

## ORIGINAL ARTICLE

# Effectiveness and safety of an extended-release tablet of sodium valproate for the prophylactic treatment of migraine: Postmarketing surveillance in Japan

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## Key words

extended-release tablet, migraine prophylaxis, observation study, postmarketing surveillance, sodium valproate.

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## Abstract

**Background:** Sodium valproate is a standard drug for first-line prophylactic treatment of migraine. However, little information is available of its use in Japanese patients.

**Aim:** To evaluate the effectiveness and safety of an extended-release tablet of sodium valproate in the prophylactic treatment for Japanese patients with migraine by postmarketing surveillance.

**Methods:** This was a prospective, multicenter and non-interventional observation study in routine clinical practice. A total of 1222 patients with migraine of all age groups (aged <10 to ≤80 years) and both sexes (17.3% men and 82.7% women) from 169 sites were enrolled.

**Results:** Migraine frequency during a 4-week period was reduced from  $10.2 \pm 6.0$  days in 1040 patients to  $5.0 \pm 4.6$  days in 944 patients ( $P < 0.001$ ): 70.8% of patients experienced remission of migraine by  $\geq 30\%$ , 59.0% by  $\geq 50\%$  and 11.8% by  $\geq 100\%$ . Multivariate analysis and stratification sampling showed that this sodium valproate tablet was the most effective in patients with more migraine days, and complete remission was observed in 29% of patients whose migraine days were less than 3 days per 4 weeks at baseline. The extended-release tablet of sodium valproate reduced migraine intensity and duration of migraine attacks. The incidence of adverse drug reactions was 6.3% (67/1070 patients) and well tolerated. However, four pregnancies were discovered in this survey.

**Conclusions:** This first large observation study in Japan suggests that an extended-release tablet of sodium valproate is effective and safe for the prophylactic treatment of patients with migraine in routine clinical practice.

## Introduction

Migraine is a chronic neurological disorder with heterogeneous characteristics resulting in a range of symptom profiles, burden and disability. Population-based epidemiological studies based on the International Headache Society Classification suggest that the prevalence of migraine in Japan is 6.0–8.4%.<sup>1,2</sup> Migraines are controlled by acute treatment to stop an attack or prophylactic treatment to reduce the frequency, duration or severity of attacks.<sup>3</sup> Several types of drugs, including anti-epileptics, antidepressants,  $\beta$ -blockers and calcium blockers, are recommended by the Japanese Guidelines for the Management of Primary Headache 2006 for use in the prophylactic treatment of migraines.<sup>4</sup> However, the calcium channel blocker, lomerizine, was the only drug

approved for migraine prophylaxis in Japan.<sup>5</sup> In 2004, an extended-release tablet of sodium valproate was approved, and is now widely used as an anticonvulsant drug for the treatment of epilepsy, anxiety disorder and bipolar disorder in Japan. Meanwhile, sodium valproate has been a standard drug for first-line prophylactic treatment of migraine in the USA and Europe.<sup>6,7</sup> Its clinical effectiveness and safety profiles are well-known in representative medical textbooks.<sup>8,9</sup> The Evaluation Committee on Unapproved or Off-Label Drugs with High Medical Needs of the Ministry of Health, Labor and Welfare of Japan<sup>10</sup> concluded that there is a substantial need to make sodium valproate and its extended-release formulation available for use in the prophylactic treatment of migraine, and designated it as a drug for which an Application Based on Public Knowledge<sup>11</sup> could be

submitted. In May 2011, a new indication of sodium valproate and its extended-release formulation for use in the prophylactic treatment of migraine was approved in Japan on the basis of clinical evidence from the USA and European countries.

To date, there are few reports describing the clinical outcome of sodium valproate in Japanese migraineurs. Therefore, we carried out a prospective non-interventional, observational, postmarketing surveillance of an extended-release tablet of sodium valproate to determine the effectiveness and safety when used for the prophylactic treatment of migraine in Japanese patients in routine clinical practice.

## Methods

**Study design.** This was a prospective, observational, multicenter, non-interventional postmarketing surveillance of Selenica-R, which is an extended-release tablet of sodium valproate produced by Kowa Company. The survey was carried out in accordance with the Japanese regulatory requirements stipulated in the Good Post-Marketing Study Practice. Approval was granted by the ethics committee, and written informed consent from patients was obtained according to the policies of each institution/clinic. Only physicians who treat migraine in their routine clinical practice according to the guidelines for prophylactic treatment of migraine with sodium valproate were involved in this survey. The registration period was from October 2011 to September 2012, and the survey period was from October 2011 to March 2013, during which time the enrolment of 1000 patients was planned.

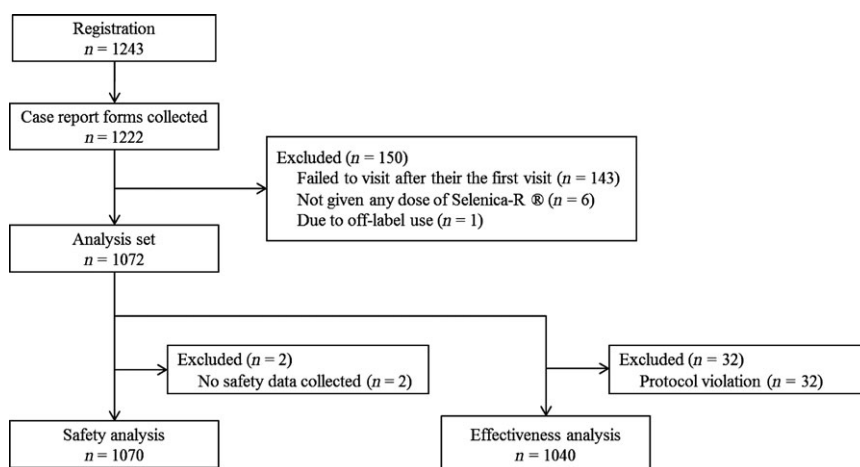
**Patients.** Patients were registered into this survey using a central registration system by Kowa Company, within 4 weeks after commencement of treatment with an extended-release tablet of sodium valproate. The patients enrolled in this survey had to meet all criteria: (i) having migraine attacks at least twice a month; (ii) with disabling

migraine refractory to acute treatment; (iii) sodium valproate-naïve for 1 year; (iv) available data on migraine attacks during the 4 weeks before the start of this survey; and (v) had not received any preventative medication for migraine or changed their preventative medication for migraine for at least 3 months before this survey.

**Observation period.** The observation period was 12 weeks. Survey data were collected every 4 weeks during the observation period, and the case report forms were collected at the end of the observation period or after early termination by discontinuation of extended-release tablet of sodium valproate therapy. Kowa Company confirmed inconsistent data with a query sheet.

**Effectiveness assessment.** Effectiveness was assigned to the changes of migraine frequency, all headache frequency including migraine and non-migraine, migraine attack intensity, migraine duration per attack, and aura and associated symptoms at the end of the observation period from baseline. The migraine and all headache frequency were defined as days of migraine attacks per 4-week period. The migraine attack intensity was measured by 0–10 on a numeric pain rating scale. The migraine duration per attack was classified into  $\leq 6$  h,  $>6$  h to  $\leq 12$  h,  $>12$  h to  $\leq 24$  h,  $>24$  h to  $\leq 48$  h,  $>48$  h to  $\leq 72$  h and  $>72$  h. The overall assessment (excellent improved, improved, no change, aggravated, very aggravated and no assessment) by the physician was carried out at the end of the observation period.

**Safety assessment.** Adverse events that occurred during the observation period were collected regardless of causality to the drug. The physician reported the name of the adverse event, date on which the event occurred, seriousness, actions carried out for the event, the outcome, date of outcome, relationship of the adverse event to the drug, factors probably related to the adverse event other than the drug and detailed symptoms course.



**Figure 1** Patient disposition. Selenica-R is an extended-release tablet of sodium valproate marked by Kowa Company.

**Table 1** Patient characteristics

Variable	No. patients	%
Analysis set	1072	
Sex		
Male	185	17.3
Female	887	82.7
First visit and follow-up visits		
First visit	463	43.2
Follow up visit	609	56.8
Age (years)		
<10	3	0.3
≥10 to <20	72	6.7
≥20 to <30	153	14.3
≥30 to <40	273	25.5
≥40 to <50	311	29.0
≥50 to <60	140	13.1
≥60 to <70	86	8.0
≥70 to <80	28	2.6
≥80	6	0.6
Mean ± SD	40.9 ± 14.1	
BMI (kg/m <sup>2</sup> )		
Mean ± SD	21.5 ± 3.5	
Subtype of migraine		
Migraine without aura	834	77.8
Migraine with aura	238	22.2
Visual symptoms	205	19.1
Sensory symptoms	23	2.1
Aphasia	1	0.1
Others	20	1.9
Associated symptoms		
No	163	15.2
Yes	909	84.8
Nausea	793	74.0
Vomiting	471	43.9
Photophobia	521	48.6
Phonophobia	426	39.7
Osmophobia	182	17.0
Duration with migraine (years)		
<1	38	3.6
≥1 to <5	168	15.8
≥5 to <10	157	14.7
≥10 to <20	276	25.9
≥20 to <30	220	20.6
≥30 to <40	137	12.9
≥40	70	6.6
Mean ± SD	16.7 ± 12.6	
Initial daily dose		
≤100 mg	10	0.9
200 mg	210	19.6
300 mg	5	0.5
400 mg	822	76.7
600 mg	3	0.3
800 mg	22	2.1
Mean ± SD	366.2 ± 105.1	

**Statistical analysis.** The analysis set included patients who had taken at least one dose of an extended-release tablet of sodium valproate and with at least one follow-up

**Table 1.** Continued

Variable	No. patients	%
Maximal daily dose <sup>†</sup>		
≤100 mg	11	1.0
200 mg	171	16.0
300 mg	4	0.4
400 mg	828	77.2
500 mg	1	0.1
600 mg	12	1.1
800 mg	44	4.1
1000 mg	1	0.1
Mean ± SD	383.9 ± 120.5	

<sup>†</sup>In Japan the maximum approved daily dose of Selenica-R for the treatment of migraine is 1000 mg. BMI, body mass index.

visit during the observation period. Patients with safety data were included in the safety analysis set, for which the number of patients with treatment-emergent adverse events was summarized by system organ class, and the number of adverse events was summarized by preferred term (Medical Dictionary for Regulatory Activities Japanese version, ver. 16.0). From the safety analysis set, the patients who met the survey criteria were involved in the effectiveness analysis set. The efficacy items requested by the survey protocol, but not available, were treated as missing values and were complemented by the last observation carried forward method. The effectiveness was analyzed in changes and change rates of migraine frequency, migraine intensity and total headache, rate of 50% and complete remission of migraine, and change of migration duration per attack by one-sample *t*-test. Remission rate was defined as the reduction rate of migraine frequency in the number of migraine days per 4-week periods from the baseline to the end of the observation period. Factors affecting the effectiveness (change rate of migraine frequency) and safety were analyzed by multiple logistic regression models.

*P*-values of 0.05 or less were regarded as significant. SAS 9.2 for Windows (SAS Institute Japan, Tokyo, Japan) was used for the statistical analyses.

## Results

**Baseline characteristics.** Of the 1243 patients registered 1222 case report forms were collected from 169 sites throughout Japan. The analysis set consisted of 1072 patients after exclusion of those did not return to the site after registration (143 patients), those registered but given no dose of an extended-release tablet of sodium valproate (6 patients) and off-label use (1 patient). Safety analysis was carried out in 1070 cases after exclusion of two patients because of lack of safety data. Of the 1072 patients, 32 were excluded from efficacy analysis because of survey protocol violation, as shown in Figure 1. A total of 793 patients completed the 12-week observation period. A total of 279 patients withdrew from the survey during the observation period due to loss of follow up (163 cases), adverse events (40 cases), lack of efficacy (32 cases) and others (44 cases).

The mean observation  $\pm$  standard deviation period was  $72.1 \pm 22.8$  days.

Table 1 summarizes the patient characteristics. Of the 1072 patients included in the analysis set, 17.3% were men and 82.7% were women. The mean age was  $40.9 \pm 14.1$  years. The migraineurs with aura was 22.2%, and associated symptoms including nausea, vomiting, visual symptoms, sensory symptoms and osmophobia were reported in 84.8% of patients with migraine. The mean migraine duration was  $16.7 \pm 12.6$  years. The mean initial daily dose of an extended-release tablet of sodium valproate was  $366.2 \pm 105.1$  mg, and the mean maximal daily dose was  $383.9 \pm 120.5$  mg. The concomitant diseases were tension headache (306), psychiatric disease (95), hypertension (59), asthma (21), epilepsy (9), cardiac disease (9), cerebral vascular disorder(5), cluster headache (5) and others (227) in 541 (50.5%) patients.

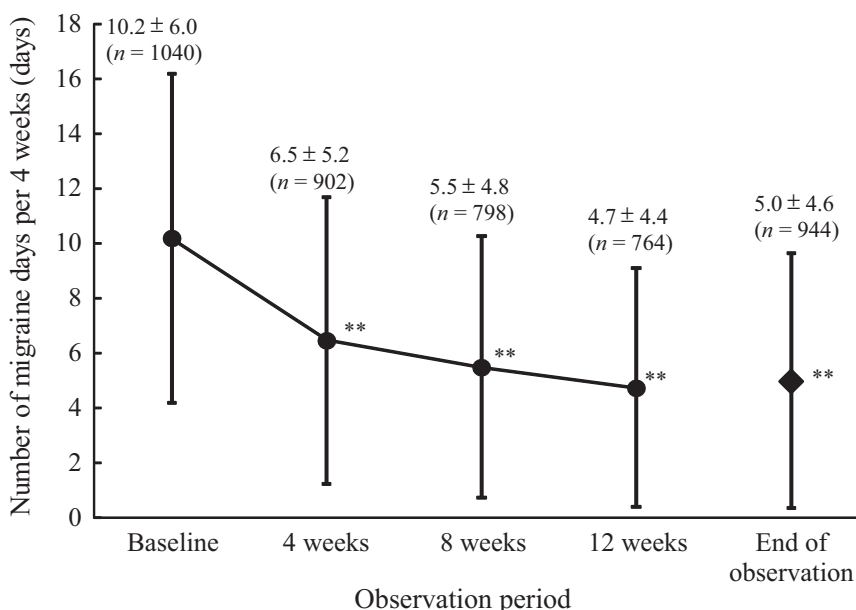
**Effectiveness.** The frequency of migraine per 4-week periods was significantly reduced from  $10.2 \pm 6.0$  days to  $5.0 \pm 4.6$  days with a reduction of  $5.2 \pm 5.7$  days ( $-46.3 \pm 45.9\%$ ) at the end of the observation period ( $n = 944$ ) from baseline ( $n = 1040$ ) as shown in Figure 2. Similarly, the total number of headaches including migraine and non-migraine days per 4-week periods changed from  $12.8 \pm 8.4$  days at baseline ( $n = 1035$ ) to  $6.7 \pm 6.8$  days at the end of the observation ( $n = 942$ ), with a statistically significant reduction of  $6.1 \pm 7.4$  days ( $43.6 \pm 51.0\%$ ;  $P < 0.001$ ). At the end of the observation period, 70.8% of patients had a remission of  $\geq 30\%$ , 59.0% of  $\geq 50\%$  and 11.8% of 100% in the number of migraine days per 4-week periods ( $n = 944$ ), respectively.

The factors affecting the effectiveness of prophylactic treatment were analyzed by multivariate analysis. The number of migraine days per 4-week periods and aura visual symptoms were found as factors affecting the effectiveness, whereas the number of treatments with triptans  $>10$ , psychiatric disorder as associated disease, nausea and sensory symptoms were factors of resistance to treatment effectiveness (Table 2). Post-hoc subpopulation analysis shows that the patients with the greatest number of migraines at baseline resulted in more reduction in migraine days after

**Table 2** Factors affecting effectiveness

Factor	Estimated value <sup>†</sup>	SE	P-value
No. migraine days per 4 weeks before treatment			
$\geq 3$ to $<8$ days	-19.944	9.621	0.038
$\geq 8$ to $<15$ days	-33.888	9.621	$< 0.001$
$\geq 15$ days	-44.644	9.935	$< 0.001$
Aura visual symptoms			
Yes	-10.158	3.808	0.008
Frequency of use of triptans before treatment			
More than 10 times	11.638	3.747	0.002
Concomitant psychiatric disorder			
Yes	11.152	5.225	0.033
Associated symptoms: Nausea			
Yes	9.043	3.472	0.009
Associated symptoms: Phonophobia			
Yes	7.183	3.133	0.022

<sup>†</sup>Estimated value: partial regression coefficient.

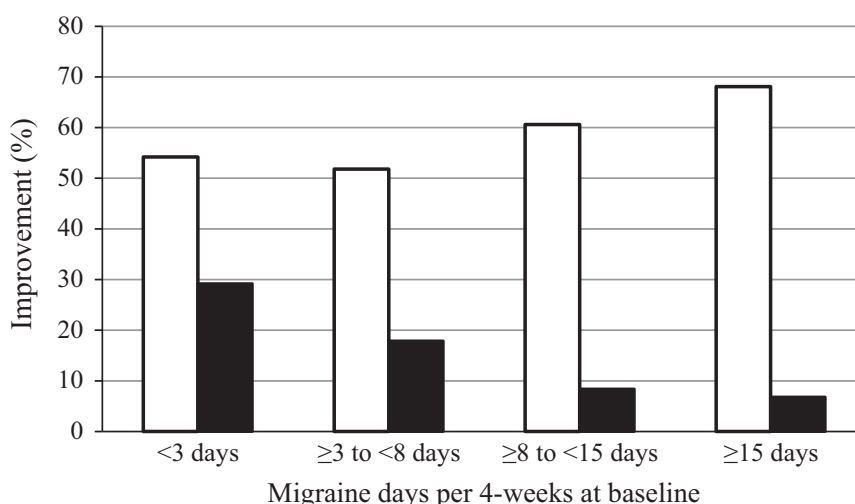


**Figure 2** Changes in the number of migraine days per 4 weeks (mean  $\pm$  SD). The figure shows that treatment with extended-release tablet of sodium valproate reduced the number of migraine days time dependently.  $**P < 0.001$ .

Group <sup>†</sup>	Baseline		End of observation		Change	P-value
	n	Mean ± SD	n	Mean ± SD		
Overall	1040	10.2 ± 6.0	944	5.0 ± 4.6	-5.2 ± 5.7 (-46.3 ± 45.9%)	< 0.001
<3 days	28	2.0 ± 0.2	24	1.6 ± 1.7	-0.4 ± 1.7 (-18.8 ± 85.7%)	0.295
≥3 to <8 days	347	4.9 ± 1.3	313	3.0 ± 2.8	-1.9 ± 2.8 (-38.2 ± 56.3%)	<.0001
≥8 to <15 days	447	10.2 ± 1.8	416	5.2 ± 3.9	-5.0 ± 3.9 (-48.7 ± 36.8%)	<.0001
≥15 days	218	19.6 ± 4.5	191	8.1 ± 6.6	-11.6 ± 7.4 (-58.0 ± 32.5%)	<.0001

**Table 3** Subpopulation analysis of change in migraine days per 4 weeks

<sup>†</sup>Patients were classified into four groups by using the number of migraine days per 4 weeks at baseline in order to elucidate the effectiveness of sodium valproate on migraine days.

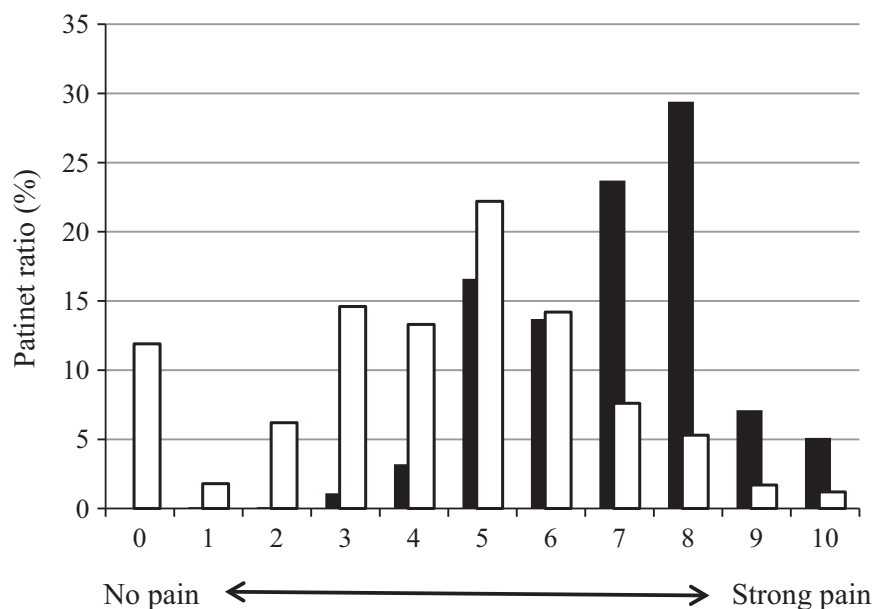


**Figure 3** The rate of patients whose migraine was improved over 50% and complete remission at the end of the observation period in the group categorized due to the number migraine days per 4 weeks at baseline. The figure shows that the higher rate of complete remission was observed in the group of less migraine days at baseline. (□) ≥50% remission, (■) complete remission.

treatment (Table 3). Complete remission of migraine attacks was achieved in 29.2% of patients whose migraine days per 4-week periods were less than 3 days at baseline (Fig. 3). No major differences in the intensity and duration of migraine attacks were observed between the subpopulations at the end of the observation period.

The mean intensity of migraine attacks assessed with a 0–10 numeric pain rating scale was improved from 7.0 ± 1.5 (n = 1040) to 4.3 ± 2.4 (n = 945), wherein there was a statistically significant decrease in migraine intensity 2.7 ± 2.5 (37.2 ± 34.4%; P < 0.001; Fig. 4). The mean duration of migraine attacks per 4 weeks was shortened after treatment in 944 cases (Supplement Fig. S1). The number of patients without migration attack was 111 of 944 patients (11.8%) at the end of observation, although all had a migraine at baseline. The number of patients whose duration of migraine attaches was less than 6 h was increased from 334 (32.1%) in 1039 patients to 485

(51.4%) in 944 patients. The administration frequency of triptans and analgesics in patients whose acute attacks had been managed with triptans or analgesics was reduced from 7.7 ± 4.7 to 4.6 ± 4.3 (36.3 ± 57.9% reduction), and from 11.5 ± 12.2 to 3.9 ± 7.2 (59.2 ± 53.2% reduction), respectively. Aura of migraine including visual symptoms, sensory symptoms and aphasia, and associated symptoms with migraine including nausea, vomiting, photophobia, phonophobia and osmophobia were also improved (Supplement Table S1). Global assessment by physicians (n = 1039) after treatment showed that migraines were “excellent improved” in 287 patients (27.6%), “improved” in 538 patients (51.8%) and “remained unchanged” in 170 patients (16.4%). Migraines did not significantly aggravate in any of the patients (0%). In 33 patients (3.2%), the clinical impression could not be assessed. The reasons for significant improvement and improvement are shown in Supplement Table S2.



**Figure 4** Changes in the migraine attack intensity. The figure shows that distribution of migraine attack intensities was shifted from strong pain to no pain by treatment with extended-release tablet of sodium valproate. (■) Baseline, (□) end of observation period.

**Safety.** As for the safety, the incidence of adverse drug reactions was 6.3% (67 patients) in 1070 cases (Table 4). The major adverse drug reactions observed were somnolence (2.2%) and nausea (0.7%). According to multivariate analysis, no factors were found to affect the safety of an extended-release tablet of sodium valproate.

Treatment was discontinued in four female patients because of pregnancy (after 5, 6, 8 and more than 12 weeks of observation): two of these patients could be followed up. One of the two patients discontinued treatment after 8 weeks, and no abnormalities were observed during pregnancy. Transient hydrocele testis was found in the newborn of this patient 4 weeks after birth. The causal relationship with an extended-release tablet of sodium valproate was denied by the physician. The other patient discontinued treatment after the 12-week observation period and no abnormalities were found either during pregnancy or in the newborn 3 months after birth.

## Discussion

A new indication of an extended-release tablet of sodium valproate for use of the prophylactic treatment of migraines in Japan was approved in 2011 using clinical study data in the USA and European countries. There have been few clinical study reports of sodium valproate in large Japanese patients. Therefore, we designed the prospective observational, multicenter, non-interventional postmarketing surveillance to evaluate the efficacy and safety in Japanese patients, and confirmed that Selenica-R, an extended-release tablet of sodium valproate marketed by Kowa Company, reduced frequency, intensity and duration of migraine in routine clinical practice. This also improved aura and the

associated symptoms with migraine, and reduced the concomitant medication with triptans and analgesics.

Patients with migraine were enrolled without any limitation in sex, age, concomitant disease and concomitant medication. However, the survey protocol was designed according to a draft guideline for prophylactic treatment of migraine with sodium valproate in Japan.<sup>12</sup> Therefore, patients who had migraine attacks twice a month or more, disabling migraine refractory to acute treatment, patients who did not tolerate acute migraine medications or in whom acute medication was contraindicated, and in patients who were at risk of permanent neurological deficit were enrolled in the present study. Furthermore, patients who were sodium valproate-naïve for 1 year, had data on their migraine attacks during the 4 weeks before the commencement and had not received any prevention medication for migraine or changed their prevention medication for migraine during 3 months before the commencement of this survey were enrolled in order to reduce the risk of selection bias. We selected study sites where physicians were treating migraineurs according to the guidelines.<sup>12,13</sup>

It is noteworthy that, according to multivariate analyses, the number of migraine days per 4-week period and aura visual symptoms were found to be factors affecting the effectiveness, whereas the number of treatments with triptans >10, psychiatric disorder, nausea and sensory symptoms were factors reducing its effectiveness. Subpopulation analysis shows that an extended-release tablet of sodium valproate was the most effective in patients with greater migraine frequencies. Complete remissions were observed in 29.2% of patients whose migraine frequencies were less than 3 days per 4-week period at baseline. The global assessment by the physician showed that 79.4% of patients had “excellent improved” or “improved.” There are a few clinical

**Table 4** Incidence of adverse drug reactions (*n* = 1070)

Adverse event	No. patients (%)
Total	67 (6.3)
Psychiatric disorders	3 (0.3)
Insomnia	2 (0.2)
Hallucinations, auditory	1 (0.1)
Nervous system disorders	33 (3.1)
Somnolence <sup>†</sup>	24 (2.2)
Dizziness	5 (0.5)
Disturbance in attention	1 (0.1)
Epilepsy <sup>†</sup>	1 (0.1)
Headache	1 (0.1)
Tremor	1 (0.1)
Ear and labyrinth disorders	2 (0.2)
Tinnitus	1 (0.1)
Vertigo	1 (0.1)
Respiratory, thoracic and mediastinal disorders	1 (0.1)
Epistaxis	1 (0.1)
Gastrointestinal disorders	20 (1.9)
Nausea	8 (0.7)
Abdominal discomfort	5 (0.5)
Abdominal pain upper	4 (0.4)
Diarrhea	3 (0.3)
Constipation	1 (0.1)
Vomiting	1 (0.1)
Epigastric discomfort	1 (0.1)
Hepatobiliary disorders	1 (0.1)
Hepatic function abnormal	1 (0.1)
Skin and subcutaneous tissue disorder	4 (0.4)
Drug eruption	2 (0.2)
Rash	2 (0.2)
General disorders and administration site conditions	10 (0.9)
Malaise	4 (0.4)
Feeling abnormal	2 (0.2)
Asthenia	1 (0.1)
Face edema	1 (0.1)
Facial pain	1 (0.1)
Edema	1 (0.1)
Investigations	2 (0.2)
Weight increased	2 (0.2)

<sup>†</sup>Serious in one patient each. The number of patients with drug-related treatment-emergent adverse events was summarized by system organ class, and the number of adverse events was summarized by preferred term (MedDRA/J ver.16.0).

reports of sodium valproate on the prophylactic treatment of migraine in Japanese patients. Oana *et al.* reported that sodium valproate was very effective (excellent: 84.2% and good: 14.5% by physicians global assessment) in 76 patients with migraine diagnosed in accordance with the International Classification of Headache Disorders of the International Headache Society.<sup>14</sup> Takeshima *et al.* reported the effectiveness and safety of sodium valproate in 142 Japanese migraineurs.<sup>15</sup> The effectiveness of sodium valproate for the prophylactic treatment of migraine has been reported in well controlled randomized clinical trials in the USA and Europe.<sup>16–18</sup> The Cochrane Database of Systematic Reviews concludes that anticonvulsants including sodium valproate are efficacious for the prophylaxis of migraine. Mean

migraine frequency was reduced by approximately one to two attacks per 4-week period as compared with placebo, and patients were more than twice as likely to have a 50% or greater reduction in the number of migraine attacks than with placebo.<sup>19,20</sup> Our data also suggest that sodium valproate was effective for the prophylaxis of migraine with the dose recommended by the guidelines.

The sex (female : male) ratio in our study was 4.8, which was bigger than the 3.6 ratio observed in a nationwide survey study on the prevalence of migraine in Japan.<sup>1</sup> Furthermore, 54.5% were within the 30–50 years age range, which was similar to previous prevalence studies in Japan<sup>1</sup> and the USA.<sup>21</sup> The mean initial daily dose and maximum daily dose of the extended-release tablet of sodium valproate were  $366.2 \pm 105.1$  mg and  $383.9 \pm 120.5$ , respectively: 76.7% of initial doses and 77.2% of maximum doses were 400 mg per day. Unlike randomized clinical trials, the dose cannot be designed in a survey protocol: therefore, information of the actual dose used in real clinical practice can be collected. Interestingly, the dose in our survey was within the 400–600 mg dose recommended by the guidelines.<sup>12</sup> The effective doses reported in the randomized study in the USA and European countries were 400–2000 mg/day,<sup>22</sup> and a dose of 500–1000 mg/day of sodium valproate has been approved in the USA. Kinze *et al.* reported that the frequency of migraine attacks was significantly reduced when serum levels of valproic acid were maintained below 50 µg/mL, and showed that a 500–600 mg dose is preferred over the higher dose.<sup>23</sup> Non-responders to a low dose of sodium valproate are known to have a resistance to the higher dose.<sup>24</sup> The use of an extended-release tablet of sodium valproate can relatively maintain the low serum levels over an extended period of time, and therefore, can be considered to be superior to previous drugs with regard to safety and efficacy.<sup>18</sup>

An extended-release tablet of sodium valproate was safe and well tolerated in our 12-week observation study. The major adverse drug reactions observed were somnolence and nausea. The adverse events observed in our survey were similar to those reviewed in the Cochrane Database of Systematic Reviews, although hair loss was not observed in our survey.<sup>19,20</sup> Despite sodium valproate prescription being prohibited for pregnant women, four pregnancies were involved in this survey, showing that there is a large risk of sodium valproate prescribing to prohibited pregnant women, given that women of child-bearing age account for a large proportion of migraine suffering patients. These risks are too difficult to assess in well-controlled clinical trials, which are usually carried out in the specified patient population under limited eligibility criteria and therefore, only postmarketing surveillance in routine clinical practice can elucidate these risks. Thus, postmarketing surveillance is of paramount importance to obtain to clinical practice feedback of the drug's use.

Randomized controlled trials can provide the highest levels of clinical evidence with the least bias, but cannot collect all data relevant to use in routine clinical practice.<sup>25</sup> Although randomized controlled trials of an extended-release tablet of sodium valproate in Japanese patients with migraine were not available, this is the first postmarketing surveillance study providing the efficacy and tolerability of

valproate for the prophylactic treatment of migraine in routine clinical practice.

This first prospective observation study of 1072 migraine patients administered an extended-release tablet of sodium valproate has proven the treatment to be effective and safe for the prophylactic treatment of migraine in routine clinical practice in Japan.

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## Supporting Information

Additional Supporting Information may be found in the online version of this article:

**Figure S1.** Changes in the duration of migraine.

**Table S1.** Change of aura and associated symptoms.

**Table S2.** Reason for global judge by physicians ( $n = 825$ ).