



## Utilization of Preventive Therapy in Korean Migraine Patients

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### ABSTRACT

**Background:** Migraine is a common neurological disorder that affects the quality of life and causes several health problems. Preventive migraine treatment can reduce migraine frequency, headache severity, and health care costs. This study aimed to estimate the utilization of migraine preventive therapy and associated factors in eligible patients. **Methods:** We studied 534 patients with migraine who were eligible for migraine preventive therapy using 2017 National Patient Sample (NPS) data from the Health Insurance Review and Assessment Service (HIRA). We estimated the migraine days by calculating the monthly average number of defined daily dose (DDD) of migraine-specific acute drug. Patients with a monthly average number of DDD of 4 or more were considered as subjects for preventive treatment. Chi-square test and multiple logistic regression analysis were used to determine the association between the preventive therapy and the influencing variables. **Results:** Less than half of the eligible patients for prophylaxis (n=234, 43.8%) were prescribed preventive therapy. Multiple logistic regression results show that migraine preventive therapy was influenced by age, the type of migraine, and some comorbidities. Patients over the age of 50 tend to receive less prophylactic treatment than under the age of 40. On the other hand, migraine patients with epilepsy or depression were more likely to receive preventive therapy. Sumatriptan was the most preferred medication for acute treatment, and propranolol was the most commonly prescribed drug for prevention. **Conclusions:** More than half of the patients who were candidates for migraine prophylaxis were not receiving suitable preventive treatment. Positive factors affecting the use of migraine prevention were the presence of comorbidities such as epilepsy and depression.

**KEYWORDS:** Migraine, prophylaxis, migraine days, defined daily dose

Migraine is a common neurological disorder that occurs in approximately 12% of adults in western countries and can significantly impair the quality of life of the patients.<sup>1,2)</sup> In Korea, 6.1% of the population suffers from migraine headaches at least once a year, and women roughly have three times higher incidence of migraine than men. It is most frequent in women aged 40-49 years and men aged 19-29 years.<sup>3)</sup>

This neurological disorder has a broad range of severity and symptoms; it is a unilateral, pulsatile pain, and aggravated by routine physical activity.<sup>4)</sup> In addition, migraine is accompanied by one or more additional symptoms such as nausea, vomiting, abdominal pain, dizziness, photophobia, and phonophobia.<sup>4)</sup> According to the International Classification of Headache Disorders 3rd edition (ICHD-3), the two major subtypes of

migraine are migraine without aura (MwOa) and migraine with aura (MwA),<sup>5)</sup> and they are not completely distinct and exclusive.<sup>5)</sup>

Appropriate acute therapy for migraine headaches can abort migraine attacks and suitable preventive treatment can reduce migraine frequency, headache severity, and health care costs.<sup>6)</sup> Acute treatments of migraines include serotonin receptor agonists (triptans), ergot alkaloids, non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, and opioids.<sup>7,8)</sup> The American Academy of Neurology (AAN) has published guidelines for preventing migraines in 2012.<sup>9)</sup> The AAN guidelines recommend metoprolol, propranolol, timolol, valproic acid/valproate/divalproex, topiramate with strong evidence, and atenolol, nadolol, amitriptyline, venlafaxine with moderate evidence.<sup>9)</sup>

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The purpose of this study was to (1) examine the utilization of migraine preventive therapy in eligible patients, (2) determine the factors influencing the use of preventive therapy, and (3) assess the frequency of drugs prescribed for migraine-specific acute therapy and preventive therapy among Korean migraine patients.

## Methods

### Data Source

We utilized the National Patient Sample data from the Health Insurance Review and Assessment Service in 2017 (HIRA-NPS-2017-0014). NPS data is health insurance claims data of almost 1 million patients and includes patients' diagnosis, procedures, surgical history, medications, institutional information, etc.<sup>10)</sup>

The patient's diagnosis was identified using *The Korean Classification of Diseases, 7th edition (KCD-7)* code. KCD code is the Korean version of *the International Classification of Diseases (ICD)* code. There are three types of health insurance in Korea: The National Health Insurance (NHI), Medical Aid (MedAid), and the Patriots & Veterans Insurance (PVI) plan. Approximately 97% of Koreans are covered by NHI, about 3% of people are covered by MedAid, and 0.5% of people by the PVI plan. The drug codes (Appendix A) were used to extract information on migraine-specific acute and preventive therapy utilization. This study was approved by the Institutional Review Board of the Pusan National University (PNU IRB/2019\_126\_HR).

### Study Population

Migraine patients with a *KCD-7* code of G43 were extracted. The patients were further classified into MWoA (G430) and MWA (G431) using *KCD-7* codes. In case a patient received both diagnoses at different times, the patient was labeled with the MWA type. The patients whose migraine subtype were not specified, were categorized into "the other migraine type". We grouped the patients by age into "<40 years", "40-49 years" and "≥50 years", and by insurance into NHI and MedAid/PVI group.

The *KCD-7* code was used to identify the following comorbidities: epilepsy, depressive disorders, insomnia, hypertension, dyslipidemia, diabetes mellitus, osteoarthritis, rheumatoid arthritis, asthma, and Thyroid gland disorders (Appendix A). The comorbidities were referred to as common diseases

occurring in more than 5% of migraine patients according to a previous study.<sup>11)</sup>

### Candidates for migraine prophylaxis

Based on the previous studies and clinical trials, we considered patients with more than four migraine days per month as candidates for preventive treatment.<sup>4,12,13)</sup> To estimate each patient's migraine days, the defined daily dose (DDD) was used. DDD is an average maintenance dose of a medication used by adults, which allows the drug used to be expressed in a standardized unit.<sup>14)</sup> We estimated how many DDD of each migraine-specific medication was prescribed to a patient per month and summed them up. One DDD was regarded as one migraine day.

### Medication utilization of migraine-specific acute and preventive treatment

Migraine-specific acute therapies include almotriptan, frovatriptan, naratriptan, sumatriptan, zolmitriptan, and a combination of ergotamine and caffeine anhydrous (hereafter referred to as ergotamine). Medications that are approved for migraine prophylaxis in Korea include amitriptyline, flunarizine, nadolol, propranolol, topiramate, and valproic acid/valproate/divalproex (Appendix A). Furthermore, we classified each ingredient of the preventive therapy into the following drug classes: Amitriptyline was grouped under antidepressants, flunarizine under calcium channel blockers (CCB), nadolol and propranolol as beta-blockers, and topiramate and valproic acid/valproate/divalproex as anticonvulsants. If any preventive drug was prescribed at least once in 2017, then we considered preventive medicine was utilized.

We evaluated the prescription pattern of migraine-specific acute therapy and preventive therapy. In the case of usage of multiple medications by a patient, the drug that had the highest number of DDD per month was regarded as the main acute therapy or main preventive therapy. Similarly, we summed the number of DDD per month for drugs belonging to a drug class, and the class with the highest number was considered the main drug class.

### Statistical analysis

Categorical variables of the patient's baseline characteristics were expressed in frequencies and percentages using frequency analysis. To determine the association between prophylactic prescription and explanatory factors in candidates for migraine

preventive therapy, we performed a chi-square test and multiple logistic regression analysis. Explanatory factors include demographic factors such as age group, sex, and insurance type; and health factors such as migraine type, migraine frequency, and comorbidities. The Hosmer-Lemeshow test was performed to check the fit of this model. We used the R Statistical Software (version 4.0.0; R Foundation for Statistical Computing, Vienna, Austria) to perform statistical analysis, and considered  $p < 0.05$  as statistically significant.

## Results

### Characteristics of study subjects

The number of patients requiring migraine prophylaxis was estimated as 534. The characteristics of study subjects and migraine prophylactic drug utilization are summarized in Table 1. Patients aged 50 years or older were the most among the three age groups (41.6%). Female patients are almost 4 times more than male patients (79.8% vs 20.2%). Most patients (96.3%) were covered with NHI. Patients with MWOA was almost 5 times more than patients with MWA. For more than half of the patients, an appropriate migraine type was not assigned due to the limited code information. The most frequent comorbidity was dyslipidemia (36.9%), followed by osteoarthritis (30.0%), then depressive disorders (24.0%).

### Preventive therapy utilization rate

Of the 534 patients, 234 (43.8%) were prescribed preventive therapy at least once in 2017 (Table 1). Migraine preventive drug use decreased with the advanced age ( $p = 0.382$ ), and was lower in men than in women ( $p = 0.170$ ). Further, migraine preventive therapy was higher in patients with epilepsy ( $p < 0.001$ ), depressive disorders ( $p < 0.001$ ), insomnia ( $p = 0.016$ ), dyslipidemia ( $p = 0.013$ ), and osteoarthritis ( $p = 0.038$ ).

### Predictors of preventive therapy utilization

Table 2 presents the results of the multiple logistic regression analysis. Patients aged 50 years or older were less likely to use preventive drugs than those under 40 years of age (odds ratio [OR]=0.513; confidence interval [CI]=0.302-0.862). Among comorbidities, epilepsy was the most influencing factor (OR=7.326; CI=2.586-26.488). Patients with depressive disorders are more than 2 times likely to utilize migraine preventive therapy (OR=2.439; CI=1.567-3.827).

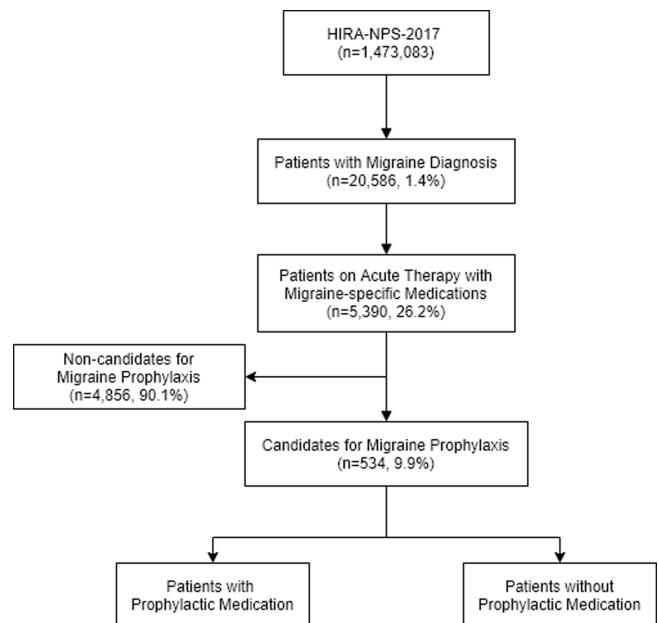


Fig. 1. Case extraction diagram. HIRA-NPS, health insurance review and assessment service-national patient sample

### Patterns of acute and preventive therapy for migraine

Table 3 presents the patterns of drugs prescribed for patients who have an indication for migraine prophylaxis. Sumatriptan was the most frequently prescribed medication as an acute treatment (29.0%), followed by ergotamine (27.3%), naratriptan (19.1%), almotriptan (10.1%), zolmitriptan (8.8%), and frovatriptan (5.6%).

The most commonly used preventive drugs were propranolol (35.0%), followed by flunarizine (32.5%), topiramate (13.7%), amitriptyline (12.8%), valproic acid/valproate/divalproex (3.8%), and nadolol (2.1%). When preventive therapies were classified by the drug class, beta-blockers were the most prescribed (37.2%), followed by CCB (32.5%), anticonvulsants (17.5%), and antidepressants (12.8%).

## Discussion

This study investigated the utilization of migraine preventive therapy in eligible patients, determined the factors influencing the use of preventive therapy, and analyzed the prescribing patterns of migraine-specific medications and preventive medications.

Patients requiring migraine prophylaxis therapy was about 10% of the migraine patients who had been prescribed acute therapy at least once ( $n = 5,390$ ). This figure is low compared

**Table 1.** Demographic characteristics and migraine prophylactic drug utilization.

		N	Prophylactic utilization (%)	p-Value
Total		534	234(43.8)	
Age group	<40	147(27.5)	71(48.3)	0.382
	40-49	165(30.9)	72(43.6)	
	≥50	222(41.6)	91(41.0)	
Sex	Male	108(20.2)	41(38.0)	0.170
	Female	426(79.8)	193(45.3)	
Insurance	NHI	514(96.3)	225(43.8)	0.914
	MedAid/PVI	20(3.7)	9(45.0)	
Migraine type	Migraine without aura	202(37.8)	113(55.9)	<0.001
	Migraine with aura	40(7.5)	17(42.5)	
	Other migraine	292(54.7)	104(35.6)	
Epilepsy	No	508(95.1)	212(41.7)	<0.001
	Yes	26(4.9)	22(84.6)	
Depressive disorders	No	406(76.0)	152(37.4)	<0.001
	Yes	128(24.0)	82(64.1)	
Insomnia	No	464(86.9)	194(41.8)	0.016
	Yes	70(13.1)	40(57.1)	
Hypertension	No	416(77.9)	178(42.8)	0.367
	Yes	118(22.1)	56(47.5)	
Diabetes mellitus	No	466(87.3)	198(42.5)	0.105
	Yes	68(12.7)	36(52.9)	
Dyslipidemia	No	337(63.1)	134(39.8)	0.013
	Yes	197(36.9)	100(50.8)	
Osteoarthritis	No	374(70.0)	153(40.9)	0.038
	Yes	160(30.0)	81(50.6)	
Rheumatoid arthritis	No	507(94.9)	222(43.8)	0.947
	Yes	27(5.1)	12(44.4)	
Asthma	No	458(85.8)	194(42.4)	0.095
	Yes	76(14.2)	40(52.6)	
Thyroid gland disorders	No	434(81.3)	190(43.8)	0.968
	Yes	100(18.7)	44(44.0)	

NHI, national health insurance; MedAid, medical aid; PVI, patriots & veterans insurance; COPD, chronic obstructive pulmonary disease

to 38.8% of migraine patients who are eligible for migraine prophylaxis in the US.<sup>2)</sup> The claim data we used did not identify the use of over-the-counter (OTC) drugs when estimating migraine days with the monthly average number of DDD of acute therapy. Since a significant number of migraine sufferers (49%) use OTC pain medications,<sup>15)</sup> those who are candidates for migraine preventive treatment might have been

underestimated in our study.

In this study, 43.8% of patients had been prescribed preventive therapy at least once in 2017, and the proportion was similar or higher than in other countries. A study in the US reported that about 39% of migraineurs had an indication for migraine prophylaxis, but only 32% of them received preventive therapy.<sup>2)</sup> Caetano et al. found that among 77

**Table 2.** Multiple logistic regression analysis of migraine prophylactic drug utilization

		Odds Ratio (OR)	95% CI	p-Value
Total (N=534)				
Age group	<40	Reference		
	40-49	0.695	0.425-1.133	0.146
	≥50	0.513	0.302-0.862	0.012
Sex	Male	Reference		
	Female	1.606	0.988-2.649	0.059
Insurance type	NHI	Reference		
	MedAid/PVI	0.608	0.198-1.736	0.362
Migraine type	Migraine without aura	Reference		
	Migraine with aura	0.657	0.310-1.371	0.266
	Other migraine	0.471	0.316-0.700	<0.001
Comorbidities	Epilepsy	7.326	2.586-26.488	<0.001
	Depressive disorders	2.439	1.567-3.827	<0.001
	Insomnia	1.266	0.709-2.265	0.425
	Hypertension	1.085	0.640-1.834	0.761
	Diabetes mellitus	1.119	0.580-2.163	0.736
	Dyslipidemia	1.532	0.947-2.488	0.083
	Osteoarthritis	1.467	0.951-2.268	0.083
	Rheumatoid arthritis	1.359	0.553-3.282	0.496
	Asthma	1.226	0.712-2.107	0.460
Thyroid gland disorders	0.687	0.406-1.149	0.157	
c-statistic		0.713		
p value of Hosmer-Lemeshow test		0.703		

NHI, national health insurance; MedAid, medical aid; PVI, patriots & veterans insurance; COPD, chronic obstructive pulmonary disease

patients who were eligible for prophylactic treatment, only 22% of them were on preventive treatment in Portugal.<sup>16)</sup> We might have overestimated the preventive drug utilization rate since we considered a patient as a preventive drug user if he/she was prescribed the index drug at least once a year. Nevertheless, more than half of the patients had not received optimal preventive therapy in Korea.

One previous study found that women experienced more frequent migraine headaches, greater disability, and more frequent consultation with their physicians about their headaches.<sup>17,18)</sup> The ratio of women to men in the population of candidates for migraine prophylaxis was 4:1, which differed in frequency by age groups. However, there was no significant relationship between sex and the use of preventive treatment in our study. Common comorbidities that occur with migraine and affect the treatment include depression, anxiety disorders,

epilepsy, sleep disorders, stroke, and other pain disorders.<sup>19)</sup> Among various comorbidities, the most frequent comorbid conditions according to the results of our study are dyslipidemia (36.9%), osteoarthritis (30.0%), depressive disorders (24.0%), and hypertension (22.1%).

Diamond et al. reported that female and elderly patients with migraine were more likely engaged with current or past utilization of preventive therapy.<sup>15)</sup> On the other hand, there was no significant relationship between sex and prescription of preventive agents according to a Netherlands study.<sup>20)</sup> We found that women received more preventive treatment, although it was not statistically significant, and preventive drug prescriptions decreased in older people aged over 50 years. This may be due to the high use of multiple medications by older patients and physicians might be concerned about adverse drug reactions, drug-drug interactions, or drug-disease

**Table 3.** Patterns of acute and preventive therapy in patients eligible for migraine prophylaxis

	N	Drug utilization (%)
Drug for acute therapy	534	100.0
Sumatriptan	155	29.0
Ergotamine	146	27.3
Naratriptan	102	19.1
Almotriptan	54	10.1
Zolmitriptan	47	8.8
Frovatriptan	30	5.6
Drug for preventive therapy	234	100.0
Propranolol	82	35.0
Flunarizine	76	32.5
Topiramate	32	13.7
Amitriptyline	30	12.8
Valproic acid/valproate/divalproex	9	3.8
Nadolol	5	2.1
Drug class of preventive therapy	234	100.0
Beta-blockers	87	37.2
Calcium channel blockers	76	32.5
Anticonvulsants	41	17.5
Antidepressants	30	12.8

interactions.<sup>20,21)</sup>

Caetano et al. reported that patients with MWA had higher rates of migraine prophylaxis compared to the patients with MWoA.<sup>16)</sup> However, our results showed the opposite trend. We were not able to draw any meaningful hypothesis from this finding since more than half of the patients were not assigned to any specific migraine subtype.

More preventive agents were prescribed in the presence of epilepsy and depressive disorder as comorbidities. This may be due to the fact that the approved migraine prophylaxis agents also have an indication of epilepsy or depression.<sup>22)</sup> In particular, depression is associated with severe migraines, and frequent migraine headaches with high severity are linked to increased use of migraine prevention treatments in these conditions.<sup>20,23)</sup>

Sumatriptan was the most frequently prescribed drug for acute treatment, followed by ergotamine. According to a study carried out in the US, sumatriptan was the most commonly used drug for acute treatment, followed by rizatriptan.<sup>11)</sup> Meanwhile, Sheftell et al. found that the most frequently

prescribed drug was sumatriptan, followed by zolmitriptan, and then rizatriptan.<sup>24)</sup> In comparison, at the time of this research, rizatriptan was not available in Korea and thereby excluded from the analysis. Since we analyzed the frequency of prescriptions by considering the highest average number of DDD per month as the main acute therapy in each patient, the results may differ due to differences in the methodology between the studies.

According to the Canadian Headache Society guideline and the European Federation of Neurological Societies (EFNS) guideline, ergotamine is not recommended for acute migraine attacks because it has lower efficacy and greater risk of side effects than triptans.<sup>25,26)</sup> However, ergotamine was the second most frequently used medication after sumatriptan in Korea. This is probably due to the cost advantage of ergotamine. Triptans were about 50 to 80 times more expensive than ergotamine at the time of this study.

The most commonly prescribed preventive medicine was propranolol, followed by flunarizine, and topiramate. In terms of drug classes, beta-blockers were the most commonly used ones. The most frequently prescribed preventive drug in a US study was topiramate.<sup>11)</sup> Another study found that beta-blockers were the most frequently used preventive drug as well as the first choice of physicians followed by TCA, CCB, anticonvulsant (topiramate) in that order.<sup>27)</sup>

According to the international guidelines of the WHO/EHF, beta-blockers, topiramate, flunarizine, sodium valproate, amitriptyline are effective for migraine prevention and are recommended for use as a first tier.<sup>28)</sup> The results of our study suggest that the medications were used according to the guidelines. Hypertension is highly prevalent in Korea as well as worldwide.<sup>29)</sup> The high prevalence of hypertension may be related to the frequent prescription of beta-blockers and CCB as migraine prophylactic medication. The choice of migraine preventive therapy should take into account not only the efficacy of the drug but also safety, tolerability, patient preferences, and comorbidities.<sup>4,30)</sup>

There are several limitations to our study. First, we used insurance claim data, originally generated for reimbursement purposes. Considering that it is not collected for research purposes, diagnostic information may be inaccurate. For example, it is difficult to compare patients with aura and without aura because migraine-type was not accurately classified and many patients were assigned to "other migraines group". Second, the claim data did not provide detailed

clinical information of the patient such as migraine severity, exact migraine frequency, medication tolerability, and adverse drug reactions. In addition, socioeconomic characteristics such as economic status, education, or health behavior were not available. Third, since the migraine days per month were replaced by the monthly average number of DDDs of acute therapy, the exact migraine days experienced by the patient could not be determined. Furthermore, when counting the number of DDD, it could have been underestimated because OTC drugs were excluded from the analysis. Fourth, it was not known whether patients were prescribed these drugs to prevent migraines or to treat other comorbid conditions.

Despite these limitations, our study provides evidence that migraine prevention therapy is underutilized in Korea. We also identified influencing factors that could predict the use of migraine prevention medications and compared the pattern of drug prescriptions with other countries. Our findings warrant further research on a reason why patients who meet the criteria for migraine prophylaxis are not receiving adequate preventive therapy.

## Conclusions

In conclusion, more than half of the eligible patients with migraine were not currently receiving prophylaxis. Positive factors affecting the use of migraine prophylaxis were epilepsy, and depressive disorders. The most commonly prescribed acute therapy for migraine relief was sumatriptan, and preventive therapy was propranolol.

## Acknowledgment

We used HIRA-NPS-2017-0014 data from the Health Insurance Review and Assessment Service for this study, but the results have no connection with the Ministry of Health and Welfare or HIRA.

## Conflict of Interest

We declare no conflict of interests.

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## Appendix A. Disease and Drug Codes

Disease and Drug Codes (<http://koicd.kr/>)

Disease (KCD-7)	
Migraine without aura	G430
Migraine with aura	G431
Other migraines	G432, G433, G438, G439
Hypertension	I10-13
Epilepsy	G40-41
Schizophrenia	F20
Depressive disorders	F32-33
Anxiety disorders	F064, F40, F410-413, F418, F419
Sleep disorders	F51, G47
Insomnia	F510, G470
Diabetes mellitus	E10-14
Osteoarthritis	M15-19
Rheumatoid arthritis	M05, M06, M080, M120, M123
Asthma	J45-46
Chronic obstructive pulmonary disease	J44
Malaise and fatigue	R53
Disorders of thyroid gland	E00-07
Dyslipidemia	E78
Obesity	E66
Drug	
Sumatriptan	233802ATB, 233803ATB
Naratriptan	415501ATB
Zolmitriptan	415601ATB
Almotriptan	499401ATB
Frovatriptan	509501ATB
Ergotamine/caffeine anhydrous	251800ATB
Amitriptyline	107501ATB, 107502ATB, 107504ATB
Topiramate	241801ACR, 241801ATB, 241802ACR, 241803ACH, 241803ATB, 241804ACH, 241804ATB
Valproic acid/valproate/divalproex	246901ATE, 246902ATE, 246903ATE, 247001ACS, 247002ACS, 229701ACR, 229701ATR, 229703ATB, 229705ATB, 229705ATR, 229706ATR, 229707ATR, 147701ATE, 147702ATR, 147801ACH
Propranolol	219901ATB, 219904ATB
Nadolol	198301ATB
Flunarizine	160501ACH