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Time-series clustering analysis for treatment pattern of lasmiditan for 2 years from the initial prescription

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Abstract

Background: Migraine is a highly prevalent neurological disorder and a leading cause of disability worldwide. Although triptans and non-steroidal anti-inflammatory drugs are widely used, a substantial proportion of patients show inadequate responses. Lasmiditan, a selective 5-HT1$_F$ receptor agonist introduced in Japan in January 2022, represents a novel acute treatment option that lacks vasoconstrictive activity and can be prescribed even in patients with cardiovascular risk. However, little is known about the trend of its long-term real-world use.

Objectives: To characterize 2-year lasmiditan prescription patterns using time-series clustering.

Design: A retrospective observational study using nationwide health insurance claims data in Japan.

Methods: Data were extracted from the REZULT database for patients aged ⩾15 years diagnosed with migraine (ICD-10 code G43) between January 2022 and December 2024. Prescription claims were analyzed in 90-day intervals for up to 24 months after the initial lasmiditan prescription. Time-series clustering was applied to identify subgroups with distinct trajectories of lasmiditan use.

Results: Lasmiditan was prescribed to 21,199 of 167,461 (12.7%) migraine patients (mean age 33.8 ± 10.3 years; 76.6% female). In the first 3 months, 86.2% received 50 mg, 12.8% received 100 mg, and 1.0% received both doses. About half were also prescribed analgesics, 66.7% triptans, and 33.9% prophylactic drugs. Lasmiditan prescriptions were gradually tapered over 2 years, with the most common long-term pattern being combination therapy with analgesics and triptans. Clustering identified three groups: Cluster 1 (massively continuous use), Cluster 2 (gradual tapering), and Cluster 3 (early discontinuation).

Conclusion: This nationwide claims-based study provides the first real-world evidence of long-term lasmiditan prescribing patterns. The identification of three distinct trajectories highlights the heterogeneity of clinical practice. It underscores the need for further research on lasmiditan's optimal use, particularly regarding combination therapy and potential medication overuse.

Keywords: lasmiditan, medication-overuse headache, migraine, national health claim data, time-series clustering

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Introduction

Migraine is a major global health issue, affecting approximately 8.4% of the population in Japan,[1] and around 15% worldwide.[2,3] Effective management requires an appropriate combination of acute and prophylactic medications. However,

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about 40% of migraine patients experience inadequate responses to existing acute treatments, such as triptans and nonsteroidal antiinflammatory drugs (NSAIDs).[4] In this context, lasmiditan is expected to serve as a new acute treatment option.

Lasmiditan, a selective 5-HT1_F serotonin receptor agonist, represents a novel class of acute migraine therapy.[5,6] Following successful phase III trials such as the SAMURAI[7] and SPARTAN[8] trials in the United States and European Union, lasmiditan became available there ahead of Japan. The MONONOFU trial in Japan showed a significant increase in patients achieving pain relief at 2 h postdose compared to placebo, with dizziness as the most common side effect.[9] Despite adverse effects such as dizziness, drowsiness, and fatigue, lasmiditan was approved in Japan in January 2022 at doses of 50, 100, and 200 mg.

A distinctive feature of lasmiditan is its ability to achieve not only pain relief but also pain freedom within 2 h, which represents a clinically meaningful endpoint in acute migraine treatment. In addition, the absence of vasoconstrictive properties allows safe use in patients with cardiovascular risk factors or contraindications to triptans, further broadening its clinical utility.[10]

While numerous studies have examined lasmiditan's efficacy and side effects,[11–15] there are no reports yet that consider the long-term perspective of how lasmiditan is prescribed in clinical practice, how it is used, and whether patients continue it or not. Understanding how lasmiditan is utilized in real-world clinical settings is crucial for optimizing its therapeutic potential. Investigating prescription patterns, including its combination with other medications[16] and the potential risk of medication-overuse headache of lasmiditan[17,18] due to excessive prescribing, could help identify important clinical issues. Clarifying these real-world treatment patterns is therefore essential for future drug development and effective management of migraine. Large-scale studies using National Health Insurance claims data have been conducted[19–21] and have the potential to clarify them.

This study analyzed health claims data to investigate lasmiditan's treatment patterns over 2 years from its initial prescription. To our knowledge, this is the first study to use a large-scale National Health Insurance claims database to investigate real-world lasmiditan prescription patterns over 2 years, applying time-series clustering to reveal distinct trajectories of its clinical use.

Materials and methods

Database information

In Japan, all residents must be covered by health insurance, provided through either employer-based or community-based insurers. The government regulates the fee schedules for medical services.[19,20] The REZULT database, managed by Japan System Techniques Co., Ltd. (Tokyo, Japan), contains health insurance claims data from employee-based insurers covering 9 million patients (https://www.jastlab.jast.jp/rezult_data). It includes over 547 million receipts from 171 insurance companies, enabling continuous longitudinal analysis of prescriptions and treatments for up to 13 years. The database records insurance claim dates, disease names, patient age and sex, and details of medical treatments, including prescriptions and healthcare institutions. Each patient is assigned a unique, anonymous identifier, ensuring comprehensive tracking of prescriptions over time.

In Japan, both single and combination analgesic agents are available over-the-counter (OTC). However, lasmiditan, triptans, and migraine prophylactic medications require a physician's prescription and are restricted to patients diagnosed with migraine. In contrast, NSAIDs, whether as single agents or in combination, can be prescribed for general headaches without a migraine diagnosis and are also used for chronic pain conditions like lower back pain. Also, oral prophylactic drugs may have been prescribed for indications other than migraine, including epilepsy, depression, or hypertension. However, the database used in this study does not specify the conditions for which these medications were prescribed.

Study population

From the REZULT database, we extracted data on patients aged 15 years or older with a diagnosis of "migraine" (ICD-10 code G43) from January 2022, when lasmiditan became available in Japan, to December 2024. Patients were included if they received their first prescription of lasmiditan between January 1, 2022, and December 31,

2022. Although the database covered the period from 2022 to 2024, a 24-month follow-up was required for all eligible patients; therefore, only those initiating treatment in 2022 were included in the present analysis. In Japan, the approved indication for lasmiditan is as follows: "This drug should only be administered when a definite diagnosis of 'migraine without aura' or 'migraine with aura' has been made according to the diagnostic criteria of the International Headache Society. The usual adult dose is 100 mg of lasmiditan orally at the onset of a migraine attack. However, depending on the patient's condition, a single dose of 50 or 200 mg may be administered. If the headache recurs after resolution, a second dose may be given, provided that the total daily dose does not exceed 200 mg." In addition, under Japanese pharmaceutical law, "adult" is defined as individuals aged 15 years or older; therefore, in practice, lasmiditan is prescribed to patients aged 15 years and above.

It is unclear whether this diagnosis was made strictly according to the International Classification of Headache Disorders, 3rd edition (ICHD-3),[22] as it represents a diagnosis for insurance claims purposes. However, the Japanese Clinical Practice Guideline for Headache Disorders 2021 is available in Japan, and usually physicians are recommended to provide care for patients with migraine diagnosed based on the ICHD-3.[23] Among them, those who had been prescribed lasmiditan and had at least 2 years of follow-up were selected for analysis.

In summary, the inclusion criteria were: (1) patients aged ⩾15 years; (2) diagnosed with migraine (ICD-10 code G43); (3) prescribed lasmiditan for the first time between January 1, 2022, and December 31, 2022; and (4) having at least 2 years of follow-up data after the initial prescription. The exclusion criteria were (1) patients with less than 2 years of follow-up after the first lasmiditan prescription and (2) patients with missing prescription or demographic information in the database.

Variables

We examined age, sex, and the number of days from the initial migraine diagnosis to the first prescription of lasmiditan. Additionally, we tracked the prescription status of acute and prophylactic migraine medications and the number of tablets prescribed every 90 days for 2 years from the initial lasmiditan prescription. The migraine medications analyzed are listed in Table 1, with their corresponding drug price list codes provided in Supplemental File 1. These medications are approved for migraine treatment in Japan and are referenced in the Japanese Clinical Practice Guideline for Headache Disorders 2021.[23] NSAIDs and oral prophylactic agents may have been prescribed for indications other than migraine, including chronic pain, fever, epilepsy, depression, or hypertension. The calcitonin gene-related peptide (CGRP)-related drugs in this study comprised galcanezumab, fremanezumab, and erenumab; eptinezumab, and gepants were not available in Japan during the study period.

Table 1. Summary of acute and prophylactic medications.

Treatment type	Drug name
Acute treatment	Lasmiditan (50 or 100 mg)
	Combination of NSAIDs
	Single NSAIDs
	Triptans
Prophylactic treatment	Calcium-channel blockers (lomerizine)
	Beta-blockers (propranolol)
	Anticonvulsants (valproic acid)
	Antidepressants (amitriptyline)
	Calcium-channel blockers (verapamil)
	CGRP-related drugs (galcanezumab, fremanezumab, erenumab)

CGRP, calcitonin gene-related peptide; NSAIDs, non-steroidal anti-inflammatory drugs.

Time-series clustering for lasmiditan prescription pattern

This study is an initial analysis of the dataset, with its approach informed by a preliminary examination of the data. Clustering, a key task in exploratory data mining, is an unsupervised learning method used to identify similarities among data points, grouping those that share common characteristics while distinguishing them from other groups. Time-series data, which track variables such as sales, temperature, or stock prices at regular intervals, present challenges in pattern

recognition. Time-series clustering helps address these challenges by identifying underlying patterns within the data.

Every 90 days from the initial prescription of lasmiditan up to 24 months, the number of tablets prescribed was recorded as tablets per 3 months. In Japan, lasmiditan is available in 50 and 100 mg tablets, and the number of tablets prescribed can be tracked in the database. However, the actual amount (mg) of lasmiditan taken by patients is unknown. Therefore, we converted the prescribed tablet count to a 100 mg dose, which is the standard single dose in Japan, for analysis. For example, if five 50-mg tablets were prescribed, this was counted as 2.5 tablets of the 100-mg standard dose; if two 200-mg doses were prescribed, this was counted as four 100-mg tablets.

The total number of tablets for all cases was graphed at 3-month intervals, and time-series clustering was performed using one-to-one Euclidean matching. To assess similarity in the time-series data, we first calculated the sum of Euclidean distances between corresponding points (one-to-one Euclidean matching). The k-means++ method was then used for clustering. The time-series data were grouped into three clusters, as this configuration yielded the highest silhouette score of 0.460 (Supplemental File 2). The silhouette score, which evaluates clustering performance, ranges from −1 (poor clustering) to +1 (highly dense clustering), with scores around zero indicating overlapping clusters. Higher scores reflect well-separated and compact clusters.[24] We decided to compare each group of clusters obtained by this time-series clustering method.

Statistical analysis

The normality of variable distributions was assessed using the Shapiro–Wilk test. Numerical variables are reported as means with standard deviations (SDs), while categorical variables are expressed as percentages. No prior statistical power calculation was performed, as the sample size was determined based on the available data. The analyses were conducted using SPSS version 28.0.0 (IBM Corp., Armonk, NY, USA), Python 3.9.0, tslearn 0.6.2, scikit-learn 0.24.2, and Matplotlib 3.5.1.

To understand the characteristics of each cluster, we compared the age, sex, and number of days from the first diagnosis of migraine to the prescription of lasmiditan (days). We also compared the proportion of treatment choices and the number of tablets taken in months 1–3, months 10–12, and months 21–24. Chi-square, Fisher exact, Kruskal–Wallis, and subsequent Dunn tests were used to compare the characteristics among the three clusters. A two-tailed p-value <0.05 was considered statistically significant. The subsequent Dunn test was performed with Bonferroni correction ($p < 0.05/3$).

Results

The characteristics of patients

Among 7,364,532 patients aged 15 years or older in the REZULT database, 167,461 (2.3%) were diagnosed with migraine via the health insurance system, and 21,199/167,461 (12.7%) met the criteria in this study. The mean (SD) age was 33.8 ± 10.3 years, and 16,242/21,199 (76.6%) were female. In the first 3 months, 18,276/21,199 (86.2%) were prescribed only 50 mg tablets of lasmiditan, 2706/21,199 (12.8%) only 100 mg tablets of lasmiditan, and 217/21,199 (1.0%) both dosages. About 49.9% of them were prescribed single NSAIDs, and 66.7% received triptans. The prophylactic drugs were prescribed to 33.9% of them, and 1.1% received CGRP-related drugs. It cannot be excluded that NSAIDs or oral prophylactic drugs were prescribed for other conditions, such as chronic pain, fever, epilepsy, depression, or hypertension. CGRP-related drugs included galcanezumab, fremanezumab, and erenumab. In Japan, eptinezumab and gepants are not available in the study period. Other characteristics are presented in Table 2, with the full version provided in Supplemental Table 1.

We analyzed the prescription trends of acute treatment drugs every 3 months. Lasmiditan and triptan prescriptions declined significantly between months 4 and 6 compared to the initial 3 months, followed by a gradual decrease. In contrast, NSAID prescriptions also declined but remained more stable than those of lasmiditan and triptans (Figure 1(a)).

Further analysis of acute treatment drug combinations revealed that lasmiditan was frequently prescribed alongside NSAIDs or triptans at first. Over time, the most common prescription pattern became NSAIDs alone, followed by all three

Table 2. Characteristics of each cluster (partially omitted, full description in Supplemental Table 1).

Variables	Total	SD or %	Cluster 1	SD or %	Cluster 2	SD or %	Cluster 3	SD or %	*p*-Value	Subsequent analysis
n	21,199	100%	2906	13.7%	7307	34.5%	10986	51.8%		
Age	33.8	10.3	36.0	9.9	34.0	10.4	33.0	10.3	<0.001	3<2<1
Sex, male: female	16,242	76.6%	2331	80.2%	5821	79.7%	8090	73.6%	<0.001	3<1,2
Number of days from first diagnosis of migraine to the prescription of lasmiditan (days)	3075.2	1498.8	3950.0	1540.0	3122.1	1434.0	2812.4	1437.1	<0.001	3<2<1
Treatment choice at the initial 3 months										
Sum of lasmiditan 50 mg and 100 mg as converted to lasmiditan 100 mg (tbl/3m)	49.7	98.0	55.6	82.5	51.1	79.6	47.2	113.1	<0.001	3<2<1
Presence of single NSAIDs	10,576	49.9%	1400	48.2%	3556	48.7%	5620	51.2%	<0.001	1,2<3
Presence of triptan	14,133	66.7%	1929	66.4%	5074	69.4%	7130	64.9%	<0.001	3<2
Presence of prophylactic treatment	7180	33.9%	1012	34.8%	2508	34.3%	3660	33.3%	0.186	
Calcium-channel blockers (lomerizine)	2652	12.5%	449	15.4%	948	12.9%	1255	11.4%	<0.001	3<1
Antidepressants (amitriptyline)	3764	17.8%	493	17.0%	1288	17.7%	1983	18.1%	0.372	
Presence of any CGRP-related drugs	231	1.1%	11	0.4%	65	0.9%	152	1.4%	<0.001	1<3
Treatment choice at the initial from 10th to 12th months										
Sum of lasmiditan 50 mg and 100 mg as converted to lasmiditan 100 mg (tbl/3m)	25.5	83.1	87.5	160.2	37.4	84.1	1.2	11.0	<0.001	3<2<1
Presence of single NSAIDs	6402	30.2%	1200	41.3%	2463	33.7%	2739	24.9%	<0.001	3<1,2
Presence of triptan	5586	26.4%	1408	48.5%	2508	34.3%	1670	15.2%	<0.001	3<1,2
Presence of prophylactic treatment	3977	18.8%	886	30.5%	1756	24.0%	1335	12.2%	<0.001	3<1,2
Calcium-channel blockers (lomerizine)	1644	7.8%	419	14.4%	733	10.0%	492	4.5%	<0.001	3<1,2
Antidepressants (amitriptyline)	1784	8.4%	376	12.9%	738	10.1%	670	6.1%	<0.001	3<1,2
Any CGRP-related drugs	362	1.7%	39	1.3%	201	2.8%	122	1.1%	<0.001	3<2
Treatment choice at the initial from 21st to 24th months										
Sum of lasmiditan 50 mg and 100 mg as converted to lasmiditan 100 mg (tbl/3m)	13.1	70.1	78.2	165.2	5.2	34.1	1.2	13.3	<0.001	3<2<1
Presence of single NSAIDs	4397	20.7%	1011	34.7%	1547	21.1%	1839	16.7%	<0.001	3<1,2
Presence of triptan	3915	18.5%	1190	41.0%	1473	20.2%	1252	11.4%	<0.001	3<1,2
Presence of prophylactic treatment	2678	12.6%	778	26.7%	1014	13.9%	886	8.1%	<0.001	3<1,2
Calcium-channel blockers (lomerizine)	1127	5.3%	363	12.5%	444	6.0%	320	2.9%	<0.001	3<1,2
Antidepressants (amitriptyline)	1204	5.7%	327	11.2%	424	5.8%	453	4.1%	<0.001	3<1,2
Any CGRP-related drugs	238	1.1%	50	1.7%	116	1.6%	72	0.7%	<0.001	3<1,2

CGRP-related drugs consist of galcanezumab, fremanezumab, and erenumab.
CGRP, calcitonin gene-related peptide; m, months; NSAIDs, non-steroidal anti-inflammatory drugs; tbl, tablets.

Figure 1. Changes in the prescription patterns of acute treatment. (a) Percentage of prescriptions for three types of acute treatment drugs. (b) Further details of (a) showing the combination of acute treatment drugs. The *x*-axis represents time since the initial prescription of lasmiditan, shown in months (m) at 3-month intervals up to 24 months. The *y*-axis represents the proportion (%) of each combination of medications.
NSAIDs, nonsteroidal anti-inflammatory drugs.

acute treatment drugs together, and NSAIDs/triptans or triptans alone. Prescriptions of lasmiditan alone, lasmiditan/NSAIDs, or lasmiditan/triptans were uncommon (Figure 1(b)).

Time-series clustering results

The barycenters of the three clusters are shown in Figure 2(a), and the individual cases in each cluster are plotted in Figure 2(b) to (d). Cluster 1 included 2906 cases (13.7%), Cluster 2 included 7307 cases (34.5%), and Cluster 3 included 10,986 cases (51.8%). In all clusters, the prescription quantity of lasmiditan in the first 3 months was around 50 tablets, but there were significant differences over 2 years. Cluster 1 continued receiving approximately 80 tablets per 3 months. Cluster 2 gradually tapered off. Cluster 3 rapidly decreased the prescription of lasmiditan.

Cluster 1 had a slightly higher proportion of older women, and the time from initial diagnosis of migraine to prescription of lasmiditan was longer. We examined the differences in prescriptions during the first 3 months for each cluster. Cluster 3 had a higher percentage of NSAID prescriptions than clusters 1 and 2. Triptans were prescribed more frequently in cluster 2 than in cluster 3. Each cluster had a similar proportion of prophylactic drug prescriptions, with more than 30% receiving them. The percentage of prescriptions of lomerizine was higher in cluster 1 than in Cluster 3. The percentage of prescriptions of CGRP-related drugs was higher in Cluster 3 than in Cluster 1 (Table 2).

We analyzed the changes in prescription patterns across each cluster. The prescription trends for NSAIDs (Figure 3(a)) and triptans (Figure 3(b)) followed similar patterns: in Cluster 1, prescriptions remained consistent; in Cluster 2, they gradually tapered off; and in Cluster 3, they declined rapidly. In contrast, prophylactic treatment patterns differed. In Clusters 2 and

Figure 2. Time-series clustering results. Every 90 days from the first day when lasmiditan was prescribed, the number of tablets (tablets/3 months) was counted when converted to lasmiditan 100 mg. The number of tablets for all cases was graphed every 3 months, and time-series clustering was performed. The *x*-axis represents time since the initial prescription of lasmiditan, shown in months (m) at 3-month intervals up to 24 months. The *y*-axis represents the number of prescribed tablets per 3 months, converted to the standard 100 mg dose of lasmiditan. (a) Examples of the barycenters (centroids) of three clusters are shown. (b) Cluster 1. (c) Cluster 2. (d) Cluster 3.

3, prophylactic drug use gradually decreased alongside acute treatment drugs. However, in Cluster 1, prophylactic prescriptions remained relatively stable at around 30% (Figure 3(c)). For CGRP-related drugs, Cluster 2 showed an increase in prescriptions between the 6th and 9th months, followed by a gradual decline. Meanwhile, in Cluster 1, prescriptions steadily increased over the 2-year period (Figure 3(d)). Further details on the changes in treatment patterns for each prophylactic drug are provided in Supplemental Figure 1, with numerical data available in Table 2 and Supplemental Table 1.

Discussion

We analyzed health claims data and identified several key findings. After the initial prescription of lasmiditan, its dosage was gradually tapered down over time. The second most common long-term prescription pattern, following NSAIDs only, involved a combination of all three acute treatment drugs: NSAIDs, triptans, and lasmiditan. Additionally, more than 30% of patients prescribed lasmiditan also received prophylactic treatment within the first 3 months. To further examine treatment trends, we conducted time-series clustering on lasmiditan prescription patterns over 2 years. Three distinct clusters emerged: Cluster 1 patients continued using lasmiditan at high doses for an extended period, Cluster 2 patients gradually reduced their dosage, and Cluster 3 patients quickly discontinued it.

The silhouette score of the three-cluster solution was 0.460, indicating a moderate level of separation. This means that while the clusters reflect distinguishable prescription trends, some overlap remains between groups. Such moderate validity is not unexpected given the heterogeneity of migraine patients and the multifactorial influences on prescribing behavior. Accordingly, the clusters should be interpreted as exploratory patterns rather than strictly distinct categories.

Figure 3. Changes in the prescription patterns of each cluster. The *x*-axis represents time since the initial prescription of lasmiditan, shown in months (m) at 3-month intervals up to 24 months. The *y*-axis represents the proportion (%) of patients in each cluster receiving the corresponding drugs. Three clusters were identified: Cluster 1 (blue, 13.7%), Cluster 2 (orange, 34.5%), and Cluster 3 (green, 51.8%). (a) Proportion of NSAIDs prescription. Both single and combination NSAIDs were accounted. (b) Proportion of triptan prescription. (c) Proportion of any prophylactic medication. (d) Proportion of CGRP-related drug prescription, including galcanezumab, fremanezumab, and erenumab.
CGRP, calcitonin gene-related peptide; NSAIDs, non-steroidal anti-inflammatory drugs.

Future research incorporating patient-centered outcomes such as headache frequency, severity, and treatment response may improve the clinical interpretability of these clusters. Nevertheless, despite these limitations, this study provides novel insights into lasmiditan treatment patterns, making it the first to explore its real-world prescription patterns and the long-term trends systematically.

Continuous use of lasmiditan

One of lasmiditan's strengths is that it not only relieves symptoms but also has the effect of completely suppressing migraine attacks within 2 h postdose.[9,13] Despite concerns about side effects, a real-world study reported that 41.7% of patients prefer lasmiditan.[11] Lasmiditan also demonstrated a consistent effective response across multiple attacks,[25] and repeated use of lasmiditan may reduce side effects. Also, there is no evidence that the use of triptans in combination with other drugs increases the risk of side effects.[26]

In our study, we found two groups: one that used lasmiditan continuously to some extent (Clusters 1 and 2) and one that stopped using it immediately (Cluster 3). Of course, if the migraine has improved with prophylactic treatment, they may need less acute treatment, including lasmiditan. However, if they are quitting lasmiditan use because of side effects, it may be necessary to instruct patients to keep taking lasmiditan, as the side effects will subside with continued and multiple use. As evidence, our data show that around half of all patients (Clusters 1 and 2) use lasmiditan continuously.

We showed that about 80% of patients received 50 mg tablets of lasmiditan although the actual dosage taken was unknown. In the CENTURION

trial, all patients were started with 100 mg of lasmiditan, and about 80% of patients then continued on 100 mg or increased to 200 mg.[12] Considering that 50 mg is the most common prescription in our study, many patients may prefer either 50 or 100 mg, rather than 200 mg. Further investigation is needed to clarify the optimal dosage and usage of lasmiditan for Japanese patients.

In addition, stratified treatment according to the severity of the headache is necessary.[27,28] Unlike triptans, lasmiditan is effective even after a certain length of time has passed since the onset of the attack.[14] It might be more reasonable to take an existing medicine, such as triptan and NSAIDs, first and then add lasmiditan if they are not effective. Also, in our data, many patients were continuously prescribed all of the three types of acute treatment drugs over 2 years: lasmiditan, triptans, and NSAIDs. It is necessary to consider what combination and timing these drugs should be used.

Importance of prophylactic treatment

The proportion of patients with both lasmiditan and prophylactic drugs was 33.9% in the first 3 months. Considering the low percentages of prophylactic drug prescriptions for general migraine patients as around 10%,[19,29,30] many physicians prescribing lasmiditan consider prophylactic treatment.

A report showed the proportion of prophylactic medication prescriptions gradually increased from 15.6% to 82.2% as the number of consultations increased to 4 times, though the number of patients decreased.[29] Another report showed a similar trend in that prescriptions of prophylactic medication gradually increased over time.[19] These studies looked at the overall population of migraine patients. We have obtained another finding since our observations were made from when lasmiditan was prescribed.

Among patients prescribed lasmiditan, clusters 2 and 3 gradually decreased their proportion of prophylactic drug prescriptions with a similar decrease in acute treatment drugs. On the other hand, Cluster 1 continued to be prescribed prophylactic treatment at around 30% and higher quantitative acute treatment drugs. In particular, Cluster 2 has a peak in the use of CGRP-related drugs, after which it declines, while Cluster 1 has a gradual increase in the use of CGRP-related drugs. Our clustering results showed the clinical picture of patients as physicians really feel. Because there is a possibility of losing migraine control as in Cluster 1, aggressive prophylactic treatment, the early administration of CGRP-related drugs, and refraining from a lot of prescription of acute treatment drugs should be considered when prescribing lasmiditan to prevent differentiation into Cluster 1. Although we could not show a causal relationship, lomerizine was often prescribed in Cluster 1 in the initial 3 months. To prevent differentiation into Cluster 1, we also need to consider which oral prophylactic medicine is best.

Lasmiditan and medication-overuse headache

The possibility of medication-overuse headaches with lasmiditan has been discussed, but it is not known whether they occur in humans.[17] Animal experiments suggest the possibility of a lasmiditan-overuse headache. Persistent exposure to lasmiditan induced cutaneous allodynia and neuroplastic changes in mice, leading to an increased expression of CGRP in trigeminal sensory afferents.[31,32] Although triptans and lasmiditan act on different receptor subtypes of 5-HT, they inhibit postsynaptic adenosine 3′,5′-cyclic monophosphate signaling cascades downstream and may pose some risk for MO development.[17]

Limitations

This study has several limitations. First, we could not determine the actual number of days lasmiditan was used throughout the study period. Instead of tracking the "number of days per month that lasmiditan was taken," we counted the "number of tablets per 90 days." Additionally, we were unable to verify whether patients took 50, 100, or 200 mg doses. Second, NSAIDs are prescribed for various conditions beyond headaches. Therefore, patients who regularly received analgesics for other chronic pain conditions, such as back pain, could not be excluded.

Third, as this study was a retrospective analysis of health claims data used for billing purposes, patients were identified solely based on the available database information. This means we could not assess migraine severity, the actual number of medications taken per day, or the use of OTC medications. Some migraine treatments, such as

anticonvulsants and antidepressants, have multiple indications, which could lead to misclassification, where patients were assumed to be receiving treatment for migraine when the medication was actually prescribed for another comorbid condition. In addition, because the analysis was entirely based on prescription claims, we could not capture patient-centered outcomes such as headache frequency, severity, or treatment efficacy. Therefore, the clinical interpretability of the identified clusters is limited.

Fourth, we could not track patients who used insurance systems not included in the REZULT database, potentially limiting the generalizability of our findings. Also, the prescription patterns are heavily dependent on the physician's policy and preferences. Various other factors that were not determined in the REZULT database should be taken into account, such as socioeconomic and regional differences. It is also necessary to consider the differences in prescriptions based on the department and physician's experience. Furthermore, in Japan, insurance coverage issues also limit treatment options,[23] so therapies recommended by the International Headache Society[10] cannot always be implemented.[10] For example, topiramate and onabotulinumtoxinA are not indicated for migraine, verapamil is sometimes prescribed for migraine, and gepants and eptinezumab were not available during the study period and still are not now (August 2025). Such differences in treatment environments across countries should be taken into account when interpreting our findings. In the future, large-scale multiinstitutional joint research worldwide, rather than health claim data, would be preferable.

Conclusion

We utilized the REZULT health insurance database to analyze the treatment patterns of lasmiditan. Following its prescription, the dosage was gradually tapered down over time. The second most common long-term prescription pattern, following NSAIDs only, involved a combination of all three acute treatment medications: NSAIDs, triptans, and lasmiditan. Additionally, more than 30% of patients who were prescribed lasmiditan also received prophylactic treatment within the first 3 months. Time-series clustering of lasmiditan treatment patterns over 2 years from the initial prescription identified three distinct clusters: Cluster 1 patients continued using lasmiditan at high doses for an extended period, Cluster 2 patients gradually reduced their dosage, and Cluster 3 patients quickly discontinued its use.

Declarations

Ethics approval and consent to participate

An ethical review was not required to analyze anonymized data that is commercially available based on the Japanese law. The requirement for written informed consent was waived because of the study's retrospective and anonymized nature. All methods were performed in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines and regulations of the Declaration of Helsinki.

Consent for publication

Not applicable.

Author contributions

Masahito Katsuki: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing.

Yuya Yamada: Data curation; Resources; Software.

Taisuke Ichihara: Data curation; Resources; Software.

Yasuhiko Matsumori: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing.

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Competing interests

M.K. received personal consultancy fees from Amgen Astellas BioPharma K.K., Daiichi Sankyo Company, Limited, Eli Lilly Japan K.K., and Otsuka Pharmaceutical Co., Ltd. during the conduct of the study. T.I. and Y.Y. are employees of Japan System Techniques Co., Ltd. Y.M. received personal consultancy fees from Amgen Astellas BioPharma K.K., Daiichi Sankyo Company, Limited, Eli Lilly Japan K.K., and Otsuka Pharmaceutical Co., Ltd. during the conduct of the study.

Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supplemental material

Supplemental material for this article is available online.

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