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Prescription patterns of antiepileptic drugs for adult patients with newly diagnosed focal epilepsy from 2006 to 2017 in Japan

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ABSTRACT

Objective: This study aimed to examine prescription patterns of antiepileptic drugs (AEDs) for adult patients with newly diagnosed focal epilepsy in Japan and whether these patterns adhere to the 2010 Japanese Society of Neurology Guidelines of Epilepsy Treatment.

Methods: Data from the JMDC Claims Database were obtained for patients aged between 20 and 65 years with newly diagnosed focal epilepsy who were prescribed AEDs between 2006 and 2017. Available prescription information up to the patient's first year was recorded and longitudinal descriptive statistics, Cochran Armitage Trend (CAT) tests, and annual percentage change (APC) were used to analyze AED trends and overall guideline adherence. In addition, logistic regression analyses were used to compare these results across different health facilities.

Results: A total of 6024 adult patients with newly diagnosed focal epilepsy were enrolled. The prescription of new AEDs increased significantly (CAT, $p < 0.001$, APC = 28.74 %) up to 36.8 % of all prescriptions in 2017 when compared to 2006. Among new AEDs, prescriptions for levetiracetam increased most rapidly and were followed by lamotrigine. In contrast, prescriptions for older AEDs, especially valproate, decreased over this same time period. The average guideline adherence rate from 2010 to 2017 was 75.3 %, and was not significantly different over time (CAT, $p = 0.55$). Health facilities with either more than 500 beds or between 20–499 beds had higher odds of prescribing new AEDs and improved guideline adherence when compared to facilities with 0–19 beds.

Conclusion: Prescription patterns of AEDs for adult patients with newly diagnosed focal epilepsy exhibited a trend from older to new AED classes between 2006 and 2017, with consistent, high guideline adherence from 2010 to 2017. Health facilities with 0–19 beds were less likely to prescribe new AEDs and completely adhere to proposed guidelines.

1. Introduction

Epilepsy is one of the most common disabling central nervous system diseases, and affects approximately 65 million individuals globally (Moshé et al., 2015). While treatable, seizure-related disorders place a heavy burden on patients with respect to experiencing prejudice, increased risk of death, and high treatment costs. Among the different classifications of epilepsy, focal epilepsy occurs most frequently and accounts for about 70 % of newly diagnosed epilepsy cases in adult patients (Hauser, 1992). Current epilepsy treatment options include a wide variety of antiepileptic drugs (AEDs) as well as surgery. However, since surgical interventions are mainly reserved for patients with drug-resistant epilepsy, the first line treatments focus on AED administration (Das et al., 2012).

Multiple factors are taken into account when AEDs are considered for epilepsy treatment. It is necessary to select AEDs based on both the type of seizure experienced and the nature of diagnosed epilepsy (French and Gazzola, 2013). Epileptic treatment is geared towards long-term symptom maintenance and usually begins with monotherapy using a single type of AED, and progresses to polytherapy when previous treatment

Abbreviations: AEDs, antiepileptic drugs; ATC, International Classification of Diseases 10th revision (ICD-10) classification, Anatomical Therapeutic Chemical; CAT, Cochran-Armitage Trend; APC, annual percentage change; OR, odds ratio; CIs, 95 % confidence intervals; TDM, therapeutic drug monitoring.

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methods are found to be ineffective (Chung et al., 2007; Cerda et al., 2015). With respect to treatment response in newly diagnosed focal epilepsy cases, the probability of controlling seizures decrease with each additional type of AED administered (Brodie et al., 2012; Kwan and Brodie, 2000). Since switching between AEDs may also increase risks of side effect and seizure recurrence (Finamore et al., 2016), it is suggested that patients should be remain on the same AED if it continues to be effective and tolerable (Kwan and Palmini, 2017). These highlights the importance of the significant patient benefit that is obtained when the initially selected AED is effective and tolerable enough to prevent switching to a different drug. In addition to this, and as is similar to other treatment practices, it is critical that prescribing physicians adhere to established treatment guidelines. In summary, optimal seizure control for adult patients with newly diagnosed focal epilepsy mainly depend on utilizing a guideline-based approach for selecting an effective first-choice AED.

In 2002, the Japanese Society of Neurology published the first version of Guideline of Epilepsy Treatment, which recommend carbamazepine, phenytoin and valproate for adult patients with newly diagnosed focal epilepsy (Japanese Society of Neurology, 2002). Several years later, there have been a number of new AEDs that being available in Japan. Therefore, in 2010, the Japanese Society of Neurology in cooperation with other societies in Japan including the Japan Epilepsy Society, Japan Neurosurgery Society, Japan Pediatric Neurology Society, and Japan Neurotherapeutics Society published a new Guideline of Epilepsy Treatment, which built on the 2002 guidelines and provided additional recommendations for new AEDs (Japanese Society of Neurology, 2002; Japanese Society of Neurology, 2010). In line with this, for adult patients with newly diagnosed focal epilepsy, the 2010 guideline recommends first-line therapy utilizing carbamazepine, lamotrigine, or levetiracetam followed by second-line treatment with phenytoin, valproate, zonisamide, or topiramate (Japanese Society of Neurology, 2010).

This study aimed to identify trends in prescription patterns with regard to prescribing new AEDs for adult patients with newly diagnosed focal epilepsy as well as determining the degree of physician adherence to the 2010 Guideline of Epilepsy Treatment. Furthermore, this study aimed to use this data to evaluate differences in prescribing patterns as well as guideline adherence across different health facilities. In addition, this study provides valuable information to researchers as well as medical doctors with respect to prescribing practices for AEDs in adult patients with newly diagnosed focal epilepsy, highlights different prescribing habits present across health facilities, while also providing a geographical perspective using data derived from the Japanese health care system.

2. Methods

2.1. Data collection

This study used the medical claims database supplied by JMDC Inc. The JMDC Claims Database is an epidemiological receipt database that has collected receipts and medical examination data from multiple health insurance associations since 2005. The JMDC Claims Database included claims collected until 2017 from more than 120 health insurance associations and reimbursement data from 7.5 million insured people, which covers approximately 6 % of the Japanese population. This database includes records of all visits for each patient in chronological order as well as all claims regarding performed tests, treatments, prescriptions, and procedures. The following information was recorded in the database: patient demographic information, health facilities accessed and pharmacy claims, clinical diagnoses as coded by the International Classification of Diseases 10th revision (ICD-10) classification, and medication information as coded by the World Health Organization Anatomical Therapeutic Chemical (ATC) classification (Tanaka et al., 2015; Yonekura et al., 2018).

2.2. Study sample

We examined data contained within the JMDC Claims Database between 2006 and 2017 and identified patients aged between 20 and 65 years that had diagnosed as focal epilepsy for at least two times with corresponding ICD-10 codes G40.1, G40.2 and G40.9. Among these cases, in order to identify newly diagnosed patients, we included patients who were first diagnosed as focal epilepsy from 6 months after the start of observation. Moreover, since AEDs can be prescribed to other diseases than epilepsy, we included those being performed MRI and EEG before the diagnosis of focal epilepsy and excluded those comorbid with neuropsychiatric disorders [anxiety (ICD-10 codes F40-F43), depression (ICD-10 codes F32 F33), bipolar disorder (ICD-10 codes F31), ADHD (ICD-10 codes F90), sleep disorder/apnea (ICD-10 codes F51 G47), movement disorder/tremor (ICD-10 codes F44.4, F98.4, G25.8-G25.9, R25)] and pain disorders [migraine headache (ICD-10 codes G43), chronic pain (ICD-10 codes R52.1-R52.2), fibromyalgia (ICD-10 codes M79.7), neuropathic pain (ICD-10 codes M79.2)] (Ottman et al., 2011) as means to minimize this confounding factor. Among the patients that were eligible for inclusion in this study, only those that had visits with prescriptions for AEDs with corresponding ATC Code N03A, were enrolled in the study. In order to focus on AED use for chronic instead of acute epilepsy treatments, we excluded prescriptions that were administered as injections. We selected each patient's first year of prescription or the whole period of prescription, if it lasted for less than one year, and recorded the most frequently prescribed AED in this period as that patient's prescription. The year when prescriptions were started was denoted as the prescription year. If two or more AEDs were equally frequently prescribed, the earliest prescribed AED was recorded. Based on these inclusion criteria, we extracted 6024 adult patients with newly diagnosed focal epilepsy and their first-choice AED prescription for analysis.

Classification of older and new AEDs in Japan depends on whether the AEDs was approved before or after 1990 (Terada and Inoue, 2012). Thus, ethosuximide, carbamazepine, clonazepam, phenobarbital, phenytoin, primidone, zonisamide, sultiame, valproate, and acetylpheneturide belong to the class of older AEDs. Clobazam, gabapentin, topiramate, lamotrigine, lacosamide, perampanel, and levetiracetam are characterized as new AEDs. It should be mentioned that zonisamide was first developed and approved in Japan in 1989. Thus, unlike North America and Europe, zonisamide is classified as older AED in Japan. In order to identify the association between approval year and prescription, for new AEDs, the year of approval was recorded in results. We then focused on prescription patterns, older-to-new AED trends, and guideline adherence in the 6024 patients, and further analyzed these results across different health facilities. However, since the guideline was published in 2010, when evaluating the overall guideline adherence, we focused on the time period from 2010 to 2017 and excluded AEDs that were approved after 2010. According to the Ministry of Health, Labor and Welfare, Japan (2019c) we classified health facilities into three sizes based on number of beds: 0–19, 20–499, and 500+ (more than 500).

2.3. Statistical analysis

For statistical analyses, we first summarized patient characteristics and AED prescriptions. Data were analyzed from two perspectives: the prescription trend from older to new AEDs and prescription adherence to the 2010 guideline. For both analyses, we used longitudinal descriptive statistics and determined the trend of prescription patterns using the Cochran-Armitage Trend (CAT) test. A p-value <0.05 was considered statistically significant. For cases of statistical comparisons that yielded significance ($p < 0.05$ using the CAT test), we calculated the annual percentage change (APC) in order to evaluate the trend speed.

Due to the possibility that our screening process which including patients who were first diagnosed as focal epilepsy from 6 months after the start of observation and excluding those comorbid with

neuropsychiatric disorders and pain disorders may contain some bias, two other screening process with one different part each were fitted. One was including patients who were first diagnosed as focal epilepsy from 3 months after the start of observation, the other was excluding those comorbid with neuropsychiatric disorders. We therefore repeated the main analysis twice using these two screening process as two sensitivity analysis.

Moreover, to compare prescription patterns and guideline adherence among different health facilities, we used multivariable logistic regression analysis adjusted for age, gender, prescription year and health facilities to estimate the odds ratio (OR) and 95 % confidence intervals (CIs). All statistical analyses were performed using the statistical analysis software (SAS) program version 9.4 (SAS Institute Inc., Cary, NC, USA).

2.4. Ethics approval

This study was approved by the Ethics Committee of Kyoto University Graduate School and Faculty of Medicine (Approval number: R1685, August 9, 2018). Study approval waived the requirement for additional informed consent due to the anonymous nature of the data.

3. Results

3.1. Patient characteristics

Of the 87687 patients diagnosed as focal epilepsy at least two times in JMDC Claims Database from January 2006 to December 2017, 16,412 adult patients with focal epilepsy were included as they were between 20 and 65 years and having performed MRI and EEG before the diagnosis of focal epilepsy. From these cases, 10881 adult patients with focal epilepsy taking AEDs for chronic treatment were identified after excluding those who did not take AEDs, take AEDs for acute use or with missing data related to prescription date. Lastly, in order to focus on newly diagnosed patients, we excluded those first diagnosed within 6 months after the start of observation and determined 6024 patients who were eligible for the study after fulfilling all of the inclusion criteria. The average patient age was 43.8 (standard deviation: 12.5) years and the number of male patients exceeded that of female patients (56.0 % vs. 44.0 %). Among adult patients with newly diagnosed focal epilepsy, 34.5 % visited health facilities with 20–499 beds, 29.0 % visited health facilities with 500+ beds, and 36.5 % visited health facilities with 0–19 beds (Table 1).

3.2. Prescription patterns

From 2006–2017, there were 17 different AEDs prescribed in Japan. Ten of these were classified as older AEDs, and seven were new AEDs. Among older AEDs, valproate were most frequently prescribed at the beginning of the study period, but the prescription rate consistently decreased especially from 2015 for females (Table B1) over the 12-year study period. Apart from that, the prescription of carbamazepine and phenytoin also decreased. Although clonazepam was not prescribed most frequently, prescription rates were steadily maintained. Among new AEDs, although there was one new AED approved in 2000, it was not prescribed until 2008 and it was not until 2010 that all new AEDs approved before 2010 were prescribed. The data showed that levetiracetam was prescribed most frequently and had the most rapid increase in prescription rate especially from 2015, up to 26.3 % of all prescriptions in 2017, followed by lamotrigine, which increased to 6.5 % in 2017 (Table 2).

3.3. Trends across new and older AEDs

From 2006–2017, the prescription rate of older AEDs decreased consistently (CAT: $p < 0.001$; APC=-3.07 %), and accounted for 63.2 % of all prescriptions in 2017, while that of new AEDs increased rapidly (CAT: $p < 0.001$; APC = 28.74 %), accounting for 36.8 % of all prescriptions in 2017 (Fig. 1). Among different health facilities, the prescription rate of new AEDs in those with 0–19 beds, 20–499 beds, and 500+ beds all increased significantly (CAT: $p < 0.001$, Fig. 2). The increasing speed of health facilities with 500+ beds was the fastest, leading the prescription rate of new AEDs up to 50.7 % of all prescriptions in 2017 (APC = 39.59 %, Fig. 2), followed by facilities with 20–499 beds and approached 43.4 % in 2017 (APC = 31.02 %, Fig. 2). In addition, the prescription rate of new AEDs in health facilities with 500+ beds (OR versus 0–19 beds: 2.81, 95 % CI: 2.43–3.26) and 20–499 beds (OR versus 0–19 beds: 2.19, 95 % CI: 1.89–2.54) were higher than health facilities with 0–19 beds (Table 3).

3.4. Guideline adherence

From 2010–2017, while the average rate of all treatment choices guideline adherence to the Guideline of Epilepsy Treatment 2010 was not significantly changed at 75.3 % (CAT: $p = 0.55$), the first-line choice guideline adherence increased obviously (CAT: $p < 0.001$, APC = 14.14 %, Fig. 3). Among different health facilities, only the guideline adherence of health facilities with 500+ beds increased slightly (CAT: $p = 0.008$, APC = 1.99 %, Fig. 4). In addition, the guideline adherence rate for health facilities with 20–499 beds (OR versus 0–19 beds: 2.77, 95 % CI: 2.43–3.16) and 500+ beds (OR versus 0–19 beds: 2.72, 95 % CI: 2.37–3.12) were higher than health facilities with 0–19 beds (Table 3).

3.5. Sensitivity analysis

For the sensitivity analysis using the screening process that including patients who were first diagnosed as focal epilepsy from 3 months after the start of observation, we identified 6368 cases (Table A1). For the sensitivity analysis using the screening process that excluding those comorbid with neuropsychiatric disorders, we identified 6222 cases

Table 1
Characteristics of adult patients with newly diagnosed focal epilepsy from 2006 to 2017.

Year	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	Total
Patients' number	38	74	68	133	221	293	749	609	677	757	1056	1349	6024
Variable													
Age (years)													
Mean (SD)	43.5 (10.7)	38.8 (12.0)	40.7 (11.3)	40.0 (12.4)	42.3 (11.3)	43.6 (11.6)	42.4 (12.5)	44.3 (11.9)	44.0 (11.9)	42.9 (13.0)	44.9 (12.8)	45.0 (12.4)	43.8 (12.5)
Gender (%)													
Female	40.0	35.9	39.1	45.4	41.1	48.5	45.2	43.5	43.1	44.8	45.0	42.2	44.0
Number of health facility beds (%)													
0–19	40.0	43.6	53.1	39.1	43.0	43.4	34.4	34.8	37.2	38.8	34.4	33.8	36.5
20–499	44.0	28.2	32.8	35.6	29.6	32.3	36.6	34.1	33.0	32.9	33.8	38.6	34.5
500+	16.0	28.2	14.6	25.3	27.4	24.3	29.0	31.2	29.8	28.3	31.8	27.6	29.0

SD: standard deviation.

Table 2
Prescription Patterns of AEDs for adult patients with newly diagnosed focal epilepsy from 2006 to 2017.

Year	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
Older AEDs (%)												
Ethosuximide						0.3	0.2		0.2	0.1	0.1	
Carbamazepine	28.5	25.4	19.1	17.8	17.2	16.5	19.3	21.9	21.4	18.2	15.0	12.9
Clonazepam	24.0	23.3	20.0	19.0	18.8	22.2	21.3	18.2	23.8	19.6	20.4	20.3
Phenobarbital	1.0			0.6	1.3	1.2		0.5	0.3	0.5	0.5	0.3
Phenytoin		5.1	12.5	13.8	7.0	5.7	4.1	7.1	3.7	4.9	2.6	2.6
Primidone							0.2	0.1	0.2	0.1	0.1	0.1
Zonisamide			6.3	4.0	5.7	4.5	4.1	4.8	3.0	3.5	3.3	3.1
Sultiame										0.1	0.1	0.2
Acetylpheneturide											0.1	
Valproate	46.5	46.2	35.9	35.1	41.1	43.1	41.1	36.8	38.3	32.1	27.9	23.9
New AEDs (%)												
Clobazam (2000)			1.6	6.3	3.8	1.5	2.7	2.7	1.1	2.4	2.4	1.8
Gabapentin (2006)			3.1	2.9	3.2	0.9	1.1	0.2	0.5	0.5	0.6	0.3
Topiramate (2007)			1.6	0.6	1.0	0.3	1.1	0.9	0.3	1.2	0.7	0.8
Lamotrigine (2008)					0.9	3.0	3.8	3.7	4.8	6.4	6.3	6.5
Levetiracetam (2010)					0.1	0.9	1.0	3.2	2.6	10.5	19.9	26.3
Lacosamide (2016)												1.1
Perampanel (2016)												0.1

AED: antiepileptic drug. For each new AED, the year of approval is provided in parenthesis.

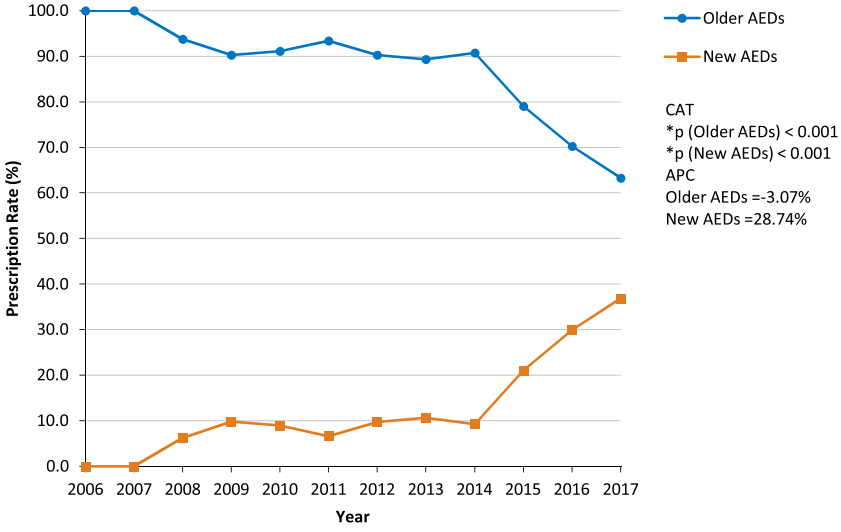

Fig. 1. Older-to-new AED prescriptions trend for adult patients with newly diagnosed focal epilepsy from 2006 to 2017. The calculation method was the number of older AEDs (or new AEDs) prescriptions each year divided by the number of all AEDs prescriptions each year. The results of the CAT tests and APC are provided next to the graph. AED: antiepileptic drug; CAT: Cochran-Armitage Trend; APC: annual percentage change; *: p value below 0.05 (CAT test); APC was calculated only when p value was below 0.05.

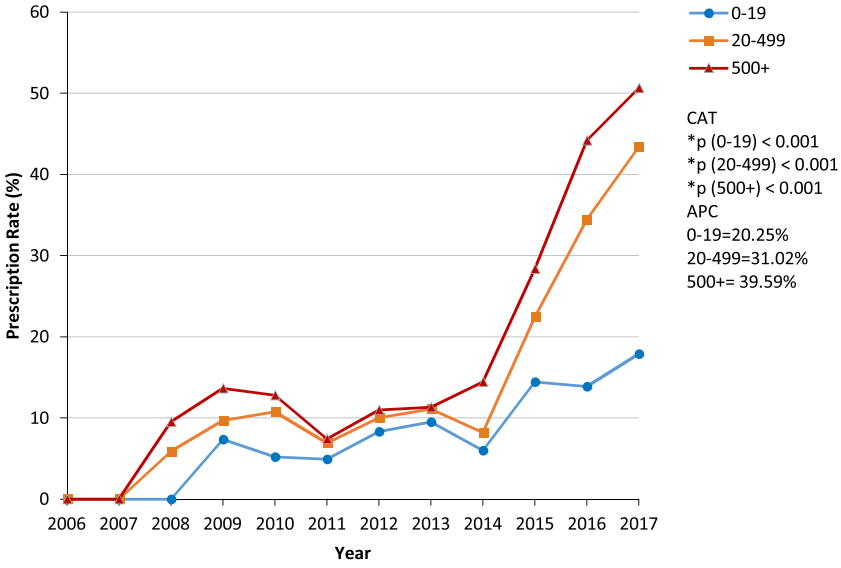

Fig. 2. Older-to-new AED prescription trends for adult patients with newly diagnosed focal epilepsy among different health facilities from 2006 to 2017. The calculation method was the number of new AEDs prescriptions each year divided by the number of all AEDs prescriptions each year. Next to the graph, the results of the CAT tests and APC are provided. 0–19, 20–499, 500+: number of health facility beds; AED: antiepileptic drug; CAT: Cochran-Armitage Trend; APC: annual percentage change; *: p value below 0.05 (CAT test); APC was calculated only when p value was below 0.05.

Table 3
Multivariable Logistic Regression Analysis of the prescription patterns of AEDs for adult patients with newly diagnosed focal epilepsy among different health facilities adjusted for age, gender, prescription year and health facilities.

Variable	Older-to-New AEDs Trend from 2006-2017			Guideline Adherence from 2010-2017		
	Adjusted* Odds Ratio	95 % CIs	p value	Adjusted* Odds Ratio	95 % CIs	p value
20–499 beds	2.19	1.89-2.54	<0.001	2.77	2.43-3.16	<0.001
500+ beds	2.81	2.43-3.26	<0.001	2.72	2.37-3.12	<0.001
0–19 beds		Reference			Reference	

CIs: confidence intervals.
* Odds ratio adjusted for age, gender, prescription year and health facilities.

(Table A3). Both of the sensitivity analysis showed similar prescription pattern to the main analysis (Table A2, Table A4), which again demonstrated the prescribing trend from older to new AEDs (Figs. A1, A3) along with high levels of consistent guideline adherence (Figs. A2, A4) from 2006 to 2017.

4. Discussion

This study delineated year over year changes with regards to first-choice selection of AEDs prescribed to adult patients with newly diagnosed focal epilepsy in Japan across a period of 12 years using a nationwide data set from JMDC Claims Database and further compare prescription patterns and guideline adherence among different health facilities. A prescribing trend from older to new AEDs along with high levels of consistent guideline adherence were identified, particularly in health facilities with 20–499 beds and those with more than 500 beds.

Since 6 out of 7 new AEDs were approved and marketed in Japan within this 12-year period, we were able to capture dynamic changes in prescription patterns. We found features regarding the prescription of

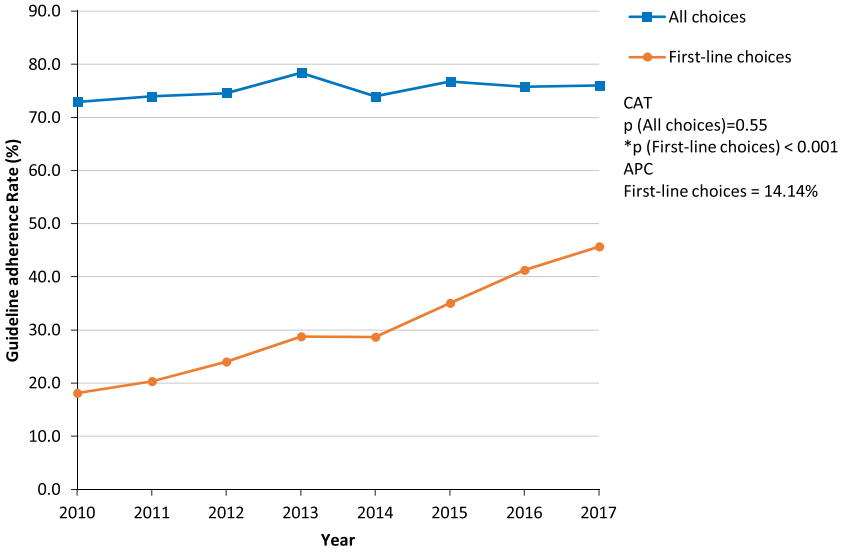

Fig. 3. Guideline adherence of AED prescriptions for adult patients with newly diagnosed focal epilepsy from 2010 to 2017. The calculation method was the number of AEDs prescriptions following all choices (or the first-line choices) of the guideline each year divided by the number of all AEDs prescriptions each year. The result of the CAT tests are provided next to the graph. AED: antiepileptic drug; CAT: Cochran-Armitage Trend; APC: annual percentage change; *: p value below 0.05 (CAT test); APC was calculated only when p value was below 0.05.

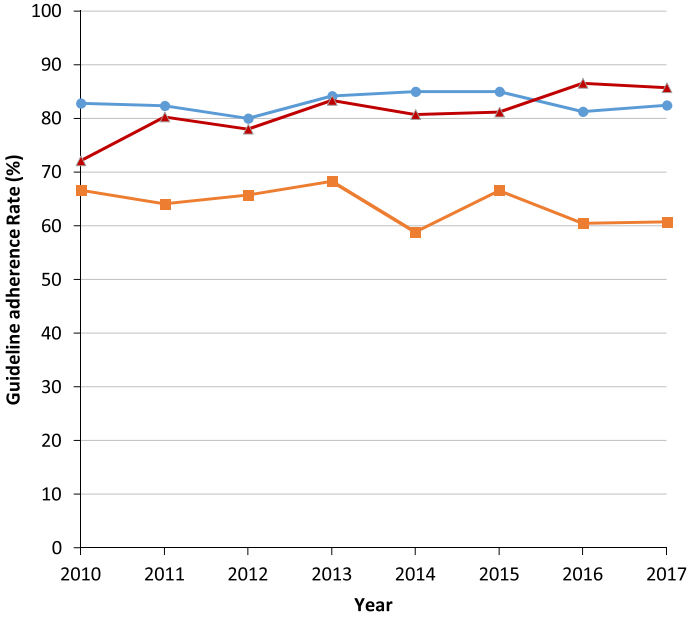

Fig. 4. Guideline adherence of AED prescriptions for adult patients with newly diagnosed focal epilepsy among different health facilities from 2010 to 2017. The calculation method was the number of AEDs prescriptions following all choices of the guideline each year divided by the number of all AEDs prescriptions each year. Next to the graph, the results of the CAT tests are provided. 0–19, 20–499, 500+: number of health facility beds; AED: antiepileptic drug; CAT: Cochran-Armitage Trend; APC: annual percentage change; *: p value below 0.05 (CAT test); APC was calculated only when p value was below 0.05.

new AEDs that were similar to those reported through therapeutic drug monitoring (TDM) of AEDs in the UK, this same report stated that publication of new guidelines could results in identifiable changes in prescription patterns (Patsalos et al., 2018). In Japan, the time lag between approval and first prescription of new AEDs before 2010 was longer than the same time lag after 2010, and the prescription of lamotrigine started to increase rapidly from 2010. As for levetiracetam, it was not until 2015 that the prescription start to increase extremely quickly, which may because levetiracetam was approved as add-on therapy in 2010 and as monotherapy in 2015, this pattern indicated that during the period of monotherapy prohibition, it may be difficult to prescribe new drugs at first. Besides, the increasing prescription of lamotrigine and levetiracetam may be a result of the Guideline of Epilepsy Treatment 2010 recommendation for them. This is similar to Ertl et al. (2016)' s study in Germany, which showed the overwhelming switch to levetiracetam since 2008 when German clinical practice guidelines recommended lamotrigine and levetiracetam in focal epilepsy, due to this guideline, the prescription of levetiracetam increased significantly from 19.6 % in 2008 to 58.9 % in 2014. These findings all demonstrate the important influence of implementing reliable guidelines. Meanwhile, regardless of the number of new AEDs that were approved, older AEDs will continue to be prescribed and recommended by guidelines as they work especially well in treating a specific subset of symptoms (Japanese Society of Neurology, 2010).

Similar to the Medicaid Analytic extract data set from the USA surveyed by Liu et al. (2017), our study also showed that prescription rates of carbamazepine and valproate slowly decreased while those of lamotrigine and levetiracetam rapidly increased across 2006–2017, which play an important role in shifts in prescription trends from older to new AEDs. The underlying reasoning for this change may be consistent with the electronic primary care records data in the UK that were surveyed by Pickrell et al. (2014), who stated that increased prescriptions of lamotrigine and decreased prescriptions of carbamazepine would indicate that although the efficacy of these drugs are similar, physicians still tend to choose AEDs that have better overall tolerability; increased prescriptions of levetiracetam and decreased prescriptions of valproate indicate that physicians tend to prescribe AEDs with a lower rate of drug interactions and side effects. Besides, our study showed that the prescription of valproate has a pronounced decrease from 2015 onwards and that of females decrease more obviously. This pattern was also showed in Virta et al. (2018)'s study in Finland and according to the same study, the reason may be that the European Medicines Agency (EMA) raised the awareness not to prescribe valproate in females due to teratogenic effects in November 2014. Moreover, it is noteworthy that in Japan, until 2017, generic forms of new AEDs were not available. Therefore, new AEDs were more expensive compared to older AEDs during the study time period (Ministry of Health, Labor and Welfare, Japan, 2018). Nevertheless, as Liu et al. (2017) reported, although new AEDs were more expensive, the prescription of new AEDs increased rapidly since they were expected to be more beneficial for patients and physicians tended to prescribe new AEDs possibly due to lower risk of adverse effects and increased treatment adherence. Even so, since the majority of existed epilepsy patients will keep their AEDs stable, the trend towards prescribing new AEDs only influence newly diagnosed patients and some bad-controlled existed patients, which is a small part of all epilepsy patients. Consequently, as Willems et al. (2019) reported, the overall prescription patterns in the general population only show limited changes and despite the increasing use of new AEDs, the overall costs (budget impact) for the health system may not be hugely affected.

Our study also showed that, the adherence to the Guideline of Epilepsy Treatment 2010 was consistently high and the first-line choice adherence continuously increased from 2010–2017, which indicated that regardless of increases in medication costs, Japanese physicians consistently and increasingly adhered to the newer guidelines. Studies examining the guideline adherence rate in other countries found a 66.5 % adherence rate to the 2008 German Neurological Society guidelines for patients with newly diagnosed and chronic epilepsy in Germany (Strzelczyk et al., 2016). Similarly, in France the rate of determination of serum levels of AEDs based on French guidelines was 84 % (Hanin et al., 2017). The guideline adherences rates for these countries as well as Japan are high and may possibly be impacted by the fact that all of these countries have adopted universal healthcare (Hossein and Gerard, 2013). While in the USA, although there are reports that adherence to guidelines did not vary significantly based on insurance status, it has been demonstrated that uninsured patients were three times more likely to have worse seizure control (Ladner et al., 2015), and patients who only had Medicaid or Medicare insurance also experienced lower guideline adherence (Harlan et al., 2005). These findings suggest that health insurance systems may play an important role in physician adherence to recommended guidelines. In addition, it has been shown that higher medical expenses and larger numbers of people within health insurance systems results in higher physician guideline adherence (Harlan et al., 2005). Therefore, in order to improve guideline adherence, in addition to consistent dissemination and education, involving patients in treatment decisions, as well as monitoring guideline adherence (Baron et al., 2017), a universal health insurance system may also prove beneficial.

Our study found that compared to health facilities with 0–19 beds, facilities with more than 500 beds and those with 20–499 beds had a more significant trend of switching from older to new AEDs, this was particularly apparent in facilities with more than 500 beds. This is consistent with a large study in the UK, which reported that physicians from larger health facilities were more knowledgeable regarding epilepsy diagnosis and more inclined to prescribe new AEDs (Poole et al., 2000). In addition, health facilities with more than 500 beds and those with 20–499 beds also maintained higher guideline adherence when compared to facilities with 0–19 beds. In Japan, most health facilities with more than 500 beds and 20–499 beds are public hospitals owned by the government, universities, or associations and are located in cities while most facilities with 0–19 beds are private clinics owned by several or even one physician and are located in both cities and rural areas (Ministry of Health, Labor and Welfare, Japan, 2019a). Therefore, compared with clinic-based physicians, hospital-based physicians may have increased access to updated information regarding both new AEDs as well as prescribing guidelines, which would potentially explain the increase in new AED prescription and guideline adherence. Lawal et al. (2016) and Furuhata et al. (2017) also reported that there are clinical pathways and prescription rules in many hospitals, which are regularly updated and set based on specific guidelines to ultimately help improve quality of health and physicians in these hospitals tend to adhere to those established pathways and rules. With regards clinic-based physicians, Saini et al. (2017) reported that some clinic-based physicians prefer to prescribe medications by relying on their own experience and knowledge rather than basing decisions on published guidelines. Moreover, since clinic-based physicians tend to be older than hospital-based physicians, and rural clinic-based physicians tend to be even older (Ministry of Health, Labor and Welfare, Japan, 2019b), their clinical knowledge may not be up to date due to potential geographical inconveniences, unfamiliarity with internet use, as well as lack of organization and communication. For instance, in our study, unlike health facilities with 20–499 beds or 500+ beds (hospitals), the physicians in health facilities with 0–19 beds (clinics) prescribed clonazepam most frequently, which is neither a new AEDs nor in the guideline recommendations (Table B2). Therefore, it is important that new AEDs and guidelines should be more directly disseminated to health facilities with 0–19 beds (clinics). Apart from that, the reason why clinic-based physicians are less inclined to prescribe new AEDs may also be that compared with hospital-based physicians, who are more indifferent to the finance, clinic-based physicians are more realistic and sensitive to the medical cost, as a result, they are less liable to prescribe expensive drugs for the sake of patients. This may be able to be proved in the future when compared after appearing generic forms of new AEDs.

4.1. Strengths and limitations

Our study had several strengths that are worth mentioning. Our study is the first to investigate guideline adherence and prescription patterns of AEDs for adult patients with newly diagnosed focal epilepsy in Japan, and can be used to provide important information regarding global antiepileptic studies. Our study used a large-scale database for analysis, which allowed us to obtain a large sample size of adult patients with newly diagnosed focal epilepsy, even after methodology minimized confounding related to AED prescriptions by including those being performed MRI and EEG before the diagnosis of focal epilepsy and excluding those comorbid with neuropsychiatric disorders and pain disorders.

Our study also had several limitations. First, since this is a retrospective database study, there may be biases including the likely restriction of analysis with respect to defining whether patients were prescribed the right AEDs for focal epilepsy and not based on their individual characteristics. Second, although we included a total of 6024 patients from the JMDC Claims Database, the number of patients included prior to 2010 was low and as a result these data need to be interpreted more cautiously. Third, our study only evaluate the prescription patterns of valproate across different sex in Japan, which have a potential for fetal teratogenicity in women of childbearing age (Inoyama and Meador, 2015; Vajda et al., 2014). Therefore, the contribution of these characteristics to prescription patterns and guideline adherence of other AEDs need to be examined in later studies. Lastly, our study did not evaluate AEDs utilization, which is important since it can be used to measure the effectiveness of AEDs. For example, Margolis et al. (2014) utilized treatment persistence of AEDs as a surrogate marker of effectiveness, which is similar to the effectiveness measurement (time to treatment failure) used by Marson et al. (2007) in the SANAD study. While AEDs prescription pattern cannot be used to measure the effectiveness and may be heavily influenced by other factors beyond publication of guidelines such as marketing pressures. Consequently, further study about AEDs utilization should be performed in the future.

5. Conclusions

Our study demonstrated changes in prescription patterns of AEDs for the treatment of adult patients with newly diagnosed focal epilepsy in Japan, found a trend of increased reliance on new AEDs between 2006 and 2017 and a consistently high physician adherence to the Guideline of Epilepsy Treatment 2010 from 2010 to 2017. Furthermore, our study also showed that health facilities with 0–19 beds (clinics) were less inclined to prescribe new AEDs and adhere to established guidelines.

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Declaration of competing interest

None of the authors have any competing interests to declare.

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This study is based on data from the JMDC. The interpretation and conclusions contained herein do not represent those of the JMDC.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.eplepsyres.2020.106503.

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