Medication Overuse and Headache Burden
Results From the CaMEO Study

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Neurology: Clinical Practice June 2021 vol. 11 no. 3 216-226 doi:10.1212/CPJ.0000000000001037

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.
Migraine is a prevalent chronic neurologic disease characterized by painful, debilitating attacks. The goal of acute treatment is to relieve symptoms and restore function. 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.

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. 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. Thus, the number of days taking migraine acute medications can exceed the number of migraine or headache days.

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. 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, but no significant changes occurred among the ICHD-2, ICHD-3-beta, and the final ICHD-3 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<sup>a</sup> |
|--------------------------------|-----------------|----------------------|---------------------|
| **Age, y, mean (SD)**          | 43.2 (13.8)     | 40.7 (14.5)          | <0.001<sup>b</sup>  |
| **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/m²)**      | 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**      |                 |                      | <0.001              |
| Median (IQR)                   | 10.0 (4.3, 16.7)| 2.0 (1.0, 4.7)       | <0.001<sup>c</sup> |
| Mean (SD)                      | 11.2 (8.2)      | 3.7 (4.4)            | <0.001<sup>b</sup> |
| **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<sup>c</sup> |
| **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<sup>c</sup> |
| **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<sup>c</sup> |
| **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<sup>c</sup> |
| **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<sup>c</sup> |
| **ED/UC use for headache (≥1 visit in past 6 mo)** | 380 (12.8) | 453 (3.3) | |
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 \( \geq 15 \) 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 \( \chi^2 \) 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

| Table 2 | Single-Medication Use, Single-Class AMO, and Overall AMO Among People With Migraine in CaMEO |
|---------|---------------------------------------------------------------|
| Medication | Acute medication use | Overusing individual medication classes |
| | N | % of CaMEO population | N | % of medication class users | % of CaMEO population |
| 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 (Rx/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 | 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; Rx = prescription.

Denominator for this column is overall CaMEO analysis population (N = 16,789).

Denominator for this column is total number of medication users in each row.

Combination analgesic includes survey responses of Excedrin, barbiturates, and Midrin.
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/m² or greater: 42.2% vs 33.8%; \( p < 0.001 \) \( \chi^2 \) test); were less likely to have a 4-year college degree (39.8% vs 46.1%; \( p < 0.001 \) \( \chi^2 \) 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%; \( p < 0.001 \) \( \chi^2 \) 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/CP/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/CP/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 | p Value* | <15 MHDs | ≥15 MHDs | p Value* |
|------------------------------------------|----------|----------|----------|----------|----------|----------|
| **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**                  |          |          |          |          |          |          |
| PMSb                                     | 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 | p Value* |
|------------------------------------------|---------|---------|---------|
| Endometriosisb | AMO (n = 2021) | No AMO (n = 13,292) | p Value* |
| Value | 105 (9.2) | 469 (6.2) | <0.001 |
| 69 (11.7) | 25 (7.5) | 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.

a Comparison between the AMO and non-AMO groups in respective headache frequency category with the χ² test.
b Calculations are based on the total sample number, not female respondents only.

depression (PHQ-9; p < 0.001; χ² test), moderate to severe anxiety (GAD-7; p < 0.001; χ² test), moderate to severe interictal burden (MIBS; p < 0.001; χ² test), moderate to severe headache-related disability (MIDAS; p < 0.001; χ² test), and a higher incidence of ED/UC use for headache within the past 6 months (p < 0.001; χ² 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 regression 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. European studies demonstrated that female sex, headache frequency, comorbid pain conditions, comorbid psychiatric conditions, and type of overused medication are associated with
AMO is associated with the risk of migraine disease progression from episodic migraine (EM) to chronic migraine (CM). 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 the baseline frequency of MHDs. 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. Taken together, the results of these studies show a pronounced disease-related burden in those who overuse acute medications for migraine.

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.

*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.

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 ≥ 10 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   | 0.98 (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 ≥ 5 | 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) | 2.67 (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) |
| HA currently managed by a specialist | 1.29 (1.07–1.56) | 1.66 (1.17–2.37) | 2.36 (1.70–3.27) — — |
| MIBSc | 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) |
|          | 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) |
| 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) |

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The true burden related to AMO/MOH may be underestimated in practice, as diagnostic criteria for MOH require 15 MHDs. 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.

Disclosure
T.J. Schwedt has served as a consultant for AbbVie, Alder, Amgen, ATI, Aural Analytics, Avanir, Biohaven, Cipla, Click Therapeutics, Dr. Reddy’s Laboratories, Eli Lilly, Equinox, Ipsen Bioscience, Lundbeck, Nocira, Novartis, Promius Pharma, Salvia, Second Opinion, Teva, Xoc, and Weber and Weber; he holds stock options in Aural Analytics, Nocira, and Second Opinion and has received research funding from Amgen. D.C. Buse has received grant support and honoraria from AbbVie, Amgen, Avanir, Biohaven, Dr. Reddy’s/ Promius, Eli Lilly and Company, and Teva and for work on the editorial board of Current Pain and Headache Reports. C.E. Argoff has served as a consultant for Lilly, Novartis, and Teva and has received honoraria from AbbVie, Amgen, Lilly, Novartis, Teva, and TheraCina; he has received royalties from Elsevier for Pain Management Secrets and Raj’s Practical Management of Pain. M.L. Reed is Managing Director of Vedanta Research, which has received research funding from AbbVie, Amgen, Dr. Reddy’s Laboratories, Eli Lilly, GlaxoSmithKline, Merck & Co., Inc., and the National Academy of Clinical Trials.

Acknowledgment
Writing and editorial assistance was provided to the authors by Peloton Advantage, LLC, an OPEN Health company, Parsippany, NJ. The opinions expressed in this article are those of the authors. The authors received no honoraria/fees or other form of financial support related to the development of this article.

Study Funding
This study was sponsored by Allergan (prior to its acquisition by AbbVie).
Headache Foundation. Vedanta Research has received funding directly from AbbVie for work on the CaMEO Study. K.M. Fanning is an employee of Vedanta Research, which has received research funding from AbbVie, Amgen, Dr. Reddy’s Laboratories, Eli Lilly, GlaxoSmithKline, Merck & Co., Inc., and the National Headache Foundation. Vedanta has received funding directly from AbbVie for work on the CaMEO Study. C.R. Hussar is an employee of Peloton Advantage, LLC, an OPEN Health company. A.M. Adams is an employee of AbbVie and may hold AbbVie stock. R.B. Lipton serves on the editorial boards of Neurology and Cephalalgia and as senior advisor to Headache; he receives research support from the NIH; he also receives support from the Migraine Research Foundation and the National Headache Foundation; he has reviewed for the National Institute of Aging and the National Institute of Neurological Disorders and Stroke; serves as consultant, advisory board member, or has received honoraria from AbbVie, Alder, Amgen, Axsome, Dr. Reddy’s, electroCore, Eli Lilly, eNeura Therapeutics, GlaxoSmithKline, Merck, Novartis, Teva, and Vedanta; he receives royalties from Wolff’s Headache, 8th edition (Oxford University Press, 2009) and Informa; and he holds stock options in Biohaven and eNeura Therapeutics. Full disclosure form information provided by the authors is available with the full text of this article at Neurology.org/cp.

**Publication History**

Received by Neurology: Clinical Practice July 30, 2020. Accepted in final form January 4, 2021.

**Appendix Authors**

| Name                  | Location                      | Contribution                                                                 |
|-----------------------|-------------------------------|------------------------------------------------------------------------------|
| Todd J. Schwedt, MD   | Mayo Clinic, Phoenix, AZ      | Interpreted the data; drafted the manuscript for intellectual content; and revised the manuscript for intellectual content |
| Dawn C. Buse, PhD     | Albert Einstein College of Medicine, Bronx, NY | Designed and conceptualized the study; major role in the acquisition of data; drafted the manuscript for intellectual content; and revised the manuscript for intellectual content |
| Charles E. Argoff, MD | Albany Medical Center, Albany, NY | Interpreted the data; drafted the manuscript for intellectual content; and revised the manuscript for intellectual content |
| Michael L. Reed, PhD  | Vedanta Research, Chapel Hill, NC | Designed and conceptualized the study; major role in the enrollment of patients and the acquisition of data; interpreted the data; drafted the manuscript for intellectual content; and revised the manuscript for intellectual content |

**Appendix (continued)**

| Name                        | Location                      | Contribution                                                                 |
|-----------------------------|-------------------------------|------------------------------------------------------------------------------|
| Kristina M. Fanning, PhD    | Vedanta Research, Chapel Hill, NC | Interpreted the data; drafted the manuscript for intellectual content; and revised the manuscript for intellectual content |
| Cory R. Hussar, PhD         | Peloton Advantage, LLC, an OPEN Health company, Parsippany, NJ | Interpreted the data; drafted the manuscript for intellectual content; and revised the manuscript for intellectual content |
| Aubrey Manack Adams, PhD    | AbbVie, Irvine, CA            | Designed and conceptualized the study; major role in the acquisition of data; interpreted the data; drafted the manuscript for intellectual content; and revised the manuscript for intellectual content |
| Richard B. Lipton, MD       | Albert Einstein College of Medicine, Bronx, NY | Designed and conceptualized the study; major role in the acquisition of data; interpreted the data; contributed to data analysis; drafted the manuscript for intellectual content; and revised the manuscript for intellectual content |

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