYs) | 39.51 | 132.90 | 38.12 | 95.46 | 132.07 | 31.29 | 52.04 | 24.67 | <0.0001 |
| Number of visits (per person) | 28.1 ± 29.6 | 27.3 ± 27.1 | 25.6 ± 28.1 | 27.4 ± 28.4 | 25.7 ± 23.1 | 34.6 ± 33.4 | 28.3 ± 29.9 | 29.4 ± 32.0 | <0.0001 |
| Total outpatient visit cost | 1281 ± 2715.7 | 1475 ± 2624.6 | 1405 ± 3640.1 | 1188 ± 2333.8 | 969 ± 1393.1 | 1487 ± 4421.3 | 1229 ± 1849.0 | 1297 ± 2570.5 | <0.0001 |
| Emergency department visit | 1275(29.8) | 147(29.3) | 369(33.1) | 86(28.1) | 70(25.4) | 95(25.5) | 140(27.7) | 368(30.6) | <0.0001 |
| Patients ≥1 visit (%)  | 438(10.2) | 45(9.0) | 140(12.6) | 48(15.7) | 27(9.8) | 18(4.8) | 44(8.7) | 116(9.7) | <0.0001 |
| Incidence rate (per PYs) | 0.11 | 0.10 | 0.14 | 0.18 | 0.10 | 0.05 | 0.09 | 0.11 | <0.0001 |
| Number of admissions (per person) | 1.4 ± 1.0 | 1.5 ± 1.0 | 1.4 ± 1.3 | 1.3 ± 0.7 | 1.3 ± 0.5 | 1.8 ± 1.9 | 1.4 ± 0.8 | 1.3 ± 0.6 | 0.7857 |
| Length of stay (per admission) | 20.3 ± 61.7 | 33.4 ± 40.0 | 23.8 ± 58.8 | 7.1 ± 12.2 | 4.9 ± 5.7 | 17.1 ± 24.0 | 14.9 ± 49.6 | 35.6 ± 96.3 | <0.0001 |
| Total hospitalization cost (USD) | 3588 ± 6939.9 | 3223 ± 3981.9 | 2732 ± 5924.0 | 4101 ± 8681.9 | 2741 ± 4187.7 | 2795 ± 3099.2 | 3220 ± 6244.9 | 4024 ± 7237.2 | 0.7558 |
| Out-patient visit       |         |                   |         |                   |                   |                   |                   |                   |
| Patients ≥1 visit (%)  | 2996(70.0) | 405(80.7) | 871(78.1) | 234(76.5) | 257(93.1) | 199(53.5) | 322(63.8) | 708(59.0) | <0.0001 |
| Incidence rate (per PYs) | 2.12 | 3.54 | 3.09 | 2.92 | 11.41 | 1.07 | 1.66 | 1.33 | <0.0001 |
| Number of visits (per person) | 6.4 ± 5.0 | 6.5 ± 4.8 | 6.3 ± 3.8 | 6.4 ± 6.2 | 6.1 ± 3.4 | 6.0 ± 4.0 | 6.4 ± 4.2 | 6.7 ± 6.7 | 0.4144 |
| Total outpatient visit cost (USD) | 272 ± 329.9 | 220 ± 295.9 | 319 ± 365.0 | 262 ± 284.3 | 263 ± 308.9 | 295 ± 561.4 | 254 ± 275.3 | 274 ± 292.5 | 0.0012 |
| Emergency department visit | 308(7.2) | 34(6.8) | 108(9.7) | 26(8.5) | 14(5.1) | 11(3.0) | 29(5.7) | 86(7.2) | <0.0001 |
| Patients ≥1 visit (%)  | 0.08 | 0.07 | 0.05 | 0.04 | 0.05 | 0.06 | 0.06 | 0.08 | 0.0004 |
| Incidence rate (per PYs) | 1.4 ± 1.0 | 1.6 ± 1.2 | 1.3 ± 1.3 | 1.3 ± 0.7 | 1.3 ± 0.3 | 1.5 ± 1.1 | 1.4 ± 0.9 | 0.5059 | <0.0001 |
| Number of visits (per person) | Total emergency visit cost (USD) | 1478 ± 2206.5 | 933 ± 777.3 | 1122 ± 1273.3 | 1576 ± 2528.5 | 672 ± 746.7 | 1827 ± 1982.8 | 1118 ± 997.7 | 1712 ± 2630.7 | 0.5597 |

HCRU indicates Healthcare cost and resource utilization; ASM: Anti-seizure medication; Mono: Monotherapy; LTG: Lamotrigine; LEV: Levetiracetam; OXC: Oxcarbazepine; PER: Perampanel; CBZ: Carbamazepine; TPM: Topiramate; VAL: Valproate; PYs: Person years; SD: Standard Deviation; USD: U.S. dollars.

Healthcare utilization was measured among healthcare users only.

The number of patients with ≥1 visit is presented as the frequency and percentages and the number of visits and total cost are presented as mean ± SD.

P-values for incidence rate per person-years was derived from Poisson regression model whereas the p-values for length of stay and the number of admissions and visits were derived from Kruskal–Wallis test.

All-cause healthcare utilization refers to all hospital visits whereas epilepsy-related healthcare utilization refers to visits in relation to epilepsy.
4.2. Limitations

Several limitations should be taken into consideration for interpretation of the results. First, due to the nature of the claims data, it was not possible to verify whether the prescribed medication was taken by the patient. Second, the claims data do not provide information on the reason for discontinuation of medication; therefore, we cannot distinguish whether the withdrawal from ASM was due to patients’ needs or preferences on the therapeutic approach. Third, there was a possibility of miscategorizations and coding errors that may have led to underestimation or overestimation of the epilepsy-related events. Although Park et al. reported approximately 70% of accuracy of KCD-7 coding for primary and secondary diagnosis recorded in the Korean national health insurance database, Lee et al. found variations in diagnostic validity for epilepsy by age and gender [19,29]. They also found that there were patients who were prescribed ASMs without the diagnostic codes for epilepsy. Furthermore, we were unable to identify details of seizure type that might impact on choice of add-on therapy owing to clinical data. Lastly, the duration of epilepsy was not investigated in this study and it should be cautiously considered when interpreting the results of our study.

5. Conclusions

Better adherence was observed in LTM, LEV, OXC, and PER groups than in CBZ, TPM, and VAL groups. For healthcare utilization, the incidence rates of all-cause hospitalization and emergency department visits were found to be the lowest in PER. For epilepsy-related hospitalization and emergency visits, the incidence rates were the lowest in CBZ. LEV and CBZ had the lowest incidence rates of all-cause and epilepsy-related outpatient visits, respectively. Regarding the expenses for medical care, PER showed the lowest cost for hospitalization, outpatient, and emergency visits by all cause.

Funding

This work was supported by Eisai Korea Inc and Open Access Fees were also funded by Eisai Korea Inc.

7. Data availability

The datasets generated for this study will not be publicly available as the Health Insurance Review and Assessment (HIRA), known as the provider of the National Health Insurance data, does not provide data without granting a permission from the HIRA review committee.

Declaration of Competing Interests

Jung-Ae Kim received research grants from Eisai Korea Inc and Sang Kun Lee received research grants from IQVIA Korea. Remaining authors have declared that they have no competing interests to disclose.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2021.108459.

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