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Trends of anti-seizure medication prescribing pattern in traumatic brain injury patients for the prevention of posttraumatic seizure in Taiwan

Hsin-Tien Lee [a,1], Fen-Fen Liao [b,1], Sui-Sum Kung [c], Shang-Jyh Hwang [d,e,f], Kun-Pin Hsieh [b,g,*]

[a] Master Program in Clinical Pharmacy, School of Pharmacy, College of Pharmacy, Kaohsiung Medical University, 100, Shin-Chuan 1st Road, Kaohsiung City 80708, Taiwan
[b] Department of Pharmacy, Kaohsiung Medical University Hospital, 100, Shin-Chuan 1st Road, Kaohsiung City 80708, Taiwan
[c] Division of Neurosurgery, Department of Surgery, Kaohsiung Medical University Hospital, 100, Shin-Chuan 1st Road, Kaohsiung City 80708, Taiwan
[d] School of Medicine, College of Medicine, Kaohsiung Medical University, 100, Shin-Chuan 1st Road, Kaohsiung City 80708, Taiwan
[e] Division of Nephrology, Department of Internal Medicine, Kaohsiung Medical University Hospital, 100, Shin-Chuan 1st Road, Kaohsiung City 80708, Taiwan
[f] Institute of Population Health Sciences, National Health Research Institutes, Zhunan Town, Miaoli County 350, Taiwan
[g] School of Pharmacy, College of Pharmacy, Kaohsiung Medical University, 100, Shin-Chuan 1st Road, Kaohsiung City 80708, Taiwan

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ABSTRACT

Traumatic brain injury (TBI) patients are recommended to receive anti-seizure medication (ASM) as posttraumatic seizure (PTS) prophylaxis. However, the utilization of ASM, including the prescription patterns and associated clinical characteristics, is limited in Taiwan. Thus, this study aimed to investigate the ASM trends and clinical characteristics. This retrospective cohort study enrolled TBI patients who received levetiracetam, phenytoin, and valproic acid during hospitalization using the National Health Insurance Research Database between 2012 and 2019. The primary outcome was the trend of the ASMs based on the index year. The duration of levetiracetam prescription was categorized as short-term (seven days or less) or long-term (more than seven days). Logistic regression identified the factors associated with long-term usage. A total of 64,461 TBI patients were included. Levetiracetam usage increased yearly, while phenytoin declined. Among the levetiracetam users, 5681 (30.38%) were short-term users, and 13,016 (69.62%) were long-term users. Diagnoses of contusions, intracranial hemorrhage, other intracranial injuries, receiving operations, and a history of cerebrovascular disease were significantly associated with longer duration. Conclusions This study revealed the rising trend of levetiracetam usage, indicating its potential as an alternative to phenytoin. TBI patients with more severe conditions were more likely to receive longer prescriptions.

Introduction

Traumatic brain injury (TBI) is brain damage caused by the external force [1]. It is a leading cause of injury-related death and contributes significantly to health loss and disability [2,3]. Posttraumatic seizures (PTS) are a common neurologic complication following TBI, impacting rehabilitation progress and potentiating secondary brain injury [4]. To reduce PTS, clinical practice commonly involves administering prophylactic antiseizure medications (ASMs) to TBI patients [5].

Phenytoin, valproic acid, and levetiracetam are the most frequently prescribed ASM for seizure prevention and have been proven effective in preventing PTS [6,7]. Based on the Guidelines for the Management of Severe Traumatic Brain Injury, giving 7 days of phenytoin is the standard early PTS prophylaxis in TBI patients [8]. However, concerns have been raised regarding phenytoin due to potential drug interactions and its association with adverse drug events, such as Stevens-Johnson syndrome [9]. In addition, both phenytoin and valproic acid, the first-generation ASMs, require therapeutic drug monitoring due to their narrow therapeutic index and severe adverse events [10]. Consequently, levetiracetam, a second-generation ASM, emerged as the preferred choice due to its safer pharmacology profile and comparable prevention [11]. Several randomized control trials have shown the efficacy of

Abbreviations: ASM, Anti-seizure medication; PTS, Posttraumatic seizure; TBI, Traumatic brain injury.

* Corresponding author at: School of Pharmacy, College of Pharmacy, Kaohsiung Medical University, No. 100, Shih-Chuan 1st Road, Sanmin Dist., Kaohsiung City 80708, Taiwan.
E-mail address: kphsieh@kmu.edu.tw (K.-P. Hsieh).

[1] Hsin-Tien Lee and Fen-Fen Liao have equal contributions to this article.

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levetiracetam for early PTS prevention in severe TBI patients compared to phenytoin [12,13].

According to previous surveys conducted by neurological physicians and specialists in the UK, levetiracetam has become the preferred prophylaxis over phenytoin and valproic acid [14]. In Taiwan, adherence to guidelines is typically observed in initiating PTS prevention and ASM usage [8]. Despite this, research on ASM utilization remains limited, and insights into the prescription practices specific to Taiwan are lacking. Considering the significance of PTS prevention and the distinct circumstances in Taiwan compared to other countries, it is crucial to understand the clinical prescription pattern in Taiwan.

Levetiracetam has been approved for use in treating seizures in Taiwan since 2008. In Taiwan, adherence to guidelines is typically observed in initiating PTS prevention, and ASM Studies have reported the extended duration of levetiracetam usage in Taiwan [15]. Levetiracetam is recommended to be prescribed for one week to prevent early post-traumatic seizures (PTS) rather than being employed for a more extended period to reduce late PTS incidence. Despite the considerable advancements in the short-term efficacy and safety profiles of ASMs, the research on the long-term use of ASMs remained uncertain. Unraveling the factors that influence the decision regarding the duration of levetiracetam usage is essential. Thus, this study aimed to investigate the ASM trends and identify potential factors associated with the duration of prescribed levetiracetam among TBI patients for PTS in Taiwan.

Methods

Study design and data sources

This retrospective cohort study utilized data extracted from Taiwan's National Health Insurance Research Database (NHIRD) between January 2011 and December 2020. NHIRD is a population-based claims database containing health records for nearly 99 % of the 23 million population of Taiwan[16]. The datasets of NHIRD include detailed information on outpatients, hospitalizations, and prescription details. The diagnostic coding follows the International Classification of Diseases, 9th and 10th Revision, Clinical Modification (ICD-9-CM and ICD-10-CM). The de-identified ID was employed to protect individual privacy. This study was approved by the Institutional Review Board of Kaohsiung Medical University Hospital on October 22, 2022 (KMUHIRB-E(I)-20220187).

Cohort selection

We included newly admitted-diagnosed traumatic brain injury patients between January 1, 2012, and December 31, 2019. TBI patients were identified by the records of ICD-9-CM and ICD-10-CM diagnosis codes in inpatient records (ICD-9-CM: 800, 801, 803, 804, 850, 851, 852, 853, 854, 959.01; ICD-10-CM: S02.0, S02.1, S02.8, S02.9, S06, S07, S09.8, S09.9). In this study, levetiracetam, phenytoin, and valproic acid were defined as the primary ASMs, while other ASMs were defined as the second-line ASMs. Patients who received the primary ASMs in hospitalization were included. The first TBI diagnosis date from the emergency room or hospitalization was selected as the index date. Patients with the following characteristics were excluded: those under 20 years old, with seizure records within one year before the index date, with unknown sex data, who received more than one primary ASM, and who received second-line ASMs during hospitalization. To classify the prophylaxis of ASM, patients with multiple ASM use records during hospitalization were identified as patients who had experienced seizures during the hospital stay and were excluded.

Exposure definition

The analysis cohort consisted of patients who received one primary ASM as monotherapy during hospitalization and were categorized into three groups: levetiracetam users, phenytoin users, and valproic acid users. Within the levetiracetam user subgroup, the cohort was further divided based on the prescription duration within one year after the index date, including short-term users (seven days or less) and long-term users (more than seven days). The duration was calculated from the index date to the date of discontinuation after discharge. Anatomical Therapeutic Chemical (ATC) codes of the antiseizure medications for this study were summarized in the Supplement Table S1.

Covariates

Baseline characteristics were assessed of sex, age, type of TBI, whether an operation was performed in hospitalization, data of comorbidities, Charlson Comorbidity Index (CCI) score[17], division classification, and income level within one year before the index date. The age group was divided into two groups (20–64 and ≧65). The type of TBI included contusions, concussion, skull fracture, intracranial hemorrhage, and other intracranial injuries (see Supplement Table S2). Operations were recorded in NHI codes summarized in Supplement Table S3. Comorbidities and CCI were identified using ICD-9-CM and ICD-10-CM and included hypertension, diabetes, cerebrovascular disease, alcoholism, and chronic kidney disease (CKD) stage five and end-stage renal disease (ESRD).

Study outcomes

Initially, we conducted the trends among ASMs between 2012 and 2019. The proportions of ASMs of each year were estimated according to the calendar year based on the index date. Secondly, we investigated the factors associated with the duration of levetiracetam between short-term and long-term users.

Statistical analysis

The categorical data were shown as numbers (%) and analyzed with the Chi-square test. The continuous data were presented as mean with standard deviation (SD) and median with interquartile range (IQR) and compared using a *t*-test or Wilcoxon rank sum test. Logistic regression evaluated the factors associated with duration and presented them as odds ratio (OR) and 95 % confidence interval (CI). The statistical significance was defined as a p-value of < 0.05. Data were analyzed by SAS version 9.4.

Results

Three hundred sixty-four thousand seventy-six patients were newly admitted to the hospital with TBI diagnosed between January 1, 2012, and December 31, 2019. After excluding the ineligible patients, there were 64,461 patients included in the analysis cohort, consisting of 18,697 (29.01 %) patients on levetiracetam monotherapy, 15,382 (23.86 %) patients on phenytoin monotherapy, and 30,382 (47.13 %) patients on valproic acid monotherapy. Fig. 1 shows the screening process of patient selection.

Baseline characteristics of ASM users

Among the three groups, males were more than females. The mean (±SD) age were 62.95 (19.04), 62.51 (19.13), and 60.81 (19.06) years old in patients receiving levetiracetam, valproic acid, and phenytoin, respectively. A significantly higher proportion of intracranial hemorrhage and other intracranial injuries diagnosed were seen in the levetiracetam group compared to the valproic acid and phenytoin group. In contrast, the proportion of concussions, contusions, and skull fractures was lowest in the levetiracetam group across the three groups. Among the three groups, patients receiving valproic acid received a higher percentage of operation, while the levetiracetam group received a

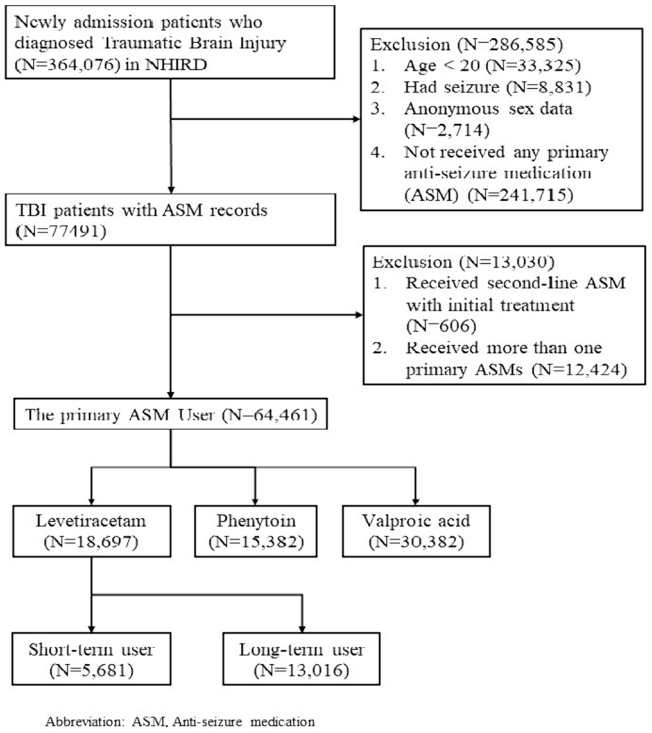

Fig. 1. Flow chart of the study cohort.

higher percentage of ICP monitor and CCI score (Table 1).

Trends in ASM use

Fig. 2 presents the trend of ASM prescribed in hospitalization from 2012 to 2019. At the beginning of 2012, the highest amount was shown with phenytoin (LEV vs. VPA vs. PHT: 1 % vs. 45 % vs. 54 %). The percentage of levetiracetam rose while the percentage of phenytoin declined. Since 2016, with the continually growing, levetiracetam has more than phenytoin and was the most widely prescribed after 2018. At the end of the study, levetiracetam had the highest percentage (56 %), followed by valproic acid (36 %) and phenytoin (8 %).

Baseline characteristics of levetiracetam users

Among the 18,697 patients who received levetiracetam, there were 5,681 (30.38 %) short-term users and 13,016 (69.62 %) long-term users (Table 2). The median age between short-term and long-term users was similar (65 vs. 66 years old, p-value = 0.085). The median length of hospital stay was significantly longer in the long-term users than in the short-term users (11 vs. 6 days, p-value < 0.0001). Intracranial hemorrhage was the most common type of TBI in both groups, occurring 88.12 % in the short-term users and 90.43 % in the long-term users. Compared to the short-term users, more long-term users had received operation (31.71 % vs. 22.37 %, p-value < 0.0001) and intracranial pressure monitor (21.23 % vs. 15.10 %, p-value < 0.0001) during hospitalization. The proportion of comorbidities was no different between the two groups, except for hypertension and cerebrovascular disease. Within the division classification, both groups have the highest percentage across all categories in Taipei, Central, and KaoPing areas. Taipei, Northern and Eastern had a higher percentage among those with a longer duration of LEV use, while Central had a higher percentage among those with a short duration of LEV use.

Table 1
Baseline characteristics of the ASM users.

	Levetiracetam	Valproic acid	Phenytoin	p-value[a]
N (%)	18,697 (29.01)	30,382 (47.13)	15,382 (23.86)	
Sex				
Male	12,046 (64.43)	19,921 (65.57)	10,269 (66.76)	<0.0001
Female	6,651 (35.57)	10,461 (34.43)	5113 (33.24)	
Age				
Mean (SD)	62.95 (19.04)	62.51 (19.16)	60.81 (19.06)	<0.0001
Median (p25, p75)	66 (51, 78)	65 (50, 78)	63 (48, 76)	<0.0001
Age group				
20–64	8955 (47.90)	17,187 (56.57)	8,710 (56.62)	0.9782
≧65	9742 (52.10)	13,195 (43.43)	6,672 (43.38)	
Length of stay				
Mean (SD)	15.36 (19.71)	15.86 (24.72)	14.48 (21.72)	<0.0001
Median (p25, p75)	9 (5, 18)	9 (5, 18)	9 (5, 17)	<0.0001
Type of TBI				
Contusions	878 (4.70)	2,593 (8.53)	1,332 (8.66)	<0.0001
Concussion	388 (2.08)	714 (2.35)	526 (3.42)	<0.0001
Skull fracture	3,865 (20.67)	6,716 (22.11)	3,328 (21.64)	0.0009
Intracranial hemorrhage	16,777 (89.73)	25,046 (82.44)	11,876 (77.21)	<0.0001
Other intracranial injuries	2,318 (12.40)	2,948 (9.70)	999 (6.49)	<0.0001
Operations				
Operations	5,399 (28.88)	9,126 (30.04)	4,380 (28.47)	0.0007
ICP Monitor	3,621 (19.37)	5,560 (18.30)	2,536 (16.49)	<0.0001
CCI				
Score 0	9,148 (48.93)	15,862 (52.21)	8,565 (55.68)	0.0121
Score 1	3,671 (19.63)	5,762 (18.97)	2,721 (17.69)	
Score≧2	5,878 (31.44)	8,758 (28.83)	4,096 (26.63)	
Comorbidity				
Hypertension	7,412 (39.64)	11,910 (39.20)	5,630 (36.60)	<0.0001
Diabetes	4,291 (22.95)	6,939 (22.84)	3,158 (20.53)	<0.0001
Cerebrovascular disease	2,196 (11.75)	3,814 (12.55)	1,779 (11.57)	0.0022
Alcoholism	563 (3.01)	473 (1.56)	436 (2.83)	<0.0001
CKD stage 5 and ESRD	569 (3.04)	1144 (3.77)	425 (2.76)	<0.0001

Abbreviations: CCI, Charlson comorbidities index; CKD, chronic kidney disease; ESRD, end-stage renal disease; ICP, intracranial pressure.
[a] The differences between levetiracetam users, valproic acid users, and phenytoin users were presented in p-value.

Factors associated with short-term and long-term use of levetiracetam

The results showed that receiving long-term levetiracetam was associated with the more extended hospital stay (OR = 1.054, 95 % CI =

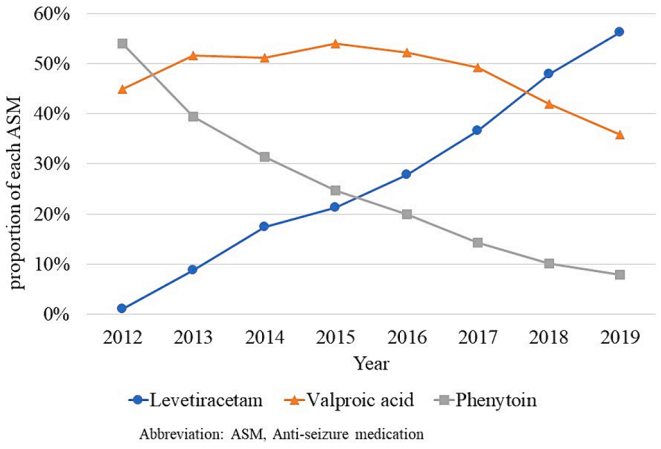

Fig. 2. Trends of primary anti-seizure medications by year.

1.05–1.058, p-value < 0.0001), diagnosed with contusions (OR = 1.181, 95 % CI = 1.013–1.377, p-value = 0.034), diagnosed intracranial hemorrhage (OR = 1.214, 95 % CI = 1.097–1.343, p-value = 0.0002), diagnosed other intracranial injuries (OR = 1.127, 95 % CI = 1.02–1.246, p-value = 0.0193), received operation (OR = 1.605, 95 % CI = 1.492–1.726, p-value < 0.0001), had cerebrovascular disease (OR = 1.162, 95 % CI = 1.041–1.297, p value = 0.0076). In addition, patients diagnosed with concussion diagnosed (OR = 0.77, 95 % CI = 0.622–0.952, p value = 0.016) and having CKD stage 5 and ESRD (OR = 0.821, 95 % CI = 0.681–0.988, p value = 0.0371) were more likely to receive short-term levetiracetam after injury (Table 3).

Discussion

This study investigated the prescription pattern of ASM use and the clinical characteristics of levetiracetam users among TBI patients for PTS in Taiwan real-world settings. The results indicated that levetiracetam users, with higher CCI scores and a history of alcoholism, differ from valproic acid users linked to cerebrovascular disease, CKD stage 5, and ESRD. The distinction may arise from pharmacokinetics, where levetiracetam is associated with urinary excretion in its unmetabolized form, and valproic acid undergoes liver metabolism. In clinical practice, due to its safer pharmacological profile and reduced drug-drug interaction risk in higher CCI patients, levetiracetam may be preferred for severe cases. The results also revealed an increasing trend of levetiracetam usage and a decline in phenytoin usage, which is consistent with the findings reported by Harris et al. [11], which indicated the change from phenytoin to levetiracetam among mild TBI patients from 2013 to 2018. The survey conducted in the UK revealed a similar preference for levetiracetam as the first choice of prophylaxis [14]. Of the physicians initiating prophylaxis, 75 % of responders opted for levetiracetam, followed by phenytoin (20 %) and valproic acid (5 %). Similar patterns have been illustrated in another European survey, where 49 %, 31 %, and 17 % of respondents indicated a preference for levetiracetam, phenytoin, and valproic acid separately [18].

The decline of phenytoin might relate to its adverse events from dose-related to pharmacogenomic-related side effects. The most life-threatening side effects are severe cutaneous adverse drug reactions (SCAR), strongly associated with the genetic polymorphisms affecting immunological responses and drug-metabolizing enzymes, especially in the Asian population [19]. Regarding the immunological reaction, phenytoin and its metabolites might be considered foreign antigens, triggering an immune response through binding to human leukocyte antigens (HLA) [20]. Studies indicate that Asian patients carrying HLA-B*15:02, HLA-B*13:01, and HLA-B*51:01 alleles have a higher risk of phenytoin-induced SCAR [21]. Additionally, concerning the drug-metabolizing enzymes, CYP2C9*3 carriers are strongly associated with

Table 2
Baseline characteristics of levetiracetam users.

	Levetiracetam	Short-term users	Long-term users	p-value[a]
N (%)	18,697 (100)	5681 (30.38)	13,016 (69.62)	
Sex				
Male	12,046 (64.43)	3644 (64.14)	8402 (64.55)	0.5923
Female	6651 (35.57)	2037 (35.86)	4614 (35.45)	
Age				
Mean (SD)	62.95 (19.04)	62.57 (19.16)	63.11 (18.98)	<0.0001
Median (p25, p75)	66 (51, 78)	65 (50, 78)	66 (51, 78)	0.085
Age group				
20–64	8955 (47.90)	2754 (48.48)	6201 (47.64)	0.2926
≧65	9742 (52.10)	2927 (51.52)	6815 (52.36)	
Length of stay				
Mean (SD)	15.36 (19.71)	9.18 (13.97)	18.06 (21.20)	<0.0001
Median (p25, p75)	9 (5, 18)	6 (3, 10)	11 (6, 23)	<0.0001
Type of TBI				
Contusions	878 (4.70)	240 (4.22)	638 (4.9)	0.0442
Concussion	388 (2.08)	153 (2.69)	235 (1.81)	<0.0001
Skull fracture	3865 (20.67)	1235 (21.74)	2630 (20.21)	0.0173
Intracranial hemorrhage	16,777 (89.73)	5006 (88.12)	11,771 (90.43)	<0.0001
Other intracranial injuries	2318 (12.40)	683 (12.02)	1635 (12.56)	0.3038
Operations				
Operations	5399 (28.88)	1271 (22.37)	4128 (31.71)	<0.0001
ICP Monitor	3621 (19.37)	858 (15.1)	2763 (21.23)	<0.0001
CCI				
Score 0	9148 (48.93)	2870 (50.52)	6278 (48.23)	0.0121
Score 1	3671 (19.63)	1097 (19.31)	2574 (19.78)	
Score≧2	5878 (31.44)	1714 (30.17)	4164 (31.99)	
Comorbidity				
Hypertension	7412 (39.64)	2173 (38.25)	5239 (40.25)	0.0101
Diabetes	4291 (22.95)	1303 (22.94)	2988 (22.96)	0.9758
Cerebrovascular disease	2196 (11.75)	585 (10.3)	1611 (12.38)	<0.0001
Alcoholism	563 (3.01)	170 (2.99)	393 (3.02)	0.9211
CKD stage 5 and ESRD	569 (3.04)	190 (3.34)	379 (2.91)	0.1132
Division				
Taipei	5692 (30.44)	1537 (27.00)[b]	4155 (73.00)[b]	<0.0001
Northern	2225 (11.90)	608 (27.33)[b]	1617 (72.67)[b]	
Central	3856 (20.62)	1467 (38.04)[b]	2389 (61.96)[b]	
Southern	2106 (11.26)	624 (29.63)[b]	1482 (70.37)[b]	
KaoPing	3778 (20.21)	1155 (30.57)[b]	2623 (69.43)[b]	
Eastern	804 (4.30)	226 (28.11)[b]	578 (71.89)[b]	
Unknown	236 (1.26)	64 (27.12)[b]	172 (72.88)[b]	
Income level				
<=24,000	12,582 (67.29)	3869 (68.1)	8713 (66.94)	0.0513
>24,000	5601 (29.96)	1641 (28.89)	3960 (30.42)	
Unknown	514 (2.75)	171 (3.01)	343 (2.64)	

Abbreviations: CCI, Charlson comorbidities index; CKD, chronic kidney disease; ESRD, end-stage renal disease; ICP, intracranial pressure.

[a] The difference between short-term and long-term users was presented in p-value.

[b] Row percentages indicate the percent of Levetiracetam cases within the district that had a short or longer duration of use.

poor metabolism that reduces the clearance of phenytoin [22]. Since phenytoin has a narrow therapeutic index, the implications of building up the serum level might result in a higher risk of side effects. The Taiwan Drug-Injury Relief System (TDRS) study revealed the association between phenytoin and severe cutaneous adverse drug reactions [23]. From 1996 to 2016 in Taiwan, there were 82 (9 %) cases of Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS/TEN) and 38 (13 %) cases of drug reaction with eosinophilia and systemic symptoms (DRESS) related to phenytoin. Although it is suggested to identify individuals at risk of severe side effects based on the pharmacogenetic test, in Taiwan, it is not common clinical practice to start the pharmacogenetic test before initiating phenytoin [24]. As a result, cautious prescribing of phenytoin is advised, weighing the overall benefits against potential complications.

Since levetiracetam was indicated as the seizure treatment, studies have highlighted the benefit of levetiracetam. Compared to first-generation ASMs, levetiracetam exhibits linear pharmacokinetics, higher bioavailability, less protein binding, and is excreted unchanged via the kidneys [25]. The noteworthy drug-drug interactions related to major CYP450 metabolism and the need for routine therapeutic drug monitoring are absent. While levetiracetam has been linked to behavioral and psychiatric adverse events, severe cutaneous adverse reactions have not been associated with its use [26].

Previous studies have reported a comparable preventive effect of levetiracetam. Szaflarski et al. conducted a single-blinded, randomized controlled trial that revealed an incidence rate of early PTS [12]. There was no significant difference in occurrence between levetiracetam and phenytoin users among severe traumatic brain injury patients. A *meta*-analysis study also exhibited no significant disparity in preventing overall PTS when comparing levetiracetam to phenytoin (OR = 1.02, 95 % CI = 0.72–1.45, p-value = 0.89, $I^2 = 0$ %) [27]. Despite the 2017 Brain Trauma Foundation TBI Guidelines not endorsing levetiracetam as an alternative to phenytoin due to insufficient evidence concerning the specific population and outcome definitions, it still underscored the growing importance attributed to levetiracetam [8].

In this study, the prevalence of long-term users of levetiracetam was notably more significant than that of short-term users. Our study identified a variance in contrast to the findings observed in the UK, where most physicians prescribed for seven days, followed by 14 days and 10 days [14]. Furthermore, the duration of ASM prophylaxis in the European study exhibited significant variability, reflecting its reliance on the patients' condition (33 %) [18]. These findings indicated the prescribing preferences might be attributed to the different clinical practices, which consider the distinctive and diverse presentation of patients with TBI.

This study revealed the association between the duration of prescription and several clinical characteristics. Patients with more severe illnesses were more likely to receive levetiracetam prescriptions over extended periods. Patients diagnosed with contusion and intracranial hemorrhage are related to severe sequelae of TBI [28,29]. Receiving an operation during hospitalization is considered to be a more severe level [8,30]. In addition, considering the excretion by the kidney, patients with cerebrovascular disease and CKD stage 5 and ESRD are linked to short-term use.

To our knowledge, this study is the first cohort study estimating the trend of ASM use in TBI patients in Taiwan. The NHIRD provides a relatively large sample size with the population-based database. However, there are several limitations. First, the information required for measuring the severity of TBI was unavailable due to the limitations of databases. This study included TBI patients with overall severity without the Glasgow Coma Scale data. Instead, receiving an ICP monitor was the surrogate indicator in this study. Second, several clinical data, such as brain computed tomography results and post-traumatic seizures incidence, were not accessible in the NHIRD. This absence may impact the selection and duration of ASM, introducing a potential limitation to the study. Third, our study's lack of detailed insurance reimbursement data limits our ability to account for differences in division classifications. It is plausible that individuals with severe traumatic brain injuries (TBIs) are more frequently referred to higher-tier hospitals. This referral pattern could lead to certain divisions having more medical centers and a higher patient volume, potentially contributing to the disparities observed in our findings. The last point is that healthcare providers often refer to U.S. guidelines. Still, they also consider other factors, such as the severity of the injury, imaging results, personal clinical judgment, and local protocols. Our database focused on reimbursement records, primarily documents procedures without detailing the outcomes. Consequently, it may not capture additional considerations related to these procedures.

Conclusions

This study evaluated the retrospective cohort using NHIRD to investigate the prescription pattern for PTS in TBI patients in Taiwan. A noticeable rise in levetiracetam prescription was observed yearly,

Table 3
Factors associated with the duration of levetiracetam prescription.

Variables		Univariate analysis			Multivariable analysis[a]		
		OR	**95 % CI**	**P-value**	**OR**	**95 % CI**	**P-value**
Sex	Female vs. Male (ref)	0.982	(0.921–1.048)	0.5919	0.993	(0.93–1.06)	0.8236
Age		1.001	(1–1.003)	0.0736	1	(0.998–1.002)	0.8906
Length of hospital stay		1.053	(1.049–1.056)	<0.0001	1.054	(1.05–1.058)	<0.0001
Type of TBI	Contusions vs. No (ref)	1.169	(1.004–1.36)	0.0443	1.181	(1.013–1.377)	0.034
	Concussion vs. No (ref)	0.664	(0.541–0.816)	<0.0001	0.77	(0.622–0.952)	0.016
	Skull fracture vs. No (ref)	0.912	(0.845–0.984)	0.0173	0.906	(0.835–0.983)	0.0173
	Intracranial hemorrhage vs. No (ref)	1.275	(1.154–1.408)	<0.0001	1.214	(1.097–1.343)	0.0002
	Other intracranial injuries vs. No (ref)	1.051	(0.955–1.156)	0.3074	1.127	(1.02–1.246)	0.0193
Operation	Operation vs. No operation (ref)	1.611	(1.499–1.732)	<0.0001	1.605	(1.492–1.726)	<0.0001
CCI	Score 1 vs. score 0 (ref)	1.073	(0.987–1.166)	0.099	1.045	(0.951–1.148)	0.3617
	Score≧2 vs. score 0 (ref)	1.111	(1.034–1.193)	0.004	1.109	(1.005–1.225)	0.0404
Comorbidity	Hypertension vs. Never (ref)	1.088	(1.02–1.159)	0.0101	1.062	(0.984–1.146)	0.1205
	Diabetes vs. Never (ref)	1.001	(0.93–1.078)	0.9758	0.924	(0.845–1.011)	0.0857
	Cerebrovascular disease vs. Never (ref)	1.23	(1.113–1.36)	<0.0001	1.162	(1.041–1.297)	0.0076
	Alcoholism vs. Never (ref)	1.009	(0.841–1.212)	0.9212	0.975	(0.808–1.178)	0.7951
	CKD stage 5 and ESRD vs. Never (ref)	0.867	(0.726–1.035)	0.1135	0.821	(0.681–0.988)	0.0371

Abbreviations: CCI, Charlson comorbidities index; CKD, chronic kidney disease; ESRD, end-stage renal disease; OR, odds ratio; Ref, reference.

[a] Adjust variables: age, sex, intracranial hemorrhage, receiving operation, hypertension, diabetes, cerebrovascular disease, alcoholism, CKD stage 5 and ESRD, and CCI score.

indicating levetiracetam as an alternative to other ASMs. Factors associated with a longer duration of levetiracetam prescription were related to the greater severity of TBI. These findings highlighted levetiracetam as a promising option for PTS prevention in TBI patients and reflect local clinical practice in Taiwan. Further studies are needed to validate these findings and the effectiveness of levetiracetam by including the Glasgow Coma Scale and other clinical characteristics factors.

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Ethical Statement

The study was performed in accordance with the Declaration of Helsinki. Ethical clearance was approved by the Institutional Review Board of Kaohsiung Medical University Hospital (KMUHIRB-E(I)-20220187). Informed consent requirements were waived as the de-identified medical data from the NHIRD was utilized.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used ChatGPT 4 in order to improve readability and language. After using this tool/service, the authors reviewed and edited the content as needed and took full responsibility for the content of the publication.

CRediT authorship contribution statement

Hsin-Tien Lee: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Conceptualization. **Fen-Fen Liao:** Writing – review & editing, Methodology, Conceptualization. **Sui-Sum Kung:** Writing – review & editing, Methodology, Conceptualization. **Shang-Jyh Hwang:** Writing – review & editing, Conceptualization. **Kun-Pin Hsieh:** Writing – review & editing, Resources, Methodology, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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