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〔Original Short Communication〕

A 7-year longitudinal survey of valproate prescription in women of childbearing age in Japan using a publicly available National Insurance Claims Database Japan

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Abstract

【Introduction】Pharmacological treatments with valproate should be avoided where possible in childbearing-aged and pregnant women with epilepsy and bipolar disorder because they increase the risk of major congenital malformations. We previously reported a valproate prescription status in 2014 using publicly available National Insurance Claims Database（NDB Open Data Japan）. This study aimed to evaluate the changes over time in valproate prescription using the NDB Open Data, which was released after the previous research（2015–2020）.
【Methods】Following the previous study, we used prescription data from April 2015 to March 2021 from the NDB Open Data Japan. We examined the available prescription data of valproate in female and male outpatient data classified as total childbearing age（15–49 years）, younger childbearing age（15–29 years）, older childbearing age（30–49 years）, and non-childbearing age（≥ 50 years）. We determined the association between valproate prescription and sex at childbearing age, comparing to the non-childbearing age, and the odds ratio（OR）was estimated.
【Results】The proportion of valproate prescription for younger women of childbearing age（15–29 years）showed a significant downward trend from 2014 to 2020. Also, The OR of women of younger childbearing age（15–29 years）was decreased from 2014 to 2020 and 0.89（in 2014）, 0.77（in 2015）, 0.72（in 2016）, 0.69（in 2017）, 0.67（in 2018）, 0.63（in 2019）, and 0.63（in 2020）.
【Discussion】The proportion of valproate prescriptions for younger women of childbearing age（15–29 years）decreased every year between 2014 and 2019, likely influenced by factors such as safety concerns during pregnancy, changes in treatment guidelines favoring alternative medications, and improved patient education about the potential risks associated with valproate use during pregnancy.

***Key words*: National Insurance Claims Database, NDB Open Data Japan, Epilepsy and Bipolar Disorder, Valproate, Major Congenital Malformations**

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Valproate is an anticonvulsant that was approved in the 1960s and is widely prescribed for the treatment of epilepsy and bipolar disorder[1]. It increases the risk of major congenital malformations, such as neural tube defects and intellectual disability of the offspring, when administered to pregnant women[2,3]. Therefore, pharmacological treatments with valproate should be avoided where possible in childbearing-aged and pregnant women with epilepsy and bipolar disorder [2,4]. Considering that at least 40% of pregnancies are unplanned or unintended, as indicated by several epidemiologic studies[5-7], physicians, neurologists, and psychiatrists consulting patients with epilepsy and bipolar disorder should avoid prescribing drugs with a high risk of teratogenicity, especially valproate, in girls and women of childbearing age.

Yoshimura and his colleagues' report[8]shows that the number of valproate prescription for female outpatients of childbearing ages (15–49 years) was only slightly lower than that for male outpatients of the same ages in Japan during the fiscal year 2014 (April 2014 to March 2015) by using the publicly available National Insurance Claims Database (NDB Open Data Japan, Available from https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/0000177182.html). Given that valproate is contraindicated in pregnant

Table 1 List of drugs included in the analysis.

year	2014		2015		2016		2017	
rank	Drug Name	Number	Drug Name	Number	Drug Name	Number	Drug Name	Number
1	DEPAKENE R Tablets 200mg	250,275,573	DEPAKENE R Tablets 200mg	238,498,163	DEPAKENE R Tablets 200mg	208,727,622	DEPAKENE R Tablets 200mg	189,225,500
2	DEPAKENE R Tablets 100mg	52,296,229	SODIUM VALPROATE SR TABLETS 200mg "TOWA"	58,898,731	SODIUM VALPROATE SR TABLETS 200mg "TOWA"	79,065,556	SODIUM VALPROATE SR TABLETS 200mg "TOWA"	93,609,282
3	SODIUM VALPROATE SR TABLETS 200mg "TOWA"	48,534,974	DEPAKENE R Tablets 100mg	50,786,340	SODIUM VALPROATE SR TABLETS 200mg "AMEL"	49,523,189	SODIUM VALPROATE SR TABLETS 200mg "AMEL"	55,460,632
4	SODIUM VALPROATE SR TABLETS 200mg "AMEL"	30,755,214	SODIUM VALPROATE SR TABLETS 200mg "AMEL"	38,179,839	DEPAKENE R Tablets 100mg	45,578,733	DEPAKENE R Tablets 100mg	42,428,592
5	VALERIN 200mg	29,031,571	VALERIN 200mg	28,655,214	VALERIN 200mg	28,290,863	VALERIN 200mg	27,699,638
6	Depakene Tablets 200mg	28,031,861	DEPAKENE 200mg	25,703,493	DEPAKENE 200mg	22,411,278	DEPAKENE 200mg	20,208,696
7	SELENICA-R Tablets 200mg	20,011,132	SELENICA-R Tablets 200mg	19,705,873	SELENICA-R Tablets 200mg	18,598,325	SELENICA-R Tablets 200mg	17,669,718
8			SODIUM VALPROATE SR TABLETS 100mg "TOWA"	9,922,283	SODIUM VALPROATE SR TABLETS 100mg "TOWA"	13,601,067	SODIUM VALPROATE SR TABLETS 100mg "TOWA"	16,665,039
9			SELENICA-R Tablets 400mg	8,071,923	SELENICA-R Tablets 400mg	8,251,796	SELENICA-R Tablets 400mg	8,324,722
10			VALERIN 100mg	6,472,630	SODIUM VALPROATE SR TABLETS 100mg "AMEL"	6,585,430	SODIUM VALPROATE SR TABLETS 100mg "AMEL"	8,225,244
11			Depakene Tablets 100mg	6,071,116	VALERIN 100mg	6,575,044	VALERIN 100mg	6,444,059
12			SODIUM VALPROATE SR TABLETS 100mg "AMEL"	3,828,097	Depakene Tablets 100mg	5,482,374	Depakene Tablets 100mg	5,152,090
13			SODIUM VALPROATE TABLETS 200mg "AMEL"	3,651,038	SODIUM VALPROATE TABLETS 200mg "AMEL"	4,371,308	SODIUM VALPROATE TABLETS 200mg "AMEL"	4,801,140
14			EPIRENAT 200mg	1,224,126	SODIUM VALPROATE TABLETS 200mg "FUJI-NAGA"	2,096,522	SODIUM VALPROATE TABLETS 200mg "FUJI-NAGA"	1,975,845
15			SODIUM VALPROATE TABLETS 200mg "TCK"	1,117,580	SODIUM VALPROATE TABLETS 200mg "TCK"	1,129,351	SODIUM VALPROATE TABLETS 200mg "TCK"	1,045,880
16			SODIUM VALPROATE TABLETS 200mg "FUJI-NAGA"	905,677	SODIUM VALPROATE TABLETS 100mg "AMEL"	696,892	SODIUM VALPROATE TABLETS 100mg "AMEL"	858,324
17			SODIUM VALPROATE TABLETS 100mg "AMEL"	444,327	SODIUM VALPROATE TABLETS 100mg "FUJI-NAGA"	173,509	SODIUM VALPROATE TABLETS 100mg "FUJI-NAGA"	211,895
18			EPIRENAT 100mg	65,486	SODIUM VALPROATE TABLETS 100mg "TCK"	32,574	SODIUM VALPROATE TABLETS 100mg "TCK"	35,948
19			SODIUM VALPROATE TABLETS 100mg "FUJI-NAGA"	59,478				

year	2018		2019		2020	
rank	Drug Name	Number	Drug Name	Number	Drug Name	Number
1	DEPAKENE R Tablets 200mg	160,794,361	DEPAKENE R Tablets 200mg	145,605,892	SODIUM VALPROATE SR TABLETS 200mg "TOWA" *1	149,704,708
2	SODIUM VALPROATE SR TABLETS 200mg "TOWA"	115,750,175	SODIUM VALPROATE SR TABLETS 200mg "TOWA" *1	124,521,637	DEPAKENE R Tablets 200mg	134,034,819
3	SODIUM VALPROATE SR TABLETS 200mg "AMEL"	64,169,267	SODIUM VALPROATE SR TABLETS 200mg "AMEL"	67,397,112	SODIUM VALPROATE SR TABLETS 200mg "AMEL"	67,398,262
4	DEPAKENE R Tablets 100mg	37,026,896	DEPAKENE R Tablets 100mg	33,373,271	DEPAKENE R Tablets 100mg	30,851,018
5	VALERIN 200mg	27,462,477	VALERIN 200mg	27,356,211	SODIUM VALPROATE SR TABLETS 100mg "TOWA" *2	28,012,152
6	SODIUM VALPROATE SR TABLETS 100mg "TOWA"	21,234,958	SODIUM VALPROATE SR TABLETS 100mg "TOWA" *2	24,097,130	SELENICA-R Tablets 200mg	16,026,108
7	DEPAKENE 200mg	17,502,846	SELENICA-R Tablets 200mg	16,099,877	DEPAKENE 200mg	14,837,432
8	SELENICA-R Tablets 200mg	16,720,534	DEPAKENE 200mg	15,943,153	VALERIN 200mg	13,955,594
9	SODIUM VALPROATE SR TABLETS 100mg "AMEL"	10,532,655	SODIUM VALPROATE SR TABLETS 100mg "AMEL"	12,194,129	SODIUM VALPROATE SR TABLETS 100mg "AMEL"	13,944,514
10	SELENICA-R Tablets 400mg	8,352,684	SODIUM VALPROATE SR TABLETS 200mg "TOWA" *1	9,241,656	SODIUM VALPROATE SR TABLETS 200mg "DSP"	13,206,170
11	VALERIN 100mg	6,657,646	SELENICA-R Tablets 400mg	8,503,483	SELENICA-R Tablets 400mg	8,804,092
12	SODIUM VALPROATE TABLETS 200mg "AMEL"	5,502,281	VALERIN 100mg	6,935,269	SODIUM VALPROATE TABLETS 200mg "AMEL"	6,450,488
13	Depakene Tablets 100mg	4,546,196	SODIUM VALPROATE TABLETS 200mg "AMEL"	5,795,303	VALERIN 100mg	4,379,426
14	SODIUM VALPROATE TABLETS 200mg "FUJI-NAGA"	1,977,853	Depakene Tablets 100mg	4,227,347	Depakene Tablets 100mg	3,983,817
15	SODIUM VALPROATE TABLETS 100mg "AMEL"	1,126,284	SODIUM VALPROATE TABLETS 200mg "FUJI-NAGA"	1,956,922	SODIUM VALPROATE SR TABLETS 200mg "TOWA" *1	2,736,714
16	SODIUM VALPROATE TABLETS 200mg "TCK"	1,059,352	SODIUM VALPROATE SR TABLETS 100mg "TOWA" *2	1,295,392	SODIUM VALPROATE SR TABLETS 100mg "DSP"	2,602,078
17			SODIUM VALPROATE TABLETS 200mg "TCK"	1,016,809	SODIUM VALPROATE TABLETS 200mg "FUJI-NAGA"	2,203,945
18			SODIUM VALPROATE TABLETS 100mg "AMEL"	873,696	SODIUM VALPROATE SR TABLETS 100mg "TOWA" *2	1,128,754
19					SODIUM VALPROATE TABLETS 100mg "AMEL"	1,027,421

In 2014, data was provided for only the top 30 antiepileptic drugs; since 2015, data was provided for the top 100 drugs. Only tablets were extracted and analyzed in this study.
*1&*2: Listed separately due to name change

women as a general rule[9], this finding demonstrates the possibility that valproate prescription to girls and women in preconception period with due consideration of increasing the teratogenic risks was insufficiently implicated in Japan in 2014–2015. Therefore, the recent guidelines[10-13]indicate that valproate prescription should be avoided for childbearing-age women with potential pregnancy as much as possible. However, there were few studies regarding changes of valproate prescription in Japan after the fiscal year 2014.

The present study aimed to evaluate the changes over time in valproate prescription to girls and women

of childbearing age using the NDB Open Data, which was released after the previous research (2015–2020). Drugs used in the analysis is described in Table 1.

In this study, we used prescription data from April 2015 to March 2021 from the NDB Open Data Japan. We examined the available prescription data of valproate in female and male outpatient data classified as total childbearing (age: 15–49 years), younger childbearing (age: 15–29 years), older childbearing (age: 30–49 years), and non-childbearing age (age: ≥ 50 years). The odds ratio (OR) was defined according to a following method. The proportion of the number of tablets prescribed to women of childbearing age (15–29 and 30–49 years) to the number prescribed to women aged ≥ 50 years was compared with the odds of the case group. The proportion of the number of tablets prescribed to men in the same age group as women of the childbearing age to the number of tablets prescribed for men ≥ 50 years was compared with the odds of the control group. The OR was finally calculated using the odds of the case and control groups. Specifically, a drug with an OR > 1.000 was prescribed at a higher rate to women of childbearing age than it was to men of the corresponding age. In contrast, an OR < 1.000 indicated that the drug was prescribed at a lower rate to women of childbearing age than to men of the corresponding age.

Table 2 describes the number and percentage of valproic acid prescriptions by number of prescribed tablets and by gender and age groups. The proportion of valproate prescription for younger women of childbearing age (15–29 years) showed a significant downward trend from 2014 to 2020. In 2014, the proportion of valproate prescriptions for women aged 15-29 years was 15.4% in 2014. Subsequently, the proportion of valproate prescriptions for women of childbearing age (15–29 years) gradually decreased each year thereafter and was 13.8% (in 2015), 13.1% (in 2016), 12.4% (in 2017), 11.9% (in 2018), 11.2% (in 2019), and 11.1% (in 2020).

The proportion of valproate prescriptions for men aged 15–29 years slightly decreased; the proportion of valproate prescriptions was 16.6% (in 2014), 16.6% (in 2015), 16.5% (in 2016), 16.2% (in 2017), 15.9% (in 2018), 15.8% (in 2019), and 15.6% (in 2020). In contrast, the proportion of valproate prescriptions for women aged ≥ 50 years had dramatically increased: 46.5% (in 2014), 48.1% (in 2015), 48.6% (in 2016), 49.6% (in 2017), 50.5% (in 2018), 51.5% (in 2019), and 52.0% (in 2020). The proportion of valproate prescriptions for people aged 30–49 years did not change significantly in both men and women.

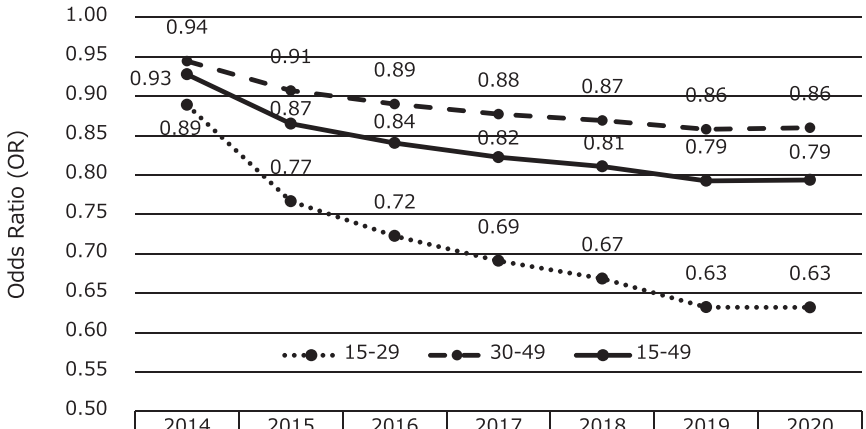
Figure 1 shows the odds ratio by total childbearing [15–49 years], younger childbearing [15–29 years], and older childbearing age [30–49 years], respectively.

OR > 1.000 indicates that the drug is prescribed at a significantly higher rate to women of childbearing age (15–29 or 30–49 years) than to male outpatients of the corresponding age. Also Figure 1 shows that the OR of women of childbearing age (15–29 years) dramatically decreased from 2014 to 2019. However, from 2019 to 2020, it remained flat.

The present longitudinal study indicated that the

Table 2 Number and percentage of valproic acid prescriptions by number of tablets prescribed and by gender and age groups.

		2014		2015		2016		2017		2018		2019		2020	
sex	ages	Number (Tablets)	%	Number (Tablets)	%	Number (Tablets)	%	Number (Tablets)	%	Number (Tablets)	%	Number (Tablets)	%	Number (Tablets)	%
Female	Total	125,451,907	100.0	257,015,500	100.0	255,950,711	100.0	256,704,291	100.0	255,859,758	100.0	257,703,190	100.0	261,429,277	100.0
	15–49	67,123,273	53.5	133,450,440	51.9	131,537,897	51.4	129,472,272	50.4	126,738,184	49.5	125,094,374	48.5	125,512,279	48.0
	15–29	19,296,528	15.4	35,364,648	13.8	33,422,118	13.1	31,949,349	12.4	30,396,313	11.9	28,955,148	11.2	29,019,209	11.1
	30–49	47,826,746	38.1	98,085,792	38.2	98,115,779	38.3	97,522,924	38.0	96,341,871	37.7	96,139,226	37.3	96,493,071	36.9
	> 50	58,328,634	46.5	123,565,060	48.1	124,412,814	48.6	127,232,019	49.6	129,121,574	50.5	132,608,816	51.5	135,916,998	52.0
Male	Total	147,684,031	100.0	322,344,772	100.0	320,728,276	100.0	320,532,959	100.0	318,451,831	100.0	319,610,458	100.0	320,026,527	100.0
	15–49	81,764,629	55.4	178,987,985	55.5	178,683,008	55.7	177,262,260	55.3	174,400,475	54.8	173,697,385	54.3	172,111,588	53.8
	15–29	24,534,648	16.6	53,527,477	16.6	52,816,062	16.5	52,072,337	16.2	50,735,764	15.9	50,404,156	15.8	49,980,578	15.6
	30–49	57,229,981	38.8	125,460,508	38.9	125,866,946	39.2	125,189,924	39.1	123,664,710	38.8	123,293,229	38.6	122,131,011	38.2
	> 50	65,919,402	44.6	143,356,786	44.5	142,045,269	44.3	143,270,699	44.7	144,051,356	45.2	145,913,074	45.7	147,914,939	46.2



	2014	2015	2016	2017	2018	2019	2020
15-29	0.89	0.77	0.72	0.69	0.67	0.63	0.63
30-49	0.94	0.91	0.89	0.88	0.87	0.86	0.86
15-49	0.93	0.87	0.84	0.82	0.81	0.79	0.79

Fig. 1 Transition over time of the odds ratio that was indicated between valproate prescription and sex in patients of childbearing women age.

proportion of valproate prescriptions for younger women of childbearing age [15–29 years] decreased every year between 2014 and 2019. Our finding was consistent with the recent survey for general practitioners in UK, reporting a trend toward a decrease in the prescription of valproate to women of childbearing age from 2004 to 2018[10].

Because this study is an observational study using NDB open data and the causal relationship is unclear, the decreased use of valproate in younger women of childbearing age [15–29 years] for every year between 2014 and 2019 may be influenced by several factors, including concerns about its safety during pregnancy, changes in treatment guidelines, increased use of alternative medications, and improved patient education. Multiple academic societies, including the European Academy of Neurology, issued a statement on the need to limit the use of valproate in girls and women of childbearing potential with epilepsy[11]. Additionally, the Japanese Society of Perinatal Mental Health in 2017 recommended limiting the use of valproate in girls and women of childbearing age[12](Available from http://pmhguideline.com). In addition, after the conference of Japanese Society of Perinatal Mental Health, guideline of Japanese Society of Psychiatry and Neurology had been updated to warn the use of valproate during perinatal period[13]. Also, concerns about the safety of valproate use during pregnancy have led to warnings from regulatory agencies, such as the US Food and Drug Administration (FDA), the European Medicines Agency (EMA), Japan's Ministry of Health, Labor and Welfare (Available from https://www.mhlw.go.jp/content/11121000/000486507.pdf) and, the Japanese Society of Perinatal Mental Health (Available from http://pmhguideline.com) about the increased risk of birth defects and developmental disorders in the offspring[11,12,14]. These warnings have likely increased awareness among healthcare providers and patients about the potential risks associated with valproate use during pregnancy. As a result, healthcare providers may have become more cautious about prescribing valproate to women of childbearing age, and patients may have become more informed about the potential risks and more likely to request alternative treatments.

Changes in treatment guidelines may have also contributed to the decreased use of valproate in young women. For example, the American Academy of Neurology and the Japanese Society of Neurology recommend avoiding valproate as a first-line treatment in women of childbearing age and using alternative medications, such as lamotrigine, levetiracetam, or oxcarbazepine, instead[16,17]. These guidelines are based on evidence showing that these alternative

medications have lower risks of birth defects and developmental disorders in offspring, and they reflect a growing awareness of the risks associated with valproate use during pregnancy.

Increased use of alternative medications may have also played a role in the decreased use of valproate in young women. Several alternative antiepileptic drugs, such as lamotrigine and levetiracetam, have been shown to be effective in treating epilepsy and are considered safer for use during pregnancy[18]. Studies have shown that these medications have lower risks of major congenital malformations and developmental disorders than valproate[19]. The availability and efficacy of these alternative medications may have made healthcare providers and patients more willing to consider alternatives to valproate.

Improved patient education may also have contributed to the decreased use of valproate in young women. Patients may have become more informed about the potential risks associated with valproate use during pregnancy through increased awareness campaigns and patient education materials. This may have led to more informed decision-making among patients and their healthcare providers, resulting in a decrease in the use of valproate in women of childbearing age.

In summary, the trend of decreased use of valproate in young women is likely the result of a combination of factors, including concerns about the safety of valproate during pregnancy, changes in treatment guidelines, increased use of alternative medications, and improved patient education.

Limitation

The main limitation of this study was that the data presented were based on the numbers of prescribed valproate tablets obtained from the publicly accessible NDB, not on data on individual patients prescribed the drug. Additionally, the NDB open data discloses only the top 100 products, making it difficult to ascertain the total number of products (30 products in 2014). In the NDB open data, only the total administered dose data is available, making it impossible to distinguish between new prescriptions and continued prescriptions. Therefore, it is anticipated that the prescription count for valproic acid may be decreasing for new prescription cases. However, this cannot be conclusively determined in the present study.

Contributors

RS conducted data collection and data entry, performed the statistical analysis, and wrote the manuscript.DS and KY TH provided constructive comments and revised the manuscript. All authors read and approved the final manuscript.

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Conflict of interest

All authors declare that there is no conflict of interest related to this study.

Ethical approval

This study did not require ethics approval because publicly available materials were used.

Data availability

Not applicable.

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