



Trends in prescription of anti-seizure medicines for Japanese pediatric outpatients during 2013–2019



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ABSTRACT

Temporal trends in prescriptions of anti-seizure medicines (ASMs) for children, including newer ASMs, are unclear. We investigated ASM prescription trends for pediatric outpatients in Japan. The MDV analyzer[®] was used to analyze the MDV database containing de-identified hospital administrative data. Administrative data as of June 2021 including pediatric outpatients (0–17 years) with epilepsy, visiting 123 acute diagnostic procedure combination hospitals during 2013–2019, were used. Annual ASMs prescription trends were calculated, based on proportions. The Cochran–Armitage trend test evaluated the proportion of prescriptions for each ASM. ASMs most often prescribed were valproic acid, carbamazepine, and levetiracetam, regardless of sex. In girls, the proportion of valproic acid and carbamazepine prescriptions decreased from 37.93% to 26.84%, and from 24.80% to 15.78%, respectively ($p < 0.0001$). Conversely, the proportion of levetiracetam prescriptions increased from 6.40% to 28.18% ($p < 0.0001$). In boys, the proportion of valproic acid and carbamazepine prescriptions decreased, from 36.58% to 32.20% and from 26.42% to 16.85%, respectively ($p < 0.0001$). The proportion of levetiracetam prescriptions increased from 5.64% to 23.02% ($p < 0.0001$). Overall, the proportion of valproic acid and carbamazepine prescriptions declined, whereas levetiracetam prescriptions increased. Trends in ASM prescriptions among pediatric outpatients with epilepsy in Japan have shifted towards more recently available ASMs.

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1. Introduction¹

According to a systematic review and meta-analysis published by Fiest et al. in 2017, the global prevalence of epilepsy was 6.38 (95% confidence interval [CI]: 5.57–7.30) per 1000 population [1]. As per the Ministry of Health, Labour and Welfare, the number of

people with epilepsy in Japan is reportedly 5–8 per 1000 [2]. Although people of all ages can develop epilepsy, the incidence is highest in childhood [3]. Anti-seizure medicines (ASMs) are currently used to control epilepsy from childhood.

In recent years, studies from China and Netherlands on the treatment of epilepsy have reported a decrease in the proportion of prescriptions of traditional ASMs and an increase in the proportion of prescriptions of newer ASMs [4,5]. Among the newer medications, the proportion of prescriptions for lamotrigine and levetiracetam in children has noticeably increased [4,5]. However, to date, temporal trends in the prescription of ASMs in Japanese children have not been reported.

This study aimed to clarify temporal trends in the prescription of ASMs for Japanese pediatric outpatients, based on administrative data of hospital outpatients.

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¹ ASM, anti-seizure medicines; ICD-10, International Statistical Classification of Diseases, 10th Revision; PMDA, Pharmaceuticals and Medical Devices Agency.

2. Materials and methods

2.1. Database

This retrospective survey was conducted by studying a de-identified hospital administrative database assembled using the MDV analyzer[®] (Medical Data Vision Co., Ltd., Tokyo, Japan) as a tool to analyze the MDV database. This database includes information on inpatients and outpatients from numerous Japanese acute diagnostic procedure combination hospitals. The actual number of patients in the MDV database as of December 31, 2019 was 29.7 million (including deceased patients).

2.2. Study population

Pediatric outpatients with epilepsy, diagnosed according to the International Statistical Classification of Diseases, 10th Revision (ICD-10) codes [6], were divided into those with epilepsy (G40 in ICD-10) and those with status epilepticus (G41 in ICD-10). This study population consisted of outpatients aged 0–17 years with epilepsy who visited any of the 123 acute diagnostic procedure combination hospitals that provide administrative data to Medical Data Vision Co., Ltd. The patients included in this study were those who presented to any of these hospitals during the period from January 1, 2013 to December 31, 2019. The data were used as of June 2021.

2.3. Definition of target ASM prescriptions for children with epilepsy

The target ASMs in this study were oral medications that had been approved in Japan as of December 2019 (Supplementary Table S1). Prescribed drugs were tabulated for each year in the period 2013–2019, to exclude the effect of variations in prescriptions over the course of a year. An ASM was deemed to have been prescribed in a year, even if it was prescribed only once in that year.

2.4. Evaluation items

The proportion of prescriptions for each ASM was calculated and used for evaluation. As raw patient data could not be retrieved from the MDV analyzer[®], the proportion of each prescription was calculated using the data that were available, as follows.

Proportion of ASM prescriptions = Number of pediatric outpatients prescribed an ASM/Number of pediatric outpatients with epilepsy × 100

2.5. Statistical analysis

The annual proportion of each prescription was calculated from 2013 to 2019. These values were stratified according to age (0–5, 6–11, and 12–17 years). The Cochran–Armitage trend test was used to evaluate the proportion of prescriptions for each ASM. A *p*-value <0.05 was considered statistically significant. All statistical analyses were performed using R version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria) [7].

2.6. Ethical statement

The Institutional Review Board of Tohoku Medical and Pharmaceutical University Hospital approved the current study (approval number: 2019-2-066). Given the study's retrospective design, and the fact that all personal data were anonymized, the requirement for informed consent was waived.

3. Results

The numbers of children with epilepsy included in this study were 8269, 7962, 8070, 8178, 8276, 8216, and 8145 for 2013, 2014, 2015, 2016, 2017, 2018, and 2019, respectively.

3.1. ASM prescriptions in all patients

In the patients overall, the highest proportion of prescriptions among all ASMs during the study period was for valproic acid. The proportion of valproic acid and carbamazepine prescriptions decreased significantly from 37.20% to 29.75% (*p* < 0.0001) and from 25.67% to 16.37% (*p* < 0.0001), respectively. In contrast, the proportion of levetiracetam prescriptions increased significantly from 5.99% to 25.38% (*p* < 0.0001) (Table 1). The proportion of prescriptions for each ASM, stratified by age group, among all patients during the years 2013–2019 is shown in Table 2.

3.2. ASM prescriptions in girls

In girls, valproic acid accounted for the highest proportion of prescriptions up to 2018, although levetiracetam accounted for the highest proportion of prescriptions in 2019. The proportion of valproic acid and carbamazepine prescriptions decreased significantly from 37.93% to 26.84% (*p* < 0.0001) and from 24.80% to 15.78% (*p* < 0.0001), respectively, during the study period. In contrast, the proportion of levetiracetam prescriptions significantly increased from 6.40% to 28.18% (*p* < 0.0001) over this period (Table 1). The proportions of prescriptions for each ASM, stratified by age group, among girls in the years from 2013 to 2019 is shown in Table 2.

3.3. ASM prescriptions in boys

In boys also, valproic acid accounted for the highest proportion of prescriptions among all ASMs during this study period. The proportion of valproic acid and carbamazepine prescriptions decreased significantly from 36.58% to 32.20% (*p* < 0.0001) and from 26.42% to 16.85% (*p* < 0.0001), respectively, during the study period. In contrast, the proportion of levetiracetam prescriptions increased significantly from 5.64% to 23.02% (*p* < 0.0001) over this period (Table 1). The proportions of prescriptions for each ASM, stratified by age group, among boys in the years from 2013 to 2019 is shown in Table 2.

4. Discussion

This study examined trends in ASM prescriptions for pediatric outpatients in Japan. We noted that the most commonly prescribed ASMs were valproic acid, carbamazepine, and levetiracetam in both sexes. We also discovered that valproic acid and carbamazepine prescriptions are on the decline, while levetiracetam prescriptions are on the rise. Overall, during the study period, a shift toward ASMs that have become available in recent years was observed.

The use of valproic acid and carbamazepine, classified as traditional ASMs, has been reported to be on the decline in studies conducted outside of Japan [4,5]. The proportion of valproic acid and carbamazepine prescriptions decreased significantly during the study period. Despite abundant evidence for the efficacy of valproic acid, there are concerns about teratogenicity and other serious health effects [8]. The National Institute for Health and Care Excellence warns that valproic acid should not be prescribed to women and girls who are likely to give birth during their lifetime (including young girls who require epilepsy treatment into their child-

Table 1
Proportion of prescriptions for ASMs in children with epilepsy by year.

	Year							P-value
	2013	2014	2015	2016	2017	2018	2019	
All patients								
0–17 years								
Children with epilepsy, n	8269	7962	8070	8178	8276	8216	8145	
Prescriptions of any ASM, %	67.38	67.72	67.55	67.90	68.20	68.94	67.91	0.09
Valproic acid, %	37.20	36.81	35.18	34.08	33.07	32.04	29.75	<0.0001
Levetiracetam, %	5.99	7.03	11.77	16.48	20.02	23.56	25.38	<0.0001
Carbamazepine, %	25.67	25.32	24.37	22.13	20.37	18.52	16.37	<0.0001
Lamotrigine, %	3.76	4.53	4.67	5.25	5.68	5.92	5.75	<0.0001
Clobazam, %	5.50	5.78	5.24	5.18	5.16	5.17	4.81	0.01
Lacosamide, %	0.00	0.00	0.00	0.05	0.45	0.84	3.25	<0.0001
Zonisamide, %	6.36	5.73	4.93	4.26	3.79	3.59	2.98	<0.0001
Clonazepam, %	4.40	4.09	3.71	3.19	3.02	2.75	2.55	<0.0001
Topiramate, %	2.07	2.12	2.44	2.64	2.69	2.69	2.36	0.01
Perampanel, %	0.00	0.00	0.00	0.29	0.98	1.22	1.29	<0.0001
Ethosuximide, %	0.89	0.87	0.98	1.04	1.08	1.12	1.20	0.01
Girls								
0–17 years								
Children with epilepsy, n	3783	3690	3736	3768	3800	3756	3719	
Prescriptions of any ASM, %	68.75	69.00	68.90	68.15	68.47	69.70	68.51	0.95
Levetiracetam, %	6.40	6.96	12.29	17.54	20.71	25.61	28.18	<0.0001
Valproic acid, %	37.93	36.88	34.56	32.70	31.37	29.82	26.84	<0.0001
Carbamazepine, %	24.80	24.39	24.04	21.26	19.66	18.10	15.78	<0.0001
Lamotrigine, %	4.26	5.37	5.51	6.18	6.79	7.43	7.50	<0.0001
Clobazam, %	5.76	5.85	5.17	4.94	4.92	5.32	5.00	0.06
Lacosamide, %	0.00	0.00	0.00	0.11	0.45	0.69	3.33	<0.0001
Clonazepam, %	5.10	4.96	4.39	3.56	3.63	3.43	2.96	<0.0001
Zonisamide, %	6.77	5.72	4.98	4.14	3.42	3.33	2.74	<0.0001
Topiramate, %	2.30	2.30	2.70	3.03	2.84	3.06	2.72	0.04
Ethosuximide, %	1.35	1.22	1.34	1.35	1.32	1.38	1.59	0.31
Perampanel, %	0.00	0.00	0.00	0.29	0.84	1.14	1.29	<0.0001
Boys								
0–17 years								
Children with epilepsy, n	4486	4272	4334	4410	4476	4460	4426	
Prescriptions of any ASM, %	66.23	66.62	66.38	67.69	67.96	68.30	67.40	0.02
Valproic acid, %	36.58	36.75	35.72	35.26	34.52	33.90	32.20	<0.0001
Levetiracetam, %	5.64	7.09	11.33	15.58	19.44	21.84	23.02	<0.0001
Carbamazepine, %	26.42	26.12	24.67	22.88	20.98	18.88	16.85	<0.0001
Clobazam, %	5.28	5.71	5.31	5.40	5.36	5.04	4.65	0.08
Lamotrigine, %	3.34	3.82	3.95	4.44	4.74	4.64	4.27	0.001
Zonisamide, %	6.02	5.74	4.89	4.35	4.11	3.81	3.19	<0.0001
Lacosamide, %	0.00	0.00	0.00	0.00	0.45	0.96	3.19	<0.0001
Clonazepam, %	3.81	3.35	3.11	2.88	2.50	2.17	2.21	<0.0001
Topiramate, %	1.87	1.97	2.22	2.31	2.57	2.38	2.06	0.14
Perampanel, %	0.00	0.00	0.00	0.29	1.09	1.28	1.29	<0.0001

ASM: anti-seizure medicine.

Each ASM is listed in order of the proportion of prescriptions of ASMs in 2019.

Each ASM with a proportion of prescriptions of 1% or more were included in the list in 2019.

The Cochran–Armitage trend test was used for statistical analysis.

A p-value < 0.05 was considered statistically significant.

bearing years) [8]. In this study, the decrease in valproic acid prescription was more marked in girls aged 12–17 years than in girls aged 6–11 years and in boys aged 6–11 years and 12–17 years. Additionally, a higher proportion of girls aged 12–17 years had been prescribed levetiracetam than valproic acid since 2018. The proportion of lamotrigine prescribed to girls in the 12–17-years age group also increased more than in boys. This suggests that prescribers may have been concerned regarding potential congenital malformations, if the patients should become pregnant in future. Carbamazepine has also been reported to be associated with side effects of toxic epidermal necrolysis/Stevens–Johnson syndrome and was reported to be the most common drug implicated as a cause of this condition [9].

The proportion of levetiracetam prescriptions increased significantly during the study period. This was consistent with the results of previous studies [4,5]. The increase in the proportion of prescriptions for levetiracetam, a newer ASM, may be because it is better tolerated as compared with traditional ASMs, and has fewer inter-

actions with other ASMs [10]. In addition, unlike valproic acid, levetiracetam has a low risk of drug-induced congenital malformations when used by pregnant women [11].

A previous study [12] showed that lamotrigine was prescribed at a higher proportion among the newer ASMs. However, among the newer ASMs, levetiracetam comprised the highest proportion of prescriptions in this study. The package inserts for levetiracetam and lamotrigine include information on the risk of suicide and other issues. However, lamotrigine prescription may be decreasing in Japan due to the Pharmaceuticals and Medical Devices Agency (PMDA) warning about serious skin rashes [13]. In addition, in recent years, it has been reported that this drug may suppress cardiac conduction [14]. These may be reasons for the low proportion of lamotrigine prescriptions in children in Japan.

There are differences between Japan and other countries regarding the prescription of ASM. In the United States and Europe, oxcarbazepine is used as an ASM. In contrast, while oxcarbazepine has been approved by PMDA in Japan, it is not commercially avail-

Table 2
Proportion of prescriptions for ASMs in children with epilepsy, by age group, per year.

	Year							P-value
	2013	2014	2015	2016	2017	2018	2019	
All patients								
0–5 years								
Children with epilepsy, n	1896	1754	1710	1660	1693	1686	1684	
Prescriptions of any ASM, %	56.17	57.30	58.42	57.95	60.84	61.15	58.02	0.01
Valproic acid, %	29.32	29.42	29.65	27.95	28.59	30.01	27.73	0.42
Levetiracetam, %	4.69	5.99	10.18	13.01	15.77	17.38	19.77	<0.0001
Carbamazepine, %	24.31	24.91	23.98	21.69	21.85	19.51	17.10	<0.0001
Clobazam, %	4.22	4.68	4.15	4.10	4.31	4.98	4.10	0.87
Zonisamide, %	4.54	4.05	3.22	3.19	3.37	3.62	3.33	0.06
Lamotrigine, %	2.69	3.36	2.57	2.47	2.60	2.55	3.33	0.89
Topiramate, %	2.22	2.17	2.75	3.01	3.31	3.50	2.55	0.04
Clonazepam, %	3.43	3.08	2.63	2.71	2.78	2.67	2.38	0.06
Lacosamide, %	0.00	0.00	0.00	0.00	0.00	0.06	2.14	<0.0001
6–11 years								
Children with epilepsy, n	3024	2912	2989	3033	3076	2995	2995	
Prescriptions of any ASM, %	70.34	70.40	70.53	70.89	70.19	71.32	70.25	0.78
Valproic acid, %	41.01	40.38	38.98	37.72	36.15	35.39	33.16	<0.0001
Levetiracetam, %	6.51	8.24	13.42	19.68	23.47	26.91	29.12	<0.0001
Carbamazepine, %	30.42	30.36	29.64	26.61	23.57	21.27	18.63	<0.0001
Clobazam, %	7.14	7.01	6.29	6.10	5.75	6.11	6.04	0.02
Lamotrigine, %	3.77	4.12	4.25	4.85	5.23	5.34	5.34	<0.0001
Lacosamide, %	0.00	0.00	0.00	0.00	0.10	0.23	3.11	<0.0001
Zonisamide, %	6.58	5.84	5.02	4.19	3.35	3.41	2.60	<0.0001
Topiramate, %	2.22	1.99	2.11	2.41	2.47	2.54	2.37	0.19
Clonazepam, %	4.89	4.57	4.32	3.30	2.70	2.40	2.20	<0.0001
Ethosuximide, %	1.29	1.13	1.34	1.52	1.59	1.80	2.00	0.002
12–17 years								
Children with epilepsy, n	3349	3296	3371	3485	3507	3535	3466	
Prescriptions of any ASM, %	71.07	70.90	69.53	70.04	70.00	70.64	70.69	0.79
Valproic acid, %	45.06	43.72	40.52	39.97	38.15	35.33	33.21	<0.0001
Levetiracetam, %	7.23	7.92	13.11	18.22	22.50	26.96	29.95	<0.0001
Carbamazepine, %	26.87	25.76	24.30	22.87	20.53	18.27	16.94	<0.0001
Lamotrigine, %	5.11	6.31	6.67	7.89	8.33	8.60	8.19	<0.0001
Clobazam, %	6.27	6.52	5.67	6.08	5.99	5.49	5.08	0.01
Lacosamide, %	0.00	0.00	0.00	0.11	1.00	1.73	4.07	<0.0001
Zonisamide, %	8.18	7.49	6.67	5.48	4.90	4.38	3.52	<0.0001
Clonazepam, %	5.32	4.70	4.48	3.79	3.91	3.39	3.26	<0.0001
Topiramate, %	2.27	2.76	3.00	3.21	2.99	2.80	2.74	0.33
Perampanel, %	0.00	0.00	0.00	0.57	1.82	2.18	2.11	<0.0001
Girls								
0–5 years								
Children with epilepsy, n	839	799	778	740	773	758	766	
Prescriptions of any ASM, %	56.97	57.20	57.07	59.19	61.71	62.27	58.22	0.04
Valproic acid, %	29.68	27.78	26.48	27.03	27.81	29.95	26.50	0.62
Levetiracetam, %	5.13	5.26	10.15	12.97	15.27	16.89	19.58	<0.0001
Carbamazepine, %	24.31	25.66	26.09	22.97	23.29	21.90	18.28	0.0004
Clobazam, %	3.93	4.13	3.47	3.78	4.01	5.41	4.05	0.37
Lamotrigine, %	2.26	3.25	2.19	2.84	2.46	2.24	3.39	0.58
Zonisamide, %	4.41	3.63	2.70	3.11	2.85	3.56	3.13	0.24
Clonazepam, %	3.46	2.88	2.19	3.24	3.36	2.77	2.61	0.60
Topiramate, %	2.26	1.88	2.57	3.78	3.36	3.56	2.09	0.23
Lacosamide, %	0.00	0.00	0.00	0.00	0.00	0.00	2.09	<0.0001
6–11 years								
Children with epilepsy, n	1388	1326	1383	1413	1413	1341	1357	
Prescriptions of any ASM, %	72.33	72.62	72.96	70.77	70.06	73.23	71.78	0.59
Valproic acid, %	41.21	41.63	39.48	37.58	35.31	36.39	33.53	<0.0001
Levetiracetam, %	7.20	8.60	14.68	20.74	24.49	28.41	30.21	<0.0001
Carbamazepine, %	30.19	29.71	29.65	25.27	22.08	20.06	17.69	<0.0001
Lamotrigine, %	4.03	4.37	4.48	4.95	5.59	5.89	6.34	0.0004
Clobazam, %	7.71	7.99	6.72	6.30	5.45	6.19	6.12	0.01
Lacosamide, %	0.00	0.00	0.00	0.00	0.07	0.15	3.32	<0.0001
Topiramate, %	2.59	2.34	2.17	2.26	2.76	2.98	2.80	0.27
Ethosuximide, %	2.02	1.51	2.10	1.98	2.19	2.46	2.73	0.049
Clonazepam, %	6.12	5.51	5.06	3.47	2.83	2.54	2.28	<0.0001
Zonisamide, %	6.84	6.11	5.13	4.10	2.90	2.91	2.21	<0.0001
12–17 years								
Children with epilepsy, n	1556	1565	1575	1615	1614	1657	1596	
Prescriptions of any ASM, %	71.92	71.95	71.17	69.97	70.32	70.25	70.68	0.19
Levetiracetam, %	7.39	7.54	13.71	19.50	24.35	30.84	35.40	<0.0001
Valproic acid, %	46.27	43.58	39.87	36.84	34.70	29.27	26.25	<0.0001
Carbamazepine, %	24.68	23.26	22.35	20.87	19.64	16.96	15.85	<0.0001
Lamotrigine, %	6.30	7.86	8.44	9.72	10.78	11.71	11.47	<0.0001

Table 2 (continued)

	Year							P-value
	2013	2014	2015	2016	2017	2018	2019	
Clobazam, %	6.23	6.13	5.40	5.51	5.82	5.61	5.45	0.34
Clonazepam, %	6.36	6.13	5.59	4.46	5.14	4.77	4.14	0.0009
Lacosamide, %	0.00	0.00	0.00	0.25	1.05	1.45	4.01	<0.0001
Topiramate, %	2.57	3.13	3.62	3.84	3.35	3.32	3.63	0.17
Zonisamide, %	8.87	7.41	6.86	5.26	4.71	4.04	3.32	<0.0001
Perampanel, %	0.00	0.00	0.00	0.56	1.61	1.93	2.13	<0.0001
Ethosuximide, %	1.54	1.60	1.46	1.49	1.18	1.09	1.25	0.16
Boys								
0–5 years								
Children with epilepsy, n	1057	955	932	920	920	928	918	
Prescriptions of any ASM, %	55.53	57.38	59.55	56.96	60.11	60.24	57.84	0.10
Valproic acid, %	29.04	30.79	32.30	28.70	29.24	30.06	28.76	0.53
Levetiracetam, %	4.35	6.60	10.19	13.04	16.20	17.78	19.93	<0.0001
Carbamazepine, %	24.31	24.29	22.21	20.65	20.65	17.56	16.12	<0.0001
Clobazam, %	4.45	5.13	4.72	4.35	4.57	4.63	4.14	0.58
Zonisamide, %	4.64	4.40	3.65	3.26	3.80	3.66	3.49	0.14
Lamotrigine, %	3.03	3.46	2.90	2.17	2.72	2.80	3.27	0.77
Topiramate, %	2.18	2.41	2.90	2.39	3.26	3.45	2.94	0.09
Clonazepam, %	3.41	3.25	3.00	2.28	2.28	2.59	2.18	0.04
Lacosamide, %	0.00	0.00	0.00	0.00	0.00	0.11	2.18	<0.0001
6–11 years								
Children with epilepsy, n	1636	1586	1606	1620	1663	1654	1638	
Prescriptions of any ASM, %	68.64	68.54	68.43	70.99	70.29	69.77	68.99	0.38
Valproic acid, %	40.83	39.34	38.54	37.84	36.86	34.58	32.84	<0.0001
Levetiracetam, %	5.93	7.94	12.33	18.77	22.61	25.70	28.21	<0.0001
Carbamazepine, %	30.62	30.90	29.64	27.78	24.83	22.25	19.41	<0.0001
Clobazam, %	6.66	6.18	5.92	5.93	6.01	6.05	5.98	0.48
Lamotrigine, %	3.55	3.91	4.05	4.75	4.93	4.90	4.52	0.03
Zonisamide, %	6.36	5.61	4.92	4.26	3.73	3.81	2.93	<0.0001
Lacosamide, %	0.00	0.00	0.00	0.00	0.12	0.30	2.93	<0.0001
Clonazepam, %	3.85	3.78	3.67	3.15	2.59	2.30	2.14	<0.0001
Topiramate, %	1.89	1.70	2.05	2.53	2.22	2.18	2.01	0.44
Ethosuximide, %	0.67	0.82	0.68	1.11	1.08	1.27	1.40	0.008
12–17 years								
Children with epilepsy, n	1,793	1,731	1,796	1,870	1,893	1,878	1,870	
Prescriptions of any ASM, %	70.33	69.96	68.10	70.11	69.73	70.98	70.70	0.39
Valproic acid, %	44.00	43.85	41.09	42.67	41.10	40.68	39.14	0.001
Levetiracetam, %	7.08	8.26	12.58	17.11	20.92	23.54	25.29	<0.0001
Carbamazepine, %	28.78	28.02	26.00	24.60	21.29	19.44	17.86	<0.0001
Lamotrigine, %	4.07	4.91	5.12	6.31	6.23	5.86	5.40	0.01
Clobazam, %	6.30	6.87	5.90	6.58	6.13	5.38	4.76	0.01
Lacosamide, %	0.00	0.00	0.00	0.00	0.95	1.97	4.12	<0.0001
Zonisamide, %	7.59	7.57	6.51	5.67	5.07	4.69	3.69	<0.0001
Clonazepam, %	4.41	3.41	3.51	3.21	2.85	2.18	2.51	<0.0001
Perampanel, %	0.00	0.00	0.00	0.59	2.01	2.40	2.09	<0.0001
Topiramate, %	2.01	2.43	2.45	2.67	2.69	2.34	1.98	0.98

ASM: anti-seizure medicine.

Each ASM is listed in order of the proportion of prescriptions of ASMs in 2019.

Each ASM with a proportion of prescriptions of 1% or more were included in the list in 2019.

The Cochran–Armitage trend test was used for statistical analysis.

A *p*-value <0.05 was considered statistically significant.

able because pharmaceutical companies have abandoned its marketing due to the associated risk of serious skin rash. Clobazam was approved in Japan in 2000, before it was approved in the United States in 2018, however, the proportion of clobazam prescriptions decreased over time in the present study. Clobazam is regarded as a treatment for Lennox–Gastaut syndrome in the United States and is used as an adjunct to other ASMs in Japan [15]. One reason for the decrease in the proportion of clobazam prescriptions in Japan is thought to be the recent availability of newer ASMs and other drugs that are highly effective in monotherapy. In addition, the use of perampanel for focal and tonic-clonic seizures is limited to patients aged 12 years and older in Japan, and 4 years and older in Europe. In the present study, the use of perampanel has gradually increased in boys and girls aged 12 years and older.

This study had several limitations. The target population was narrowed by the limited types of diseases registered in the MDV analyzer[®]. In addition, the age of the patients at the initial diagno-

sis of epilepsy could not be assessed and patient data could not be obtained from the MDV analyzer[®]. Finally, it was not possible to exclude or identify deceased patients obtained by the MDV analyzer[®]. Despite these limitations, to our knowledge, this is the first study to have clarified temporal trends in ASM prescriptions in Japanese pediatric outpatients. In the future, we would like to investigate the prescribing status of ASM for children using data from clinical databases other than the MDV analyzer[®], to investigate the generalizability of our study results.

5. Conclusions

The ASMs most commonly prescribed to Japanese pediatric outpatients with epilepsy from 2013–2019 were valproic acid, carbamazepine, and levetiracetam, regardless of sex. Over time, the proportion of prescriptions for valproic acid and carbamazepine decreased, whereas the proportion of prescriptions for levetirac-

etam increased. Our findings suggest that the trends in prescription of ASMs in pediatric outpatients with epilepsy in Japan have shifted toward newer ASMs that have recently become available.

6. Data statement

The research data is confidential.

Author contributions

DK, TO, SK, YA, HH, RM, SH, and YW were involved in study design and data interpretation. DK and TO were involved in the data analysis. All authors critically revised the report, commented on drafts of the manuscript, and approved the final manuscript.

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Ethical statement

The Institutional Review Board of Tohoku Medical and Pharmaceutical University Hospital approved the current study (approval number: 2019-2-066). Given the study's retrospective design, and the fact that all personal data were anonymized, the requirement for informed consent was waived.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ebr.2021.100474>.

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