Original article

Treatment gaps in migraine preventive treatment-eligible patients: A hospital-based study in Thailand

Thanin Asawavichienjinda*

Department of Medicine, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand

Abstract

Background: Preventive treatment of migraine is necessary for patients with frequent attacks to avoid progression and medication overuse. Only a few studies have demonstrated the low prevalence of preventive-eligible migraine patients having received migraine preventive treatments.

Objective: To investigate the prevalence of preventive migraine treatments in eligible patients in Thailand.

Methods: A hospital registry-based cross-sectional study was conducted between January 2007 and June 2022 in migraine patients at the Chulalongkorn Comprehensive Headache Center, King Chulalongkorn Memorial Hospital, and Thai Red Cross Society. Data collected at the first visit were extracted from the patient registry. The proportion of preventive treatments among patients with variable migraine severity classified by the number of monthly migraine days was evaluated.

Results: Of the 681 patients in the registry, 572 aged ≥15 years were included. The prevalence of patients with a history of ever using migraine preventive treatment was 14.7%. There was no significant difference in the prevalence of receiving preventive treatment among the patients with variable migraine severity classified by the number of migraine days per month. Among the treatment-eligible participants, the prevalence of preventive treatment was 12.9%.

Conclusion: This was the first hospital-based study in any Eastern country that revealed a prevailing low prevalence of preventive treatments among migraine patients. Preventive treatment is critical to migraine progression. Health education on existing preventive treatments is needed to raise awareness among patients. More relevant studies are needed in Asian countries to replicate these findings. To improve the scientific quality of relevant studies, future research should be conducted by gathering data from primary sources and retrieving previous treatments from medical records.

Keywords: Medication overuse headache, migraine, prevalence, preventive-eligible, preventive treatment, treatment gaps.

Preventive treatment of migraine is necessary for those with frequent migraine attacks to avoid progression to chronic migraine (CM), medication overuse, and medication overuse headaches (MOH). [1] Based on the frequency of migraine/headache days per month, migraine can be categorized into two groups, i.e., episodic migraine (EM) (<15 days) or CM (≥15 days). [2] MOH is defined as a headache occurring ≥15 days per month with regular overuse of one or more drugs for acute treatment for >3 months. [3] For acute treatment, the use of ergot derivatives, triptans, opioids, combination analgesics, or a combination of drugs from different classes for ≥10 days per month or non-opioid analgesics, acetaminophen, or nonsteroidal anti-inflammatory drugs for ≥15 days per month is considered medication overuse. [3] Preventive treatment aims to reduce the frequency, severity, duration, and disability of attacks; increase acute treatment responsiveness and avoid escalation; enhance function and disability; improve health-related quality of life; and reduce headache-related distress and psychological symptoms. [3] Currently, it is offered to patients with ≥6 headache days per month, ≥4 headache days per month with some degree of disability, or ≥3 headache days per month with a severe degree of disability. [3] However, there has been a low prevalence of preventive-eligible

*Correspondence to: **Thanin Asawavichienjinda,** Department of Medicine, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand.
E-mail: thanin.a@chula.ac.th

patients receiving preventive treatment in clinical practice.

The literature contains only five population-based studies on the epidemiology of preventive treatment use. [4-8] They reported a low prevalence of migraine preventive treatments among those who were eligible. In the United States (US), 25.7% of 18,968 migraine patients aged ≥12 years met the criteria for receiving prevention treatment. Among the users, 13.0% reported current daily use of preventive migraine medication, 25.5% previously used it, and 43.3% never used it. [4] In addition, ~38.0% of people with EM benefit from prophylactic therapy, but only 3%–13% receive it. [5] A population-based survey in the US revealed that a majority (52.8%) of the 7,337 patients with probable migraine never used prevention; only 7.9% currently use it, whereas 19.9% had used it in the past. [6] Another report investigated prescriptions from the computerized data records of the Institute for Medical Statistics called "MediPlus" from Germany revealing that of the 21,209 patients from outpatient primary care with a documented diagnosis of migraine, only 0.12/45,669 person-years received prescriptions for prophylactics. [7] In a most recent web-based survey of 16,789 oral preventive-eligible people with migraine, defined as having ≥4 monthly headache days regardless of disability, 80.2% had never used preventive treatments, 9.8% were using it, and 10.1% had previously used it. [8] However, there have been no relevant studies in clinical populations.

The objectives of this study were to investigate the prevalence of migraine patients with a history of ever using preventive treatments among those who are eligible; the differences in the prevalence of patients receiving preventive treatment among those with variable migraine severity classified by the number of monthly migraine days; the differences in demography, clinical migraine history, and characteristics between patients with CM or CM with MOH; and between patients with a history of ever and never using migraine preventive treatment in Thailand.

Materials and methods

Study design and participants
A cross-sectional study was conducted at the Chulalongkorn Comprehensive Headache Center, King Chulalongkorn Memorial Hospital, Thai Red Cross Society, Faculty of Medicine, Chulalongkorn University, Thailand. Patients with migraine were identified from the Center's Headache Registry between January 2007 and June 2022. The inclusion criteria were patients with migraine, according to the International Classification of Headache Disorders, second,[9] third (beta version),[10] and third editions,[2] who were ≥15 years old. The diagnostic criteria for migraine among different versions, including the three editions, were similar and did not influence patient inclusion. The exclusion criteria were people with other primary headaches, secondary headache disorders, or unclassified types of headaches. Based on these criteria, 572 patients were included. The study was approved by the Institutional Review Board of the Faculty of Medicine, Chulalongkorn University (IRB no. 644/65).

Data collection
The data were extracted from patient record forms created by the center and filled in while the patients were visiting. At first visit, the following information was gathered and included in the analysis: age, gender, education level, comorbidities or coexisting diseases, duration of migraine history, monthly migraine days, history of medicines related to migraine ever used as a preventive treatment, attack duration, attack severity, and pain score as measured with the numerical rating scale, with scores ranging from 0–10.

The primary outcome was the prevalence of migraine patients with a history of ever using preventive treatments among those who were eligible. Regarding migraine medications employed as a preventive treatment, patients could answer "yes," "no," or "unknown." If yes, the name of the medication was asked. The medications were classified as preventive treatments based on the reported names. Some patients could not remember the names of the medicines they used, which were included in "unknown." The secondary outcomes were as follows: the differences in the prevalence of receiving preventive treatment among the patients with variable migraine severity classified by the number of monthly migraine days; the differences in demography, clinical migraine history, and characteristics between patients with CM and CM with MOH; and between patients with a history of ever and never using migraine preventive treatment.

Definitions

Monthly migraine days were categorized into four groups: 0–3 as very low-frequency EM, 4–7 as low-frequency EM, 8–14 as high-frequency EM, and ≥15 as CM or CM with MOH. [11] The last was combined as a CM group. Due to a lack of information on the degree of disability during migraine attacks, this study defined preventive-eligible patients as having ≥6 headache days per month, per the American Headache Society consensus statement. [3] EM was defined as headaches occurring <15 days/month and fulfilling the diagnostic criteria of migraine without aura. CM was defined as headaches occurring ≥15 days/month for >3 months, with features of migraine headache ≥8 days/month. Medication overuse was defined as taking acute non-specific medications ≥15 days/month or taking acute migraine-specific medications ≥10 days/month. MOH was defined as headaches occurring on ≥15 days/month in a patient with a pre-existing primary headache and developing as a consequence of regular overuse of acute or symptomatic headache medication (on ≥10 or ≥15 days/month, depending on the medication) for >3 months.

Statistical analysis

For categorical data, descriptive statistics were reported as proportions or percentages, and for continuous, discrete, and ordinal data, as the median with an interquartile range (IQR). The chi-square or Fisher's exact tests were utilized for categorical data when comparing two groups, and the chi-square test for K-independent samples when comparing >two groups. The Kruskal-Wallis test was used for discrete, and ordinal data when comparing >two groups, and the Mann–Whitney U test was used when comparing two groups. The CM and CM with MOH were combined into the CM group. The sample size for the prevalence of migraine patients with a history of ever using preventive treatment was calculated employing a reference of 20.0%,[8] an acceptable margin of error of 3.3%, and a false positive error rate of 5.0%. The sample size was 565 patients. Statistical analysis utilized the Statistical Package for the Social Sciences. Any missing data were excluded.

Results

Of the 681 patients from the registry, 109 were excluded because they met the exclusion criteria. A total of 572 patients were included. The diagnostic criteria for migraine among various versions, including the second, third beta, and third editions, were similar and did not influence patient inclusion. The demography, clinical migraine history, and characteristics of the patients are shown in **Table 1**. Patients with EM accounted for 50.5% of patients (289/572), CM for 37.2% (213/572), and CM with MOH for 12.2% (70/572). The overuse of acute medication was as follows: ergotamine (40/70, 57.1%), followed by analgesics, nonselective and selective COX-2 inhibitors (24/70, 34.3%), opioids (4/70, 5.7%), and triptans (3/70, 4.3%). There was a remarkably greater proportion of patients with a bachelor's degree or higher who had a lower frequency of migraine or headache days. A significantly higher proportion of patients with nausea and vomiting-associated symptoms in patients were with a higher frequency of migraine or headache days, but a slight decline in CM patients **(Table 1).**

Among the 572 patients included, 465 reported never using migraine preventive treatment, 84 ever using it and remembering the names, 21 ever using it but not remembering the names, and 2 as unknown. The overall prevalence of migraine patients with a history of confirmed ever-use preventive treatment was 14.7%, 11.1% in patients with very low-frequency EM who did not need it, 13.6% in patients with low-frequency EM or 27.3% in patients who were preventive-eligible, 15.0% in patients with high-frequency EM who needed it, and 15.2% in CM patients who required it (**Table 1**). The prevalence of patients with a history of confirmed ever-use of preventive migraine treatment among those who were eligible, with a monthly duration of migraine/headache days of ≥6 days, was 74/572 (12.9%). Preventive medications that were ever used included amitriptyline (39/84, 46.4%), followed by topiramate (22/84, 26.2%), propranolol (16/84, 19.0%), flunarizine (12/84, 14.3%), valproic acid (10/84, 11.9%), nortriptyline (9/84, 10.7%), metoprolol (4/84, 4.8%), venlafaxine

(1/84, 1.2%), and riboflavin (1/84, 1.2%). Most of the patients (67/84, 79.8%) had ever used one medicine for preventive migraine treatment. A few patients (10/84, 11.9%) had ever used two medicines, namely, amitriptyline and propranolol (3/84, 3.6%), amitriptyline and flunarizine (2/84, 2.4%), amitriptyline and topiramate (2/84, 2.4%), valproic acid and topiramate (2/84, 2.4%) and nortriptyline and topiramate (1/84, 1.2%). Very few patients (3.6%) used three medicines, including amitriptyline, flunarizine, and valproic acid (1/84, 1.2%); amitriptyline, propranolol, and topiramate (1/84, 1.2%); and metoprolol, nortriptyline, and topiramate (1/84, 1.2%). Only 2.4% ever used four medicines, including amitriptyline, propranolol, valproic acid, and topiramate. The remaining patients (2.4%) used five medicines, including amitriptyline, nortriptyline, propranolol, flunarizine, and topiramate (1/84, 1.2%), or amitriptyline, propranolol, flunarizine, topiramate, and venlafaxine (1/84, 1.2%).

There were no marked variations in demography or clinical migraine history and characteristics between patients with CM and CM with MOH, except for education level, a greater proportion of patients with a bachelor's degree or higher in patients with CM (38.5%) compared to those with CM with MOH (22.9%) ($P = 0.025$); the median duration of migraine history in patients with CM (3 years, IQR 1.0–10.0), a longer history in patients with CM with MOH (8 years, IQR 4.0–15.5) ($P < 0.001$); the median pain duration (4 h, IQR 3.0–8.0) and pain score (7.0, IQR 5–8) in patients with CM, a longer duration (7.3 h, IQR 4.0–24.0) and higher score (6.0, IQR 6.0–8.0) in patients with CM with MOH ($P = 0.005$ and 0.004, respectively), and associated symptoms of vomiting (37.1%) and phonophobia (38.5%) in patients with CM, with a greater proportion of patients with CM with MOH (61.4% and 54.3%, respectively) ($P = 0.0006$ and 0.029, respectively). In patients with CM with MOH, the prevalence of a history of ever using migraine preventive treatment was 20.0%, which was greater than the 13.6% reported for patients with CM but still was insignificant.

There was a remarkable variation in the median duration of migraine history (4 years, IQR 1.0–10.0), a longer history in patients with a history of ever using migraine preventive treatment (6 years, IQR 2.0–10.0) ($P = 0.022$), and the median pain score (7, IQR 5.0–8.0), which was greater in patients with a history of ever using migraine preventive treatment (7, IQR 6.0–8.0) ($P = 0.008$) **(Table 2).**

Discussion

This was the first hospital-based study on the prevalence of migraine patients with a history of ever using preventive treatment among those with migraine subtypes and those who were preventive-eligible. This study confirmed that a greater disability was related to a higher frequency of migraine attacks. A major proportion of patients with a bachelor's degree or higher had a lower frequency of monthly migraine or headache days. The impact of migraine on school performance has been reported. [12-14] This study also demonstrated a lower proportion of patients with migraine characteristics, especially the associated symptoms of nausea and vomiting, in CM than in EM due to the term "transformed migraine" or the chronification of migraine. [15] The proportion of these symptoms increased from very low-frequency to low-frequency and high-frequency EMs and then decreased in CM. Comparable with CM, CM with MOH was also a serious condition that was related to enhanced disability, with a greater proportion of patients with a bachelor's degree or higher in CM. Patients with CM with MOH had a longer migraine history, prolonged attack duration, and greater pain score, which may reflect difficulty in treating and disabling the condition compared to CM.

The prevalence of migraine patients with a history of ever receiving preventive treatment was as low as that reported in previous studies conducted in the US and European countries. [4, 8] The prevalence in this study ranged from 11.1% to 15.2% among migraine subgroups. The 21 patients who reported ever using medicines but not remembering the names were not included because it could not be determined whether the medicines were for acute or preventive treatment. Interestingly, patients with CM with MOH had a greater proportion (20.0%) with a history of ever using preventive treatment than did patients with CM (13.6%). This trend might be because some physicians recognize the serious condition of MOH and prescribe preventive medication. The prevalence of patients with a history of ever using preventive treatment among eligible patients was only 12.9%. Because of the low prevalence of ever using migraine preventive treatment, low-frequency EM may progress to high-frequency EM and medication overuse and then to CM or CM with MOH. This serious situation requires prompt awareness of migraine management for the public and physicians to make them understand

Table 1. Baseline data on demography and clinical migraine history and characteristics among migraine subtypes.

Baseline data	Overall (n = 572)	EM VLF (n = 36)	EM LF (n = 66)	EM HF (n = 187)	CM group (n = 283)	P-value
Median age, years (IQR)	42.5 (31.0–52.0)	38.0 (30.5–54.0)	40.5 (33.8–47.0)	44.0 (31.0–51.0)	43.0 (30.0–53.0)	0.391
Female gender, n (%)	481 (84.1)	34 (94.4)	53 (80.3)	164 (87.7)	230 (81.3)	0.069
Educational level						**< 0.0001**
Bachelor's degree or higher, n (%)	256 (44.8)	22 (61.1)	41 (62.1)	92 (49.2)	101 (35.7)	
Occupation						
Employment	488 (85.3)	29 (80.6)	57 (86.4)	167 (89.3)	235 (83.0)	0.235
Comorbidity/ Co-existing diseases presence, n (%)	387 (67.7)	22 (61.1)	43 (65.2)	118 (63.1)	204 (72.1)	0.158
Median duration of migraine history, years (IQR)	4.0 (1.5–10.0)	3.3 (2.0–11.5)	6.0 (2.4–10.0)	4.0 (1.0–10.0)	4.0 (1.2–10.0)	0.931
Median monthly migraine days (IQR)	14.0 (8.0–28.0)	2.0 (1.0–3.0)	4.0 (4.0–4.0)	8.0 (8.0–12.0)	28.0 (20.0–28.0)	**< 0.001**
Median attack duration, hours (IQR)	4.5 (3.0–8.0)	5.0 (3.0–8.0)	5.5 (3.0–8.0)	4.0 (3.5–8.0)	5.0 (3.0–8.0)	0.979
Median pain score (IQR)	7.0 (5.0–8.0)	7.0 (5.0–8.0)	7.0 (5.0–8.0)	7.0 (5.0–8.0)	7.0 (5.0–8.0)	0.189
Nausea associated symptom	389 (69.6)	21 (58.3)	49 (74.2)	147 (78.6)	181 (64.0)	**0.0025**
Vomiting associated symptom	278 (48.6)	14 (38.9)	33 (50.0)	112 (59.9)	119 (42.0)	**0.0012**
Photophobia associated symptom	272 (47.6)	13 (36.1)	33 (50.0)	90 (48.1)	136 (48.1)	0.552
Phonophobia associated symptom	241 (42.1)	12 (33.3)	26 (39.4)	84 (44.9)	119 (42.0)	0.584
Preventive treatment ever using, n (%)	84 (14.7)	4 (11.1)	9 (13.6)	28 (15.0)	43 (15.2)	0.920

EM, episodic migraine; CM, chronic migraine (15 or more monthly migraine days); CM group, chronic migraine; and chronic migraine with medication overuse headache; VLF, very low frequency (0–3 monthly migraine days); LF, low frequency (4–7 monthly migraine days); HF, high frequency (8–14 monthly migraine days); IQR, interquartile range.

Table 2. Baseline data on demography and clinical migraine history and characteristics between patients with a history of ever and never using migraine preventive treatment.

Baseline data	Overall (n = 572)	Patients with a history of ever using migraine preventive treatment (n = 84)	Patients with a history of never using migraine preventive treatment (n = 488)	P-value
Median age, years (IQR)	42.5 (31.0–52.0)	38.0 (30.0–51.8)	43.0 (31.0–52.0)	0.143
Female gender, n (%)	481 (84.1)	71 (84.5)	410 (84.0)	0.965
Educational level				
Bachelor's degree or higher, n (%)	256 (44.8)	41 (48.8)	215 (44.1)	0.490
Occupation				
Employment	488 (85.3)	77 (91.7)	411 (84.2)	0.107
Comorbidity/ Co-existing diseases presence, n (%)	387 (67.7)	57 (67.9)	330 (67.6)	0.933
Median duration of migraine history, years (IQR)	4.0 (1.5–10.0)	6.0 (2.0–10.0)	4.0 (1.0–0.0)	0.022
Migraine subtypes				
EM, n (%)	289 (50.5)	41 (48.8)	248 (50.8)	0.824
CM, n (%)	213 (37.2)	29 (34.5)	184 (37.7)	0.664
CM with MOH, n (%)	70 (12.2)	14 (16.7)	56 (11.5)	0.247
Median monthly migraine days (IQR)	14.0 (8.0–28.0)	16.0 (8.0–28.0)	12.5 (8.0–28.0)	0.674
Median attack duration, hours (IQR)	4.5 (3.0–8.0)	6.0 (3.0–8.0)	4.3 (3.0–8.0)	0.617
Median pain score (IQR)	7.0 (5.0–8.0)	7.0 (6.0–8.0)	7.0 (5.0–8.0)	0.008
Nausea associated symptom, n (%)	389 (69.6)	63 (75.0)	335 (68.6)	0.299
Vomiting associated symptom, n (%)	278 (48.6)	48 (57.1)	230 (47.1)	0.115
Photophobia associated symptom, n (%)	272 (47.6)	43 (51.2)	229 (46.9)	0.546
Phonophobia associated symptom, n (%)	241 (42.1)	40 (47.6)	201 (41.2)	0.327

CM, chronic migraine; EM, episodic migraine; MOH, medication overuse headache.

the consequences of frequent migraine attacks. In this study, patients who had a history of ever using preventive treatment had a longer migraine history than those who never used one. This may reflect the chance of patients visiting different physicians and only one knowledgeable physician prescribing preventive treatment. Moreover, they may be more aware of the medicines they took and were able to remember the names. The most common preventive medications ever used in this study were amitriptyline, propranolol, and flunarizine, which are usually prescribed by physicians in Thailand. The second most common was topiramate, which is newer than amitriptyline and propranolol and is prescribed by a newer generation of physicians. However, this study revealed that none of the patients ever used anti-CGRP medications, which may be due to their unavailability or unaffordability. The older, oral, non-specific migraine preventive medications are perceived to have poor tolerability and low efficacy. A time-based follow-up with specific migraine preventive medications in a year to assess the difference between non-specific and specific migraine preventive medications would be more valuable.

In the past, indications for preventive treatment were patients with very frequent headaches that were defined as those who experienced >2 attacks a week or those who were at risk of developing a rebound headache with acute attack medicines, or those who were at risk of developing an MOH. [16] Some experts advise preventive treatment if patients have ≥3 migraine attacks per month or take acute migraine medications for >10 days per month to prevent medication overuse and MOH. [17] Currently, it is offered earlier to reduce disability and improve the quality of life. [3] A systematic review of migraine progression revealed that one of the risk factors for CM is headache frequency. [1] People with EM who had a mean headache of 6.8 days per month at baseline were more likely to progress to CM than those with 2.6 days. [18] Migraine frequency is also a predictive factor for migraine-associated disability [19] and quality of life. [20] As the frequency of migraine attacks decreases, quality of life improves. [21] Preventive treatment can also reduce the attack intensity, which may be a risk factor for CM. [21]

The strength of this study is that it is the very first one on the prevalence of migraine patients with a history of ever using preventive migraine treatments among those who were eligible in Asia and considered enough samples to detect a high probability of truly positive results. The limitations were that it was a single-site study; only older oral non-specific migraine preventive medications and not anti-CGRP medications, were included; recall bias due to design; unidentified medical specialty of the attending physicians, such as general practitioners, general medicine physicians, internists, or general neurologists, possibly affecting the prescription of migraine preventive treatment to eligible patients; and no migraine disability assessment that is needed to be correlated with the number of monthly migraine days to suggest preventive treatments, such as ≥4 monthly migraine days with some degree of disability or ≥3 monthly migraine days with a severe degree of disability.

Implications for clinical practice include the low prevalence of preventive treatment-eligible migraine patients having received it, which may lead to the progression of EM to CM and MOH. Patients with CM have a lower risk of nausea and vomiting than those with EM, which may confirm the chronification or progression of migraine. The specific symptoms of migraine, such as nausea, vomiting, photophobia, and phonophobia, had a lower prevalence while the frequency of migraine attacks increased. Patients with CM and CM with MOH have enhanced ictal burdens, including longer durations and higher pain scores of migraine headaches than those with EM. Proper management with migraine preventive treatments should be introduced for such patients.

Conclusions

This first hospital-based study revealed a low prevalence and wide range of migraine preventive treatment gaps in patients with a history of ever using preventive treatments among those who were eligible, as was observed around the world, which may have led to the progression of EM to CM and MOH. Prompt education of physicians and patients should be initiated to make them realize the necessity of preventive treatment. Due to the exclusion of anti-CGRP medications, it would have been more valuable if a time-based follow-up was done with specific migraine preventive medications in a year or to assess the difference between non-specific and specific migraine preventive medications. Future research to improve the scientific quality of studies on the prevalence of migraine patients with a history of ever using migraine treatment should be conducted by gathering data from primary sources and retrieving previous treatments from medical records.

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