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Medication Overuse and Headache Burden

Results From the CaMEO Study

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Abstract

Objective

To estimate the relative frequency of acute medication overuse (AMO) among people with episodic migraine and chronic migraine, to characterize the types of acute medications overused for migraine, and to identify factors associated with AMO.

Methods

We analyzed data from the Chronic Migraine Epidemiology and Outcomes (CaMEO) Study (ClinicalTrials.gov, NCT01648530), a cross-sectional and longitudinal internet study that included a systematic sampling of the US population. From September 2012 to November 2013, the CaMEO Study respondents participated in different modules to collect data on the clinical course of migraine, family burden, barriers to care, endophenotypes, and comorbidities. Among people who met the criteria for migraine consistent with the International Classification of Headache Disorders, third edition (ICHD-3), we evaluated types and frequency of medications used for headache/migraine, selected comorbidities, and emergency department (ED) and urgent care (UC) use. AMO was defined by days per month of medication use as specified by ICHD-3 criteria for medication overuse headache (MOH) without the requirement for ≥15 monthly headache days (MHDs). Nested, multivariable binary logistic regression modeling was used to identify factors associated with an increased risk of AMO.

Results

Of 16,789 CaMEO respondents with migraine, 2,975 (17.7%) met the AMO criteria. Approximately 67.9% (2,021/2,975) of AMO respondents reported <15 MHDs. Simple analgesics, combination analgesics, and opioids were the medication classes most commonly overused. Factors associated with AMO in the final multivariable logistic regression model included ≥15 MHDs, moderate to severe disability, severe migraine interictal burden, use of preventive medication, and an ED/UC visit for headache within 6 months.

Conclusions

Approximately two-thirds of respondents with AMO reported <15 MHDs and therefore did not meet the criteria for MOH. Those with AMO had greater disease burden and increased ED/UC utilization relative to people with migraine but not AMO.

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Migraine is a prevalent chronic neurologic disease characterized by painful, debilitating attacks.[1–3] The goal of acute treatment is to relieve symptoms and restore function.[4] Current acute treatments are often inadequately effective, contributing to the need for more frequent dosing and overuse, thereby substantially increasing migraine burden as well as the risk of disease progression.[5–10]

Medication overuse headache (MOH) is defined by the International Classification of Headache Disorders, third edition (ICHD-3) as headache occurring ≥15 days per month in individuals with a preexisting headache disorder and regular overuse of acute medications for more than 3 months.[11] MOH implies that overuse of medication is causally related to headaches, representing a secondary headache disorder. By contrast, acute medication overuse (AMO) refers to taking specific medications ≥10 days per month for most medications or ≥15 days per month for simple analgesics. Consequently, some people with AMO may not meet the headache-day criteria for MOH. In addition, some people may use medications on headache-free days in anticipation of migraine or for other pain disorders.[12] Thus, the number of days taking migraine acute medications can exceed the number of migraine or headache days.[13]

The goal of this analysis of the Chronic Migraine Epidemiology and Outcomes (CaMEO) Study data was to estimate the relative frequency of AMO and to characterize the types of acute medications overused. We also sought to identify sociodemographic features, headache characteristics, emergency health care resource utilization, and migraine-related burden in people with and without AMO.

Methods

Study Design

CaMEO was a cross-sectional and longitudinal web-based survey that included a systematic sampling of the US population as previously described.[14] From September 2012 to November 2013, the CaMEO Study respondents participated in different modules to collect data on the clinical course of migraine, family burden, barriers to care, endophenotypes, and comorbidities.

The present cross-sectional analysis used data from the baseline screening module, core module, and endophenotype module. The baseline screening module covered sociodemographic information (age, body mass index [BMI], sex, employment, income, race/ethnicity, education, and marital status) and health information related to medical conditions, including headaches, pain disorders, and other conditions. The core module addressed headache frequency over the last 3 months (number of days). The frequency of medication use over the last 30 days (number of days and how many times per day the medication was used) was addressed by the question "Which of these medications (if any) are you currently using (or typically keep on hand) to treat your headaches?". The core module also addressed the type of medication used to treat headache, emergency health care resource use in the past 6 months (number of times each resource was used), number of nights spent in the hospital in the past 6 months related to headaches, and Generalized Anxiety Disorder 7-Item Scale (GAD-7), 9-Item Patient Health Questionnaire (PHQ-9), Migraine Interictal Burden Scale (MIBS-4), and Migraine Disability Assessment (MIDAS) questionnaire results. The endophenotype module assessed migraine features, including the presence of allodynia (using the 12-Item Allodynia Symptom Checklist [ASC-12] and 5-point frequency allodynia screener) and other comorbidities (appendix e-1, links.lww.com/CPJ/A259).

Study Respondents and Outcomes

Study respondents who met the modified ICHD-3 migraine criteria, assessed using the validated American Migraine Study (AMS)/American Prevalence and Prevention (AMPP) migraine diagnostic module, were entered into the study (note: the AMS/AMPP diagnostic module was based on ICHD-2 migraine criteria,[14,15] but no significant changes occurred among the ICHD-2,[15] ICHD-3-beta,[16] and the final ICHD-3[11] criteria related to classification of migraine). Responses to the core module were used to categorize respondents who met the AMO criteria for any single class of medications or for multiple classes. Respondents were categorized according to monthly headache frequency (calculated from a 3-month report period) of 0–4 days, 5–9 days, 10–14 days, or ≥15 MHDs. Headache characteristics were assessed in the AMO and non-AMO groups.

Patient-reported outcomes for both groups included PHQ-9, GAD-7, MIDAS, MIBS-4, ASC-12, and Migraine Severity Symptom Score (MSSS). Additional information for all assessments can be found in appendix e-1 (links.lww.com/CPJ/A259).

Emergency health care resource utilization as determined by frequency of emergency department (ED) and urgent care (UC) facility use for headache in the past 6 months was assessed in the AMO and non-AMO groups. The self-reported medical diagnosis of comorbidities reported in the endophenotype module was organized by system organ classes of the Medical Dictionary for Regulatory Activities, and comorbidities that occurred in more than 5% of the CaMEO respondents were reported by AMO status within MHD groups.

Defining AMO

To establish an operational definition for overuse by acute medication class, we chose medication use days per month criteria consistent with medication use rates in ICHD-3 criteria for MOH; AMO was identified from ICHD-3 criteria for single medication class and multiple medication class overuse. The single-class AMO group included respondents who met the AMO criteria for at least 1 class of medication: (1) use of naproxen sodium, aspirin, ibuprofen, acetaminophen, or prescription nonsteroidal anti-inflammatory drugs (NSAIDs) for ≥15 days per month or (2) use of any ergotamine, triptan, opioid, or combination analgesics (including Excedrin, barbiturates, and Midrin) for 10 or more days per

Table 1 Baseline Characteristics and Sociodemographics by AMO Status

	AMO (n = 2,975)	Non-AMO (n = 13,814)	*p* Value[a]
Age, y, mean (SD)	43.2 (13.8)	40.7 (14.5)	<0.001[b]
Female	2,297 (77.2)	10,198 (73.8)	<0.001
White race	2,547 (85.9)	11,497 (83.5)	<0.01
Obese (BMI ≥30 kg/m^2)	1,255 (42.2)	4,664 (33.8)	<0.001
Income ≥$50,000	1,621 (54.8)	8,311 (60.6)	<0.001
Employed	1,945 (65.4)	9,826 (71.1)	<0.001
College degree (4-y)	1,183 (39.8)	6,364 (46.1)	<0.001
Monthly headache days			
Median (IQR)	10.0 (4.3, 16.7)	2.0 (1.0, 4.7)	<0.001[c]
Mean (SD)	11.2 (8.2)	3.7 (4.4)	<0.001[b]
Monthly headache frequency category			<0.001
0–4 d	783 (26.3)	10,376 (75.1)	
5–9 d	688 (23.1)	2,217 (16.0)	
10–14 d	550 (18.5)	699 (5.1)	
≥15 d	954 (32.1)	522 (3.8)	
Diagnosed with migraine	1,886 (63.4)	5,781 (41.8)	<0.001
Allodynia (ASC ≥3)	1,351 (60.3)	4,469 (42.3)	<0.001
MSSS, median (IQR)	17.0 (14.0, 19.0)	15.0 (13.0, 18.0)	<0.001[c]
Headache currently managed by a specialist (neurologist, pain, or headache)	355 (11.9)	414 (3.0)	<0.001
PHQ-9			
Moderate-severe depression (score ≥10)	1,602 (53.8)	3,823 (27.7)	<0.001
Median (IQR)	10.0 (5.0, 16.0)	5.0 (2.0, 10.0)	<0.001[c]
GAD-7			
Moderate-severe anxiety (score ≥10)	1,447 (48.6)	3,575 (25.9)	<0.001
Median (IQR)	9.0 (5.0, 14.0)	6.0 (2.0, 10.0)	<0.001[c]
MIBS			
Moderate-severe interictal burden (score ≥3)	1,933 (65.0)	4,423 (32.0)	<0.001
Median MIBS score (IQR)	4.0 (1.0, 8.0)	0.0 (0.0, 4.0)	<0.001[c]
MIDAS			
Moderate-severe disability (score ≥11)	2,174 (73.1)	4,365 (31.6)	<0.001
Median (IQR)	23.0 (10.0, 50.0)	6.0 (2.0, 14.0)	<0.001[c]
ED/UC use for headache (≥1 visit in past 6 mo)	380 (12.8)	453 (3.3)	

Abbreviations: AMO = acute medication overuse; ASC = Allodynia Symptom Checklist; BMI = body mass index; ED = emergency department; GAD-7 = Generalized Anxiety Disorder 7-Item Scale; HCP = health care professional; IQR = interquartile range; MIBS = Migraine Interictal Burden Scale; MIDAS = Migraine Disability Assessment Scale; MSSS = Migraine Symptom Severity Score; PHQ-9 = 9-Item Patient Health Questionnaire; UC = urgent care.
Data are n (%) unless otherwise indicated.
[a] Comparison between the AMO and non-AMO groups with the χ^2 test except where otherwise noted.
[b] Two-tailed *t* test.
[c] Mood median test.

Table 2 Single-Medication Use, Single-Class AMO, and Overall AMO Among People With Migraine in CaMEO

	Acute medication use		Overusing individual medication classes		
Medication	N	% of CaMEO population[a]	N	% of medication class users[b]	% of CaMEO population[a]
Any single-class acute medication use for headache	14,936	89.0	2,753	18.4	16.4
Simple analgesic	13,209	78.7	1,767	13.4	10.5
NSAID (R_x/OTC)	10,215	60.8	1,218	11.9	7.3
Acetaminophen	6,516	38.8	506	7.8	3.0
Aspirin	3,025	18.0	310	10.2	1.8
Combination analgesic[c]	5,113	30.5	938	18.3	5.6
Opioid	1,947	11.6	422	21.7	2.5
Triptan	1,862	11.1	205	11.0	1.2
Ergotamine	100	0.6	19	19.0	0.1
Total AMO (single class or multiclass)	—	—	2,975	19.9	17.7

Abbreviations: AMO = acute medication overuse; CaMEO = Chronic Migraine Epidemiology and Outcomes; NSAID = nonsteroidal anti-inflammatory drug; OTC = over the counter; R_x = prescription.
[a] Denominator for this column is overall CaMEO analysis population (N = 16,789).
[b] Denominator for this column is total number of medication users in each row.
[c] Combination analgesic includes survey responses of Excedrin, barbiturates, and Midrin.

month. The multiple-class AMO group included respondents who did not meet any single-class AMO criteria but met the criteria when multiple medication classes were considered: (1) use of 2 or more classes of medication (ergotamines, triptans, simple analgesics, and opioids) but not any single medication, for 10 or more days, and (2) use of 2 or more simple analgesics (acetaminophen, aspirin, NSAID, or other) cumulatively, but not any single medication, for ≥15 days per month. Respondents could meet single-class AMO criteria for 1 or more classes of medication. Respondents meeting any criteria for AMO were categorized into the AMO subgroup, whereas those who failed to meet any criteria were categorized into the non-AMO group.

Standard Protocol Approvals, Registrations, and Patient Consents

The Albert Einstein College of Medicine Institutional Review Board approved the CaMEO Study and waived written informed consent for study volunteers, who had the right to accept or refuse participation in the survey. Data included in this analysis are from the CaMEO Study, which is registered on ClinicalTrials.gov (NCT01648530).

Statistics

Medication class use by AMO and non-AMO respondents, sociodemographics, headache frequency, depression, anxiety, migraine-related disability, migraine interictal burden, ED/UC use, and self-reported medical diagnosis of comorbidities were compared in a cross-sectional analysis. Medication class use was analyzed by counts reported in each medication class for each group.

The χ^2 test was used for testing between-group differences in categorical variables. Continuous variables including MHDs and PHQ-9, GAD-7, MIDAS, MIBS-4, and MSSS total scores were represented with medians and interquartile ranges (IQRs: Q1 and Q3). Between-group differences for continuous variables were assessed using the Mood median test between independent groups.

A series of nested multivariable binary logistic regression models was run with AMO vs non-AMO as the outcome. Covariates were entered in sequential blocks: sociodemographics, headache and respondent characteristics, psychiatric comorbidity, 6-month ED/UC use for headache or any reason, and preventive medication use. Separate models were run for any AMO, and AMO due to opioid use, triptan use, or NSAID use. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated for each variable. After each block was entered, nonsignificant variables were trimmed from the model; significance level was $p < 0.05$. No correction for multiple testing was applied. All analyses were performed using IBM SPSS Statistics Version 24.0 (IBM, Armonk, NY; 2011).

Data Availability

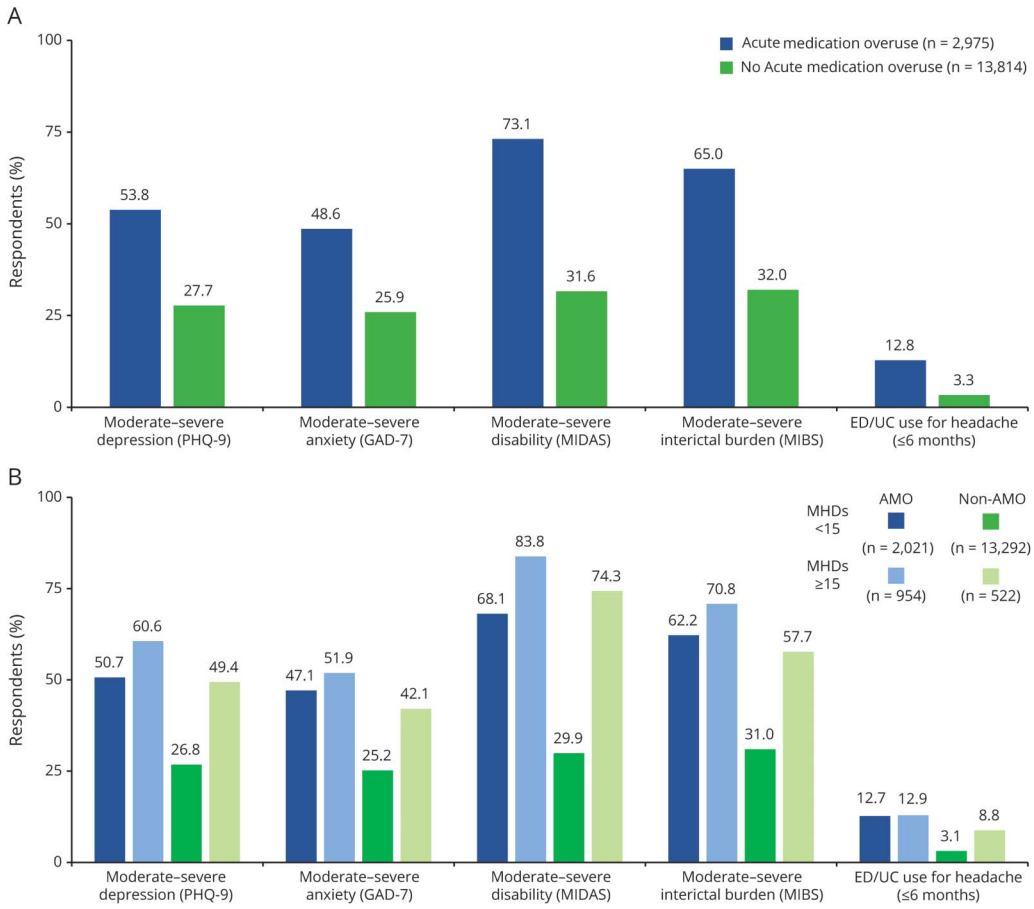
Additional data from the CaMEO Study (ClinicalTrials.gov Identifier: NCT01648530) may be requested at https://www.abbvie.com/our-science/clinical-trials/clinical-trials-data-and-information-sharing/data-and-information-sharing-with-qualified-researchers.html.

Results

Baseline Characteristics and Patterns of Acute Medication Use

Of 16,789 total CaMEO respondents with migraine, 14,936 (89.0%) reported using any acute medication to treat their

Figure 1 Migraine-Related Burden, Disability, and Comorbidities by AMO Status (A) and by AMO Status and Headache Frequency (B)



$p < 0.001$ for all comparisons between the AMO and non-AMO groups; χ^2 test. AMO = acute medication overuse; ED = emergency department; GAD-7 = Generalized Anxiety Disorder 7-Item Scale; MHD = monthly headache day; MIBS = Migraine Interictal Burden Scale; MIDAS = Migraine Disability Assessment; Mod = moderate; PHQ-9 = 9-Item Patient Health Questionnaire; UC = urgent care.

headaches. Use of any over-the-counter (OTC) medication for headache was reported by 14,279 (85.0%) respondents, and use of any prescription medication was reported by 4,902 (29.2%) respondents. A total of 4,245 (25.3%) respondents reported use of both OTC and prescription medication.

Baseline Characteristics by AMO Status

Of 16,789 respondents with migraine, 2,975 (17.7%) met the criteria for AMO, and 13,814 (82.3%) did not have AMO (table 1). Respondents with AMO, compared with those who did not meet the AMO criteria, were more likely to be obese (BMI 30 kg/m^2 or greater: 42.2% vs 33.8%; $p < 0.001$ χ^2 test); were less likely to have a 4-year college degree (39.8% vs 46.1%; $p < 0.001$ χ^2 test); had a higher median (IQR) number of MHDs (10.0 [4.3–16.7] vs 2.0 [1.0–4.7]; $p < 0.001$; Mood median test); and were more likely to have ≥15 MHDs (32.1% vs 3.8%; $p < 0.001$ χ^2 test). A total of 67.9% of respondents that met the AMO criteria had <15 MHDs (table 1). Sociodemographic features and baseline characteristics subdivided by AMO status in individuals with <15 MHDs and in those with ≥15 MHDs are shown in table e-1 (links.lww.com/CPJ/A253).

Characterization of Single-Class AMO

The majority (2,753 of 2,975 [92.5%]) of respondents with AMO met the AMO criteria for at least 1 medication class, and 7.4% (222 of 2,975) met the criteria for multiple-class AMO but not single-class AMO. Among the respondents meeting single-class AMO criteria, the overused medication classes were simple analgesics (64.2%, 1,767/2,753), combination analgesics (34.1%, 938/2,753), opioids (15.3%, 422/2,753), triptans (7.4%, 205/2,753), and ergotamines (0.7%, 19/2,753). The frequency of reported medication use and overuse among the total CaMEO analysis sample and within those reporting any use of each medication class is shown in table 2. The proportion of respondents meeting the AMO criteria for each individual class of medication was similar between respondents reporting <15 MHDs and those reporting ≥15 MHDs. Overall medication use across the AMO and MHD subgroups is shown in table e-2 (links.lww.com/CPJ/A254).

Headache-Related Burden and Comorbidities

Compared with respondents without AMO, respondents with AMO were more likely to have moderate to severe

Table 3 Comparison of Comorbidities (>5% of Total) by AMO Status Within MHD Groups

Self-report medical diagnosed comorbidity	<15 MHDs			≥15 MHDs		
	AMO (n = 2021)	No AMO (n = 13,292)	*p* Value[a]	AMO (n = 954)	No AMO (n = 522)	*p* Value[a]
Cardiac disorders						
High cholesterol	431 (28.5)	2,124 (20.9)	<0.001	221 (30.4)	86 (22.3)	0.004
Hypertension	364 (24.0)	1,868 (18.3)	<0.001	197 (27.1)	89 (23.1)	0.145
Irregular heart rhythms	167 (11.0)	845 (8.3)	<0.001	91 (12.5)	27 (7.0)	0.004
Endocrine disorders						
Underactive thyroid	160 (10.6)	809 (7.9)	0.001	89 (12.3)	31 (8.1)	0.032
Diabetes	168 (11.1)	674 (6.6)	<0.001	69 (9.5)	38 (9.9)	0.844
Gastrointestinal disorders						
Irritable bowel/IBS	185 (12.4)	830 (8.3)	<0.001	130 (18.3)	50 (13.1)	0.027
GERD	324 (21.4)	1,347 (13.2)	<0.001	178 (24.5)	93 (24.2)	0.894
Immune system disorders						
Allergies	689 (45.5)	3,686 (36.2)	<0.001	372 (51.2)	195 (50.6)	0.851
Dermatitis/eczema	160 (10.6)	972 (9.5)	0.208	90 (12.4)	36 (9.4)	0.128
Nervous system and psychiatric disorders						
Vertigo/dizziness	213 (14.1)	1,002 (9.8)	<0.001	140 (19.3)	77 (20.0)	0.774
Sleep apnea	163 (10.8)	686 (6.7)	<0.001	87 (12)	43 (11.2)	0.688
Insomnia	322 (21.3)	1,068 (10.5)	<0.001	206 (28.4)	60 (15.6)	<0.001
Anxiety	572 (37.8)	2,435 (23.9)	<0.001	320 (44.1)	149 (38.7)	0.084
Depression	627 (41.4)	2,661 (26.1)	<0.001	349 (48.1)	158 (41.0)	0.025
Panic disorder and panic attacks	207 (13.7)	849 (8.3)	<0.001	150 (20.7)	57 (14.8)	0.017
Nervousness	147 (9.7)	518 (5.1)	<0.001	92 (12.7)	32 (8.3)	0.028
Musculoskeletal and connective tissue disorders						
Neck pain	488 (32.2)	1,685 (16.5)	<0.001	269 (37.1)	121 (31.4)	0.062
Chronic back pain	436 (28.8)	1,522 (14.9)	<0.001	233 (32.1)	95 (24.7)	0.010
Chronic pain	196 (12.9)	475 (4.7)	<0.001	146 (20.1)	55 (14.3)	0.016
Arthritis	338 (22.3)	1,147 (11.3)	<0.001	148 (20.4)	67 (17.4)	0.231
Osteoarthritis	203 (13.4)	851 (8.4)	<0.001	112 (15.4)	41 (10.6)	0.028
TMD	149 (9.8)	642 (6.3)	<0.001	101 (13.9)	53 (13.8)	0.947
Respiratory, thoracic, and mediastinal disorders						
Asthma	365 (24.1)	1,823 (17.9)	<0.001	180 (24.8)	100 (26.0)	0.666
Chronic bronchitis	156 (10.3)	486 (4.8)	<0.001	85 (11.7)	38 (9.9)	0.353
Sinusitis	878 (58)	4,659 (45.7)	<0.001	432 (59.5)	221 (57.4)	0.498
Reproductive system						
PMS[b]	210 (13.9)	978 (9.6)	<0.001	123 (16.9)	54 (14)	0.206

Continued

Table 3 Comparison of Comorbidities (>5% of Total) by AMO Status Within MHD Groups *(continued)*

Self-report medical diagnosed comorbidity	<15 MHDs			≥15 MHDs		
	AMO (n = 2021)	No AMO (n = 13,292)	*p* Value[a]	AMO (n = 954)	No AMO (n = 522)	*p* Value[a]
Endometriosis[b]	105 (9.2)	469 (6.2)	<0.001	69 (11.7)	25 (7.9)	0.079

Abbreviations: AMO = acute medication overuse; GERD = gastroesophageal reflux disease; HCP = health care professional; IBS = irritable bowel syndrome; MHD = monthly headache day; PMS = premenstrual syndrome; TMD = temporomandibular joint dysfunction.
All data are n (%).
[a] Comparison between the AMO and non-AMO groups in respective headache frequency category with the χ^2 test.
[b] Calculations are based on the total sample number, not female respondents only.

depression (PHQ-9; $p < 0.001$; χ^2 test), moderate to severe anxiety (GAD-7; $p < 0.001$; χ^2 test), moderate to severe interictal burden (MIBS; $p < 0.001$; χ^2 test), moderate to severe headache-related disability (MIDAS; $p < 0.001$; χ^2 test), and a higher incidence of ED/UC use for headache within the past 6 months ($p < 0.001$; χ^2 test) (figure 1A). To evaluate the independent impact of both AMO status and headache frequency, the AMO and non-AMO groups were subdivided into those with <15 MHDs and those with ≥15 MHDs (figure 1B). AMO was consistently associated with a substantial increase in depression, anxiety, headache-related disability, migraine interictal burden, and ED/UC use for headache across both MHD subgroups.

Respondents with ≥15 MHDs had higher rates of depression, anxiety, headache-related disability, migraine interictal burden, and ED/UC use for headache compared with those reporting <15 MHDs in both the AMO and non-AMO subgroups. The observed impact of ≥15 MHDs was greater in those without AMO than in those with AMO.

Within both MHD subgroups, the percentage of respondents with self-reported medical diagnosed comorbidities tended to be greater in those with AMO compared with those without AMO (table 3). Within the <15 MHDs subgroup, the relative frequency of musculoskeletal and connective tissue disorders including neck pain, chronic back pain, arthritis, and chronic pain showed some of the largest differences between AMO groups, being approximately 2–3 times more frequent in those with AMO. Within the ≥15 MHDs subgroup, the AMO-associated differences tended to be smaller than in the <15 MHDs subgroup.

Factors Associated With AMO Based on Multivariable Binary Logistic Regression Models

To identify possible predictors of AMO status, a series of nested multivariable binary logistic models was run with nonsignificant variables removed at each step; the fully adjusted models for AMO and select acute medications are shown in table 4 (each individual nested model is shown in tables e-3–e-6, links.lww.com/CPJ/A255, links.lww.com/CPJ/A256, links.lww.com/CPJ/A257, and links.lww.com/CPJ/A258). Consistent factors identified as significant predictors of AMO in the fully adjusted models for all medication classes evaluated (any AMO, triptans, opioids, and NSAIDs) included ≥15 MHDs, moderate to severe disability (MIDAS), severe MIBS score, use of preventive medication, and ED/UC visits for headache within the previous 6 months. Overusing opioids for the acute treatment of headache was associated with a lower likelihood of employment (OR [95% CI] = 0.61 [0.47–0.79]). Overusing triptans for the acute treatment of headache was associated with a greater likelihood of diagnosis of migraine by a physician (OR [95% CI] = 4.11 [2.5–6.75]).

Discussion

Approximately 17.7% of the CaMEO Study respondents with migraine met the criteria for AMO. Opioids and combination analgesics were the most likely medications to be overused by respondents reporting use of those medications. Overall, respondents with AMO had greater headache-related disability, anxiety, depression, and ED/UC use for headache than those without AMO. Respondents with both AMO and ≥15 MHDs showed the highest total burden, but there was also a substantial negative impact of AMO in those with <15 MHDs. The differences in the relative frequency of self-reported medical diagnosed comorbidities between AMO and non-AMO respondents were greatest in the <15 MHDs subgroups, with many pain-related comorbidities exhibiting the largest differences in the AMO subgroup compared with the non-AMO subgroup. This greater relative frequency of pain-related comorbidities may contribute to the high level of medication use in those with <15 MHDs. Higher rates of anxiety may also contribute to AMO in that group. Finally, results of the nested multivariable binary logistic models show positive relationships between AMO status and migraine-related disability, interictal burden, and ED/UC use for headache.

The findings of this study are consistent with other studies evaluating AMO in people with migraine. Results from the Migraine in America Symptoms and Treatment study showed that survey respondents with AMO were more likely to be obese, have allodynia, have depression and/or anxiety, and report ≥15 headache days per month.[17] European studies demonstrated that female sex, headache frequency, comorbid pain conditions, comorbid psychiatric conditions, and type of overused medication are associated with

Table 4 Factors Associated With Risk of AMO Based on Nested Multivariable Binary Logistic Regression Models: Comparison of Final Models With Removal of Nonsignificant Covariates Except Age and Sex

Variable	Odds ratio (95% CI) for multiple outcomes			
	AMO (any)	Triptan overuse ≥10 d	Opioid overuse ≥10 d	NSAID overuse ≥15 d
Age	1.15 (1.13–1.17)	1.08 (1.02–1.15)	1.13 (1.08–1.19)	1.11 (1.08–1.14)
Female	0.9 (0.80–1.01)	0.96 (0.66–1.39)	0.67 (0.50–0.89)	1.00 (0.86–1.17)
Employed	—	—	0.61 (0.47–0.79)	—
Migraine diagnosis by physician	1.33 (1.20–1.48)	4.11 (2.50–6.75)	—	—
MIDAS ≥11 (moderate-severe disability)	2.05 (1.83–2.29)	2.31 (1.44–3.69)	1.89 (1.32–2.71)	1.67 (1.42–1.96)
Allodynia presence (ASC ≥3)	—	—	1.93 (1.44–2.60)	—
MHDs[a]				
5–9	2.65 (2.34–3.00)	3.43 (2.07–5.68)	1.71 (1.17–2.49)	2.47 (2.06–2.96)
10–14	5.99 (5.17–6.95)	6.55 (3.89–11.02)	2.87 (1.93–4.25)	4.81 (3.94–5.88)
≥15	12.37 (10.72–14.28)	6.28 (3.83–10.31)	3.43 (2.40–4.91)	7.53 (6.29–9.03)
HAs currently managed by a specialist[b]	1.29 (1.07–1.56)	1.66 (1.17–2.37)	2.36 (1.70–3.27)	—
MIBS[c]				
Mild (1–2)	1.28 (1.10–1.49)	2.73 (1.34–5.58)	1.25 (0.71–2.20)	1.17 (0.95–1.44)[d]
Moderate (3–4)	1.57 (1.36–1.83)	3.68 (1.87–7.23)	2.28 (1.39–3.74)	1.30 (1.06–1.60)
Severe (≥5)	2.16 (1.90–2.46)	4.05 (2.16–7.60)	3.32 (2.14–5.17)	1.57 (1.31–1.87)
Depression (PHQ-9 ≥10)	1.29 (1.14–1.46)	—	1.68 (1.27–2.23)	1.32 (1.12–1.56)
Anxiety (GAD-7 ≥10)	1.52 (1.34–1.72)	—	—	1.57 (1.34–1.84)
ED/UC use in past 6 mo for any reason	—	—	1.69 (1.22–2.33)	1.16 (0.94–1.44)[d]
ED/UC use in past 6 mo for headache	1.72 (1.44–2.05)	1.89 (1.31–2.71)	2.00 (1.36–2.94)	—
Use of preventive medication	2.03 (1.71–2.41)	5.12 (3.71–7.07)	1.84 (1.34–2.52)	2.22 (1.84–2.66)

Abbreviations: AMO = acute medication overuse; AMOH = acute medication overuse headache; ASC = Allodynia Symptom Checklist; CI = confidence interval; ED = emergency department; GAD-7 = Generalized Anxiety Disorder 7-Item Scale; MHDs = monthly headache days; MIBS = Migraine Interictal Burden Scale; MIDAS = Migraine Disability Assessment; NSAID = nonsteroidal anti-inflammatory drug; PHQ-9 = 9-item Patient Health Questionnaire; UC = urgent care. Only variables that were included in at least 1 final model are shown; race, income, and college degree were not included in any of the final models. "—" indicates variable trimmed from the model because of nonsignificance.
[a] The reference group was 0–4 MHDs.
[b] Specialist was defined as a neurologist, pain, or headache specialist.
[c] Reference is no interictal burden (MIBS score of 0).
[d] Variable is nonsignificant in final model.

AMO.[18–21] Migraine is associated with multiple comorbidities, which could contribute to increased medication use.[22] The many pain comorbidities of migraine could contribute to increased use of analgesics.[23] A cross-sectional, school-based study found an overall prevalence of probable MOH of 0.9%, with similar prevalence in boys and girls.[24] An overall prevalence of probable MOH of 2.0% was reported in a Saudi Arabian study, with a greater occurrence in females and participants 46–55 years of age.[25] Additional studies in Asia found that headache disorders (including MOH) are associated with a substantial overall burden, with unmet treatment needs including high rates of over-the-counter medication use.[26,27] Taken together, the results of these studies show a pronounced disease-related burden in those who overuse acute medications for migraine.

AMO is associated with the risk of migraine disease progression from episodic migraine (EM) to chronic migraine (CM).[9,13,28,29] In the AMPP study, triptan overuse alone was associated with risk of disease progression from EM to CM depending on the baseline frequency of MHDs; however, triptan use in combination with NSAIDs was not associated with an increased risk of progression, and NSAID use may be protective of progressing from EM to CM depending on MHDs.[13,28,30] In addition, opioids and barbiturate analgesics are associated with dose-dependent increased risk of CM onset across a range of frequencies.[8,13,31] Although the relationship between medication use and disease progression is not straightforward across all acute medication classes, the suboptimal treatment of migraine attacks is a risk factor for progression.

The true burden related to AMO/MOH may be underestimated in practice, as diagnostic criteria for MOH require 15 MHDs.[11] The analyses reported herein demonstrate that 68% of participants with AMO had <15 MHDs, and these respondents demonstrated substantial burden. In addition, 49% of respondents who reported AMO also reported <10 MHDs, suggesting that these respondents are taking migraine medication on days when they do not have a headache, or taking multiple different acute medications to treat each headache, thus meeting the criteria for AMO with combination use of multiple classes. In addition, some people with migraine may take acute medication preemptively to try to avoid onset of a migraine attack and/or to manage associated anxiety. This practice would be counted as a medication day, but not as a headache day, leading to respondents exhibiting AMO but failing to meet ICHD-defined criteria for MOH.[11] Health care professionals should review the frequency of acute medication use in all patients with migraine, regardless of the monthly headache frequency and especially in those with comorbid pain conditions.

Because AMO is common and associated with high disease burden in people with migraine, it is an important target for prevention and treatment. Approaches for avoiding and treating AMO and MOH include using effective acute treatments, using patient and clinician education about limiting intake of acute medications, and initiating and optimizing pharmacologic and nonpharmacologic preventive treatments.[32] Nonpharmacologic approaches include cognitive behavioral therapy that is specifically focused on AMO treatment and reducing the factors that lead to overuse of the acute medication.[20,33] Improved efficacy and outcomes for elimination of AMO are achieved when behavioral therapies are included as part of treatment.[34]

Although most acute treatments can cause AMO, emerging evidence suggests that gepants, a novel class of small-molecule calcitonin gene-related peptide (CGRP) receptor antagonists, may not. In a preclinical model of MOH, repeated administration of pharmacologically active doses of ubrogepant (a CGRP receptor antagonist) did not produce MOH-like latent sensitization in female rats.[35] In long-term safety studies, frequent use of gepants over the course of a year was associated with a reduction and not an increase in monthly migraine days.[36] Unlike most oral acute treatments for migraine for which an MOH warning is required, the prescribing information for the US Food and Drug Administration–approved gepants (ubrogepant and rimegepant) does not include a warning for MOH as is required for most oral acute treatments for migraine.[37-39] Although it is promising that the CGRP receptor antagonists might not be associated with AMO, more research is needed to fully understand the relationship between their use and MOH, especially in individuals with a high frequency of migraine days.[40]

Strengths of this study include the large sample size (16,789 CaMEO respondents with migraine) and the ability to collect detailed medication use information across a spectrum of individuals with varying migraine frequency. However, as this was a cross-sectional study, the data can only report the frequency of medication use and headache frequency separately; causality cannot be determined. The data collected are self-reported by survey respondents who met the AMO criteria. Participation bias could influence the results. Finally, due to the design of the questionnaire, we could not assess the reason for each reported medication use by respondents and could not differentiate between acute medication use to treat a headache/migraine or preemptive use in anticipation of a headache.

Respondents with AMO had more headache-related disability, anxiety, depression, and ED/UC use for headache than those without AMO in both MHD frequency groups (i.e., <15 MHDs and ≥15 MHDs). These same factors were identified as showing a significant relationship with AMO via multivariable binary logistic regression analysis. Use of comprehensive migraine treatment plans that include improved acute treatment options as well as considering guideline-based preventive treatments, including both pharmacologic and nonpharmacologic modalities, combined with appropriate education may help to reduce the relative frequency of AMO and the associated burden from possible MOH.

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References

1. Burch R, Rizzoli P, Loder E. The prevalence and impact of migraine and severe headache in the United States: figures and trends from government health studies. Headache 2018;58:496–505.
2. Goadsby PJ, Lipton RB, Ferrari MD. Migraine—current understanding and treatment. N Engl J Med 2002;346:257–270.
3. Pietrobon D, Moskowitz MA. Pathophysiology of migraine. Annu Rev Physiol 2013;75:365–391.
4. Silberstein SD. Practice parameter: evidence-based guidelines for migraine headache (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2000;55:754–762.
5. Holland S, Fanning KM, Serrano D, Buse DC, Reed ML, Lipton RB. Rates and reasons for discontinuation of triptans and opioids in episodic migraine: results from the American Migraine Prevalence and Prevention (AMPP) study. J Neurol Sci 2013;326:10–17.
6. Messali AJ, Yang M, Gillard P, et al. Treatment persistence and switching in triptan users: a systematic literature review. Headache 2014;54:1120–1130.
7. Wells RE, Markowitz SY, Baron EP, et al. Identifying the factors underlying discontinuation of triptans. Headache 2014;54:278–289.
8. Lipton RB, Fanning KM, Serrano D, Reed ML, Cady R, Buse DC. Ineffective acute treatment of episodic migraine is associated with new-onset chronic migraine. Neurology 2015;84:688–695.
9. Buse DC, Greisman JD, Baigi K, Lipton RB. Migraine progression: a systematic review. Headache 2019;59:306–338.
10. Serrano D, Kori S, Papapetropoulos S, et al. Does adding acute treatment improve migraine outcomes in patients on triptans? Results of the America Migraine Prevalence & Prevention (AMPP) Study [abstract]. Presented at: Annual Scientific Meeting of the American Headache Society; June 21–24, 2012; Los Anegles, CA.
11. Headache Classification Committee of the International Headache Society. The International Classification of Headache Disorders, 3rd edition. Cephalalgia 2018;38:1–211.
12. Lampl C, Thomas H, Stovner LJ, et al. Interictal burden attributable to episodic headache: findings from the Eurolight project. J Headache Pain 2016;17:9.
13. Bigal ME, Serrano D, Buse D, Scher A, Stewart WF, Lipton RB. Acute migraine medications and evolution from episodic to chronic migraine: a longitudinal population-based study. Headache 2008;48:1157–1168.
14. Manack Adams A, Serrano D, Buse DC, et al. The impact of chronic migraine: the Chronic Migraine Epidemiology and Outcomes (CaMEO) Study methods and baseline results. Cephalalgia 2015;35:563–578.
15. Headache Classification Subcommittee of the International Headache Society. The International Classification of Headache Disorders, 2nd ed. Cephalalgia 2004;24(suppl 1):9–160.

16. Headache Classification Committee of the International Headache Society. The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia 2013;33:629–808.
17. Schwedt TJ, Alam A, Reed ML, et al. Factors associated with acute medication overuse in people with migraine: results from the 2017 migraine in America symptoms and treatment (MAST) study. J Headache Pain 2018;19:38.
18. Hagen K, Linde M, Steiner TJ, Stovner LJ, Zwart JA. Risk factors for medication-overuse headache: an 11-year follow-up study. The Nord-Trondelag Health Studies. Pain 2012;153:56–61.
19. Katsarava Z, Muessig M, Dzagnidze A, Fritsche G, Diener HC, Limmroth V. Medication overuse headache: rates and predictors for relapse in a 4-year prospective study. Cephalalgia 2005;25:12–15.
20. Diener HC, Holle D, Solbach K, Gaul C. Medication-overuse headache: risk factors, pathophysiology and management. Nat Rev Neurol 2016;12:575–583.
21. Lampl C, Thomas H, Tassorelli C, et al. Headache, depression and anxiety: associations in the Eurolight project. J Headache Pain 2016;17:59.
22. Korolainen MA, Tuominen S, Kurki S, et al. Burden of migraine in Finland: multimorbidity and phenotypic disease networks in occupational healthcare. J Headache Pain 2020;21:8.
23. Scher AI, Buse DC, Fanning KM, et al. Comorbid pain and migraine chronicity: the chronic migraine epidemiology and outcomes study. Neurology 2017;89:461–468.
24. Philipp J, Zeiler M, Wöber C, et al. Prevalence and burden of headache in children and adolescents in Austria - a nationwide study in a representative sample of pupils aged 10-18 years. J Headache Pain 2019;20:101.
25. Al Jumah M, Al Khathaami AM, Kojan S, Hussain M, Thomas H, Steiner TJ. The prevalence of primary headache disorders in Saudi Arabia: a cross-sectional population-based study. J Headache Pain 2020;21:11.
26. Takeshima T, Wan Q, Zhang Y, et al. Prevalence, burden, and clinical management of migraine in China, Japan, and South Korea: a comprehensive review of the literature. J Headache Pain 2019;20:111.
27. Yao C, Wang Y, Wang L, et al. Burden of headache disorders in China, 1990–2017: findings from the Global Burden of Disease Study 2017. J Headache Pain 2019;20:102.
28. Raggi A, Schiavolin S, Leonardi M, et al. Chronic migraine with medication overuse: association between disability and quality of life measures, and impact of disease on patients' lives. J Neurol Sci 2015;348:60–66.
29. Xu J, Kong F, Buse DC. Predictors of episodic migraine transformation to chronic migraine: a systematic review and meta-analysis of observational cohort studies. Cephalalgia 2020;40:503–516.
30. Lipton RB, Serrano D, Nicholson RA, Buse DC, Runken MC, Reed ML. Impact of NSAID and triptan use on developing chronic migraine: results from the American Migraine Prevalence and Prevention (AMPP) study. Headache 2013;53:1548–1563.
31. Bigal ME, Lipton RB. Modifiable risk factors for migraine progression. Headache 2006;46:1334–1343.
32. Vandenbussche N, Laterza D, Lisicki M, et al. Medication-overuse headache: a widely recognized entity amidst ongoing debate. J Headache Pain 2018;19:50.
33. Evers S, Jensen R. Treatment of medication overuse headache—guideline of the EFNS headache panel. Eur J Neurol 2011;18:1115–1121.
34. Grazzi L, Usai S, Prunesti A, Bussone G, Andrasik F. Behavioral plus pharmacological treatment versus pharmacological treatment only for chronic migraine with medication overuse after day-hospital withdrawal. Neurol Sci 2009;30(suppl 1): S117–S119.
35. Navratilova E, Behravesh S, Oyarzo J, Dodick DW, Banerjee P, Porreca F. Ubrogepant does not induce latent sensitization in a preclinical model of medication overuse headache. Cephalalgia 2020;40:892–902.
36. Lipton RB, Berman G, Kudrow D, et al. Long-term, open-label safety study of rimegepant 75 mg for the treatment of migraine (study 201): interim analysis of safety and exploratory efficacy [abstract P235LB]. Headache 2019;59(suppl 1):175.
37. Ubrelvy [package insert]. Madison, NJ: Allergan USA, Inc.; 2020.
38. Imitrex [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2017.
39. Nurtec ODT [package insert]. New Haven, CT: Biohaven Pharmaceuticals, Inc.; 2020.
40. van Hoogstraten WS, MaassenVanDenBrink A. The need for new acutely acting antimigraine drugs: moving safely outside acute medication overuse. J Headache Pain 2019;20:54.

Practical Implications

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