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Research Submission

Most Bothersome Symptom in Persons With Migraine: Results From the Migraine in America Symptoms and Treatment (MAST) Study

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Objectives.—The objectives of this study were to determine the rates of nausea, phonophobia, and photophobia reported overall and as the most bothersome symptom (MBS) in individuals with migraine and to identify individual characteristics associated with each of the 3 candidate MBSs.

Background.—The MBS has emerged as an important coprimary efficacy endpoint in clinical trials of acute treatments for migraine, as recommended by the Food and Drug Administration. The current understanding of how persons with migraine designate an associated symptom as the most bothersome has been assessed primarily in the context of randomized trials.

Methods.—Respondents (n = 95,821) in the cross-sectional, observational Migraine in America Symptoms and Treatment (MAST) study were adults (aged ≥18 years) recruited from a US nationwide online research panel. A validated diagnostic screener identified 15,133 individuals who met modified International Classification of Headache Disorders (ICHD)-3 beta criteria for migraine and reported at least 1 monthly headache day (MHD) over the previous 3 months. The survey ascertained sociodemographic variables, headache-related disability, MHDs, cutaneous allodynia, medication overuse, a migraine symptom severity score, pain interference, noncephalic pain, anxiety and depression symptoms, visual aura over the previous year, and acute treatment optimization. The current analysis is based on respondents who also completed a 6-month follow-up assessment that included questions about their most bothersome headache symptom.

Results.—A total of 7518 respondents completed the 6-month follow-up, and 6045 met inclusion criteria and were included in the analysis. The mean age of respondents was 47 (SD 13.4) years, 76.0% (4596/6045) were women, and 84.8% (5103/6017) were white. Among all respondents, 64.9% reported all 3 migraine symptoms. The MBS was photophobia in 49.1% (2967/6045), nausea in 28.1% (1697/6045), and phonophobia in 22.8% (1381/6045). Respondents reporting photophobia as the MBS were more likely to be men, to be obese, and to report visual aura. Those reporting nausea as the MBS were more likely to be women, to have lower incomes, and to report lower levels of treatment optimization. Respondents reporting phonophobia as the MBS were more likely to have cutaneous allodynia and less likely to have visual aura.

Conclusion.—Most people with migraine in the MAST observational study reported all 3 cardinal symptoms of nausea, photophobia, and phonophobia. As in clinical trials, the most common MBS was photophobia. Patient profiles differed among the groups defined by their MBS.

Key words: migraine, epidemiology, coprimary endpoints, most bothersome symptom

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Abbreviations: AMPP American Migraine Prevalence and Prevention, AMS American Migraine Study, ASC-12 Allodynia Symptom Checklist, ICHD International Classification of Headache Disorders, MAST Migraine in America Symptoms and Treatment, MBS most bothersome symptom, MHD monthly headache day, MIDAS Migraine Disability Assessment Scale, MSSS Migraine Symptom Severity Score, mTOQ Migraine Treatment Optimization Questionnaire, PHQ-4 Patient Health Questionnaire, PROMIS Patient Reported Outcomes Measurement Information System, SD standard deviation, TPI Total Pain Index

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INTRODUCTION

Migraine without aura is diagnosed based on the presence of at least 2 of 4 pain characteristics and on the presence of cardinal-associated symptoms: nausea or vomiting or both photophobia and phonophobia.[1] Traditional efficacy evaluations in clinical trials of acute migraine treatments have focused on ratings of headache pain, nausea, photophobia, and phonophobia as coprimary efficacy endpoints.[2] This approach was based on the assumption that migraine is a symptom complex. It is difficult to demonstrate that treatment relieves a symptom if that symptom is not present prior to treatment. To ensure that the target associated symptoms are present before investigational treatment is administered, the US Food and Drug Administration provide alternative criteria for establishing efficacy in clinical trials of acute treatments. In the alternative method, 2 coprimary endpoints – 2-hour pain freedom and 2-hour freedom from the most bothersome symptom (MBS), as designated at screening or immediately prior to treatment[2] – are required instead of 4. By removing the need to show significant differences from placebo on 4 coprimary endpoints, the new approach also reduces sample size requirements and increases power to detect change relative to trials conducted under the older guidance.[3,4]

Conflict of Interest: Sagar Munjal is employed by and owns stock/stock options in Promius Pharma. Preeti Singh is an employee of Promius Pharma. Michael L. Reed and Kristina Fanning are employees of Vedanta Research, which has received grant support from Allergan, Amgen, Eli Lilly, Dr Reddy's Laboratories/Promius, and the National Headache Foundation. Todd J. Schwedt owns stock options from Aural Analytics, Nocira, and Second Opinion and receives royalties from UpToDate. He receives grant support from the National Institutes of Health (NIH), the US Department of Defense, the Patient-Centered Outcomes Research Institute, the American Migraine Foundation, Arizona State University, Amgen, and the Mayo Clinic. He serves as a consultant, advisory board member, or has received honoraria from Alder, Allergan, Amgen, the American Headache Society, Avanir, Dr Reddy's Laboratories/Promius, Eli Lilly, Equinox, Ipsen Biosciences, Nocira, Novartis, Teva, and XoC Pharmaceuticals. David W. Dodick reports the following conflicts: Consulting: Amgen, University Health Network, Daniel Edelman Inc, Autonomic Technologies, Axsome, Allergan, Alder, Biohaven, Charleston Laboratories, Promius, Eli Lilly, eNeura, Neurolief, Novartis, Ipsen, Impel, Satsuma, Supernus, Theranica, Teva, WL Gore, Nocira, XoC, Zosano, Upjohn (Division of Pfizer), Pieris, Revance, Equinox, Salvia, Amzak Health. Honoraria: Foresite Capital, ZP Opco, Oppenheimer, Association of Translational Medicine, Healthlogix, Medicom Worldwide, Medlogix Communications, Mednet, Electrocore, Miller Medical, PeerView, WebMD Health/Medscape, Chameleon, Academy for Continued Healthcare Learning, Sun Pharma (India), Universal meeting management, Haymarket, Global Scientific Communications, Global Life Sciences, Global Access Meetings, UpToDate (Elsevier), Oxford University Press, Cambridge University Press, Wolters Kluwer Health. Research Support: Department of Defense, National Institutes of Health, Henry Jackson Foundation, Sperling Foundation, American Migraine Foundation, Patient-Centered Outcomes Research Institute (PCORI). Stock Options/Shareholder/Patents/Board of Directors: Aural Analytics, Healint, Theranica, Second Opinion/Mobile Health, Epien (Options/Board), Nocira, Matterhorn/Ontologics (Options/Board), King-Devick Technologies (Options/Board), Precon Health (Options/Board). Patent 17189376.1-1466:vTitle: Botulinum Toxin Dosage Regimen for Chronic Migraine Prophylaxis. Dawn C. Buse has received grant support and honoraria from Allergan, Amgen, Avanir, Biohaven, Eli Lilly, Dr Reddy's Laboratories/Promius, and Teva. She is on the editorial board of Current Pain and Headache Reports. Richard B. Lipton serves on the editorial board of Neurology and Cephalalgia and as senior advisor to Headache but is not paid for his roles on Neurology or Headache. He receives research support from the NIH. He also receives support from the Migraine Research Foundation and the National Headache Foundation. He receives research grants from Allergan, Amgen, Dr Reddy's Laboratories/Promius, and Novartis. He has reviewed for the National Institute on Aging and National Institute of Neurological Disorders and Stroke and serves as consultant, advisory board member, or has received honoraria from Alder, Allergan, Amgen, Biohaven, Dr Reddy's Laboratories/Promius, electroCore, Eli Lilly, eNeura Therapeutics, GlaxoSmithKline, Merck, Novartis, Teva, and Vedanta. He receives royalties from Wolff's Headache (8th Edition, Oxford Press University, 2009) and Informa. He holds stock options in eNeura Therapeutics and Biohaven Pharmaceuticals.
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Though multiple acute treatment studies have been conducted using 2-hour MBS freedom as a coprimary endpoint,[5-17] we are not aware of data on MBS in nationally representative samples of people with migraine. The Migraine in America Symptoms and Treatment (MAST) Study was designed to assess current patterns of consultation, diagnosis, and treatment in a large representative sample of people with migraine in the United States.[18,19] The MAST study also assessed the frequency of the cardinal associated symptoms and asked respondents to identify their MBS in the 6-month follow-up survey.

The current study in a US population sample of adults with migraine had 2 objectives. First, we tried to determine the rates of reporting nausea, phonophobia, and photophobia by persons with migraine, as well as the rates at which each of these symptoms are selected as the MBS. Second, we sought to identify individual and headache characteristics associated with designation of a particular MBS.

METHODS

Study Design.—Details of the MAST study methods are available elsewhere.[18] In brief, MAST is a cross-sectional observational study of US adults who were screened for migraine and monthly headache frequency. Baseline data collection occurred between October 2016 and January 2017. A power analysis was not implemented, but the sampling plan was intended to provide sufficient numbers of persons with migraine to characterize migraine population subgroups of interest, such as acute medication users and those with frequent attacks. The study used stratified sampling to establish a final sample that was demographically representative of the US adult population based on sex, age, household income, race, marital status, and US Census region. Sample demographics were maintained within 5% of those reported in the 2015 US Census. Six- and 12-month longitudinal samples were also obtained.

Recruiting and Inclusion Criteria.—A representative sample of panel members (from Research Now, Plano, TX, USA) was invited to participate in a survey about health. Volunteers provided written informed consent. After consenting, volunteers provided sociodemographics and if they endorsed headache or migraine from a list of health problems, they were presented with the validated American Migraine Study (AMS)/American Migraine Prevalence and Prevention (AMPP) Study diagnostic migraine screening module that used modified International Classification of Headache Disorders (ICHD)-3 beta migraine criteria.[20-22] The AMS/AMPP diagnostic screening module [23,24] is based on self-report of symptoms associated with respondents' most severe headache and captures pain characteristics (unilateral location, pulsating/throbbing quality, moderate to severe intensity, exacerbation by routine activity) and associated symptoms (nausea, phonophobia, and photophobia). It has a sensitivity of 100% and specificity of 82% for migraine.[25] To minimize false positives, respondents also had to satisfy headache frequency criteria of 3 or more monthly headache days (MHDs) in the past 3 months and at least 1 MHD in the past 30 days. Respondents meeting migraine symptom criteria and headache frequency criteria (N = 15,133) were included in the baseline cohort. All 15,133 MAST baseline respondents were invited to complete the 6-month follow-up survey.

The MAST Study protocol was reviewed by Ethical and Independent Review Services (Independence, MO, USA), which granted an exemption under (45 CFR 46.101 [2]) and certified the exemption status (#16106-01) on August 31, 2016.

Main Outcome of Interest.—Respondents met migraine criteria, which meant that they endorsed either nausea and/or photophobia and phonophobia at a symptom frequency of at least half the time or more with their headaches. They were asked the following question to indicate their MBS: "Over the last 3 months, which of the following has been the single MBS when you have it with your headaches (before you take any medication)?" Respondents could select only 1 response. Respondents whose only associated symptom was nausea (ie, no photophobia or phonophobia) were assigned nausea as their MBS.[1] Respondents with more than 1 associated symptom were asked to select their MBS. In addition, the presence of each symptom occurring at least half the time or more and the number of symptoms (out of the 3 symptoms of interest) occurring at least half the time or more is reported.

Assessments.—Respondent sex (men, women); age (years); total annual household income (<$25,000, $25,000-$49,999, $50,000-$74,999, $75,000-$99,999,

≥$100,000); and race (white or not white) were obtained from single, self-report items. Body mass index (BMI) was calculated using the standard formula, and respondents were categorized as underweight (<18.5), normal weight (18.5-24.9), overweight (25.0-29.9), or obese (≥30.0).

The MAST Study assessment used validated instruments where available. Migraine-related disability was assessed with the Migraine Disability Assessment (MIDAS) questionnaire, a 5-item scale assessing missed and reduced productivity days at work, school, or home during the previous 3 months due to headache. Missed and reduced productivity days items were summed and grouped to identify disability by 4 grades: little or none (score of 0-5), mild (score of 6-10), moderate (score of 11-20), and severe (score of ≥21).

Headache frequency was measured by MHDs, which were calculated by summing responses about the number of headache days (affected by headache for all or part of the day) over the past 3 months and then dividing the result by 3.

Cutaneous allodynia was identified using the Allodynia Symptom Checklist (ASC-12), a validated 12-item questionnaire.[26] Response options were scored as 0 for never or rarely, 1 for less than half the time, and 2 for half the time or more. Scores range from 0 to 24 with respondents classified in categories; none (0-2), mild (3-5), moderate (6-8), and severe (9 or more). A sum score cut point of at least 3 was used to define the presence of cutaneous allodynia. Respondents with ASC-12 scores below 3 were classified as not having allodynia.

Assessment of medication overuse relied on ICHD-3 beta criteria,[20] and medication overuse was considered present if respondents reported using a triptan, opioid, barbiturate, combination analgesic, or ergot alkaloid on at least 10 days in the past month or a nonsteroidal anti-inflammatory drug or simple analgesic on 15 or more days in the past month. These criteria are conservative in that we could not assess potential overuse if respondents reported the use of multiple classes of medication.

The Migraine Symptom Severity Score (MSSS) is a composite index that incorporates information about the 7 ICHD-3 headache criteria (unilateral pain, pulsatile pain, moderate, or severe pain intensity, routine activities worsen pain, nausea, photophobia, and phonophobia). Respondents were asked to "describe the pain and other symptoms you have with your headaches," and response options included never, less than half the time, half the time or more, or all or nearly all the time. The overall MSSS score ranges from 0 to 21; it was calculated by adding scores ranging from 0 to 3 for each of the 7 headache features assessed. The MSSS was evaluated as a continuous score.

The Patient Reported Outcomes Measurement Information System (PROMIS) pain interference scale includes 6 items assessing pain interference related to bodily pain and headaches.[27,28] Response options for 5 of the items were not at all, a little bit, somewhat, quite a bit, and very much; for the sixth item, response options were never, rarely, sometimes, often, and always. Responses were given a value of 1 to 5, and total scores were computed by summing responses to the 6 items. Total scores were then transformed into T-scores with mean of 50 and standard deviation (SD) of 10. Higher scores indicate greater pain interference, and scores above 50 are worse than the average population.

Pain data were collected using the Total Pain Index (TPI).[29] The validated TPI assessed pain frequency and intensity in 8 specified body regions (ie, head, face, neck or shoulders, back, arms or hands, legs or feet, chest, abdomen, or pelvis) over the preceding 3 months. Pain frequency responses were scored as 0% for none of the time, 10% for a slight bit of time, 35% for some of the time, 75% for most of the time, and 100% for all of the time. The pain frequency percents were then multiplied by 11-point pain intensity ratings (0 = no pain through 10 = worst possible pain imaginable) for each body region. Total Pain Index is sum of location specific pain indexes, which yielded a score from 0 to 80.

Two subscales (depression and anxiety) of the validated 4-item Patient Health Questionnaire (PHQ-4)[30] were used to assess probable depression and/or anxiety separately. Response options for PHQ-4 were not at all (none = 0), several days (mild = 1), more than half the days (moderate = 2), and nearly every day (severe =3). Depression and anxiety subscale sum scores ranging from 0 to 6 were calculated by assigning scores of 0 to 3 to each item. On each subscale, a score of ≥3 was considered positive for screening purposes. These 2 variables were analyzed as dichotomous variables.

Visual aura (past 12 months) was considered present if a respondent (1) reported a full or partial loss of vision and/or seeing stars, lines, flashing lights, zigzag lines, or heat waves; (2) experienced these visual changes at least once in the past 12 months; and (3) had vision changes spread slowly over a period of minutes or come on all at once.

Acute treatment optimization was evaluated with the Migraine Treatment Optimization Questionnaire (mTOQ). Four of the 6 items are used to estimate treatment optimization: functional ability, pain freedom within 2 hours of treatment, sustained relief, and tolerability. Respondent answers of never, rarely, less than half the time, and half the time or more were assigned scores of 0, 0, 1, and 2, respectively. Total scores were calculated by summing responses to the 4 items and based on total score, respondents were classified as having very poor (0), poor (1-5), moderate (6-7), or maximum (8) treatment optimization.[31]

Analysis Sample.—This analysis was implemented among respondents who completed the MAST 6-month follow-up study (N = 7518), requalified to meet ICHD-3 beta migraine criteria, and had qualifying symptom responses indicating frequency of nausea, or photophobia and phonophobia occurring with headaches less than half the time, half the time or more, or all or nearly all the time (n = 6045).

Statistical Analysis.—Percentages were used to describe dichotomous variables (sex, race, presence of allodynia, presence of probable depression and/or anxiety, medication overuse, and aura) and categorical variables (age, household income, BMI, headache disability, MHDs, mTOQ, and headache symptoms). Means (SD) were used to report normally distributed continuous variables (age, BMI) and medians (Q_1, Q_3) were used to summarize variables that were not normally distributed (MSSS, PROMIS pain interference, and TPI). Chi-square tests were used to test differences ($P < .05$) for dichotomous or categorical variables. To evaluate differences ($P < .05$) for normally distributed continuous variables *F*-statistics were used and Mood's median test was used to evaluate differences ($P < .05$) for non-normally distributed continuous variables.

Three binary logistic models were run with each of the 3 candidate MBSs (nausea, photophobia, and phonophobia) as the binary outcome. The objective of this modeling was to identify the respondent characteristics associated with each of the MBSs, after adjusting for significant covariates. Preliminary models were conducted by entering variables in the following blocks: sociodemographics (sex, age, income, race, BMI); headache and respondent characteristics (MIDAS, MHDs, allodynia, medication overuse, MSSS, PROMIS, TPI); psychological symptoms (probable anxiety/depression); aura; and treatment optimization (mTOQ). After each block of variables was entered, noncontributing variables were eliminated. Only variables that were significant in 1 or more of the nested models were included in a final model for each MBS group, where all variables were entered simultaneously.

Odds ratios (OR) and 95% confidence intervals (CI) are provided. *P* values less than .05 were considered statistically significant. Online data collection methods minimized missing data such that imputation was not required. All analyses were performed in IBM SPSS Statistics, version 20.0 (IBM, Armonk, NY; 2011).

RESULTS

Sampling Results and Demographics.—Except where otherwise noted percentages are based on n = 6045 study respondents. Collection of 6-month follow-up data from MAST respondents was undertaken between April and August 2017. All 15,133 MAST baseline respondents were invited to participate in the 6-month follow-up survey; 50% (7518/15,133) completed the survey and provided usable data; and 80.4% (6045/7518) continued to meet migraine symptom criteria and were included in this analysis. The sample was 76.0% (4596/6045) women, with a mean (SD) age of 47 (13.4) years (Table 2).

Frequency and Distribution of Migraine Associated Symptoms and MBS.—Nausea was reported less than half the time or more often with headache by 75.7% (4578/6045) of respondents, photophobia by 92.3% (5582/6045), and phonophobia by 92.5% (5589/6045). In total, 4.3% (262/6045) of the sample endorsed exactly 1 of the 3 cardinal associated symptoms (nausea by definition), 30.8% (1862/6045) endorsed exactly 2 symptoms, and 64.9% (3921/6045) endorsed all 3 symptoms. Just under half of the sample (49.1%, 2967/6045) designated photophobia as their MBS,

28.1% (1697/6045) designated nausea as the MBS, and 22.8% (1381/6045) designated phonophobia as the MBS (Table 1). The group designating photophobia as the MBS had the lowest proportion of women (72.9%, 2164/2967, $\chi^2 = 31.86$, $P < .001$) and they tended to have higher incomes ($\chi^2 = 16.11$, $P = .041$) and be more represented in the overweight and obese BMI categories ($\chi^2 = 24.22$, $P < .001$). There were no statistically significant differences among MBS groups with respect to race (Table 2).

Respondent headache attack characteristics by designated MBS are provided in Table 3. Migraine-related disability was common, with 18% (1087/6045) of respondents reporting mild disability on MIDAS and 26.6% (1606/6045) experiencing severe disability, but differences across MBS groups were not significant. Almost two-thirds of the sample (60.3%, 3644/6045) had a headache frequency of 0 to 4 MHDs over the previous 3 months, and 10.9% (657/6045) reported ≥15 MHDs, indicative of chronic migraine. Overall MHD rates among MBS groups were similar. More than one-third of the sample (36.7%, 2221/6045) had mild, moderate, or severe cutaneous allodynia, and 6.5% (395/6045) had severe cutaneous allodynia. Rates of cutaneous allodynia were comparable among the 3 MBS groups. Medication overuse was common (19.2%, 1119/5814) and similar across the 3 MBS groups ($\chi^2 = 3.03$, $P = .220$). The MSSS for the sample was 18 (Q_1 15, Q_3 19), and those designating phonophobia as the MBS had slightly lower median MSSS scores (17, Q_1 15, Q_3 19) than those in the nausea and photophobia groups, although this small difference may or may not be clinically meaningful (median test $\chi^2 = 19.59$, $P < .001$).

Table 1.—Frequency and Distribution of Associated Symptoms and MBS

	N = 6045 n (%)
Overall symptom reporting	
Nausea	4578 (75.7)
Photophobia	5582 (92.3)
Phonophobia	5589 (92.5)
Number of associated symptoms	
1†	262 (4.3)
2	1862 (30.8)
3	3921 (64.9)
Symptom designated as MBS	
Nausea	1697 (28.1)
Photophobia	2967 (49.1)
Phonophobia	1381 (22.8)

†Having only 1 symptom is only possible if that symptom is nausea because according to ICHD-3 either nausea or photophobia and phonophobia were required to meet the migraine case definition.
MBS = most bothersome symptom.

The median PROMIS pain interference score for the sample was 59.1 (Q_1 55, Q_3 63.6), and a statistically significant difference among MBS groups was observed (nausea 59.1, photophobia 58.1, phonophobia 59.1; median test $\chi^2 = 8.28$, $P = .016$). The overall sample had a median noncephalic pain rating (TPI) of 8.7 (Q_1 4.3, Q_3 15.9), and median scores were similar across the 3 MBS groups (median test $\chi^2 = 2.62$, $P = .270$). About one-quarter of respondents (27.0%, 1633/6045) had probable anxiety, and the highest rates of anxiety were reported by respondents designating phonophobia as the MBS (29.3%, 405/1381), though this did not reach statistical significance ($\chi^2 = 5.94$, $P = .051$). A total of 20% (1209/6045) of respondents had probable depression, but rates did not differ across MBS groups ($\chi^2 = 2.86$, $P = .240$). About 23% (1379/6045) of the sample had aura, and the rate of aura was highest in the photophobia group (25.5%, 757/2967), followed by nausea (20.6%, 349/1697) and phonophobia (19.8%, 273/1381) ($\chi^2 = 24.43$, $P < .001$). Treatment optimization was poor or very poor in about 35% (2049/5814) of the sample, and there was less treatment optimization in the nausea MBS group ($\chi^2 = 16.63$, $P = .011$).

Binary Logistic Models.—Logistic modeling results for each of the 3 cardinal symptoms are provided in Table 4. Initial models included all covariates, but the following variables were eliminated from the final model estimates because they did not significantly contribute to predicting the presence of the selected MBS: MIDAS, MHD frequency, medication overuse, MSSS, PROMIS Pain Interference, TPI, PHQ-2 anxiety, and PHQ-2 depression. Age and sex were retained in all the models. The nausea MBS model found that men were less likely than women to designate nausea as their MBS (OR .77, 95% CI .66, .89). No age or race effects were seen. Compared with the reference group earning less than $25,000 per year, those in the $25,000

Table 2.—Respondent Sociodemographic Characteristics by Most Bothersome Symptom

	Most Bothersome Symptom					
	Nausea	Photophobia	Phonophobia	Total	χ^2/F	*P* Value
Total sample, n (%)	1697 (28.1)	2967 (49.1)	1381 (22.8)	6045 (100)		
Sex, n (%)						
Men	343 (20.2)	803 (27.1)	303 (21.9)	1449 (24.0)	31.86	<.001
Women	1354 (79.8)	2164 (72.9)	1078 (78.1)	4596 (76.0)		
Age, mean (SD), years	46 (13.3)	47 (13.6)	47 (13.1)	47 (13.4)	5.35	.005
Age group, years, n (%)						
18-24	63 (3.7)	97 (3.3)	47 (3.4)	207 (3.4)	16.95	.075
25-34	333 (19.6)	549 (18.5)	232 (16.8)	1114 (18.4)		
35-44	417 (24.6)	651 (21.9)	350 (25.3)	1418 (23.5)		
45-54	422 (24.9)	752 (25.3)	364 (26.4)	1538 (25.4)		
55-64	287 (16.9)	570 (19.2)	233 (16.9)	1090 (18.0)		
≥65	175 (10.3)	348 (11.7)	155 (11.2)	678 (11.2)		
Annual household income†, n (%)						
<$25,000	232 (14.0)	322 (11.1)	161 (11.9)	715 (12.1)	16.11	.041
$25,000-$49,999	336 (20.3)	603 (20.9)	281 (20.7)	1220 (20.7)		
$50,000-$74,999	382 (23.1)	621 (21.5)	317 (23.3)	1320 (22.4)		
$75,000-$99,999	262 (15.9)	552 (19.1)	240 (17.7)	1054 (17.9)		
>$100,000	440 (26.6)	790 (27.4)	359 (26.4)	1589 (26.9)		
Race‡, n (%)						
Not white	273 (16.2)	424 (14.4)	217 (15.8)	914 (15.2)	3.21	.201
White	1415 (83.8)	2529 (85.6)	1159 (84.2)	5103 (84.8)		
BMI, kg/m^2, mean (SD)	27.7 (7.1)	28.6 (7.5)	28.4 (7.7)	28.3 (7.5)	8.48	<.001
BMI category, n (%)						
Underweight	61 (3.6)	60 (2.0)	32 (2.3)	153 (2.5)	24.22	<.001
Normal	655 (38.6)	1008 (34.0)	487 (35.3)	2150 (35.6)		
Overweight	463 (27.3)	902 (30.4)	411 (29.8)	1776 (29.4)		
Obese	518 (30.5)	997 (33.6)	451 (32.7)	1966 (32.5)		

†Among n = 5898 respondents with household income data.
‡Among n = 6017 respondents with race data.
BMI = body mass index.

to $49,000 (OR .79, 95% CI .64, .97) and $75,000 to $99,000 (OR .70, 95% CI .56, .87) income groups were less likely to designate nausea as their MBS. Compared with respondents in the normal BMI group, those in the underweight group were 46% more likely to designate nausea as the MBS (OR 1.46, 95% CI 1.02, 2.08), and those in the overweight (17%) and obese (20%) groups were less likely to designate nausea as MBS (OR .83, 95% CI .71, .96) and (OR .80, 95% CI .70, .93), respectively. The presence of aura was associated with a 19% decrease in the likelihood of designating nausea as the MBS (OR .81, 95% CI .71, .94). Relative to individuals with maximum treatment optimization, the reference group, the odds of designating nausea as the MBS were elevated as treatment optimization decreased (moderate OR 1.20, 95% CI 1.03, 1.40; poor OR 1.22, 95% CI 1.06, 1.41; very poor OR 1.49, 95% CI 1.11, 1.99).

In the model for photophobia, men were 32% more likely than women to designate photophobia as their MBS (OR 1.32, 95% CI 1.16, 1.50). No age or race effects were observed. The odds of designating photophobia as the MBS were higher as income increased but this was only significant in the $75,000 to $99,000 group (OR 1.31, 95% CI 1.07, 1.60). For BMI, compared with persons in the normal range, only obese respondents were significantly more likely to designate photophobia as the MBS (OR 1.18, 95% CI 1.04, 1.35). Aura was associated with a 40% increase in designating photophobia as MBS (OR 1.40, 95% CI 1.24, 1.59). For treatment optimization, relative to individuals with

Table 3.—Migraine-Related Disability, Headache Frequency, Cutaneous Allodynia, Medication Overuse, Aura, Acute Treatment Optimization, and Psychiatric Comorbidity by Most Bothersome Symptom

	Most Bothersome Symptom					
	Nausea	Photophobia	Phonophobia	Total	χ^2	*P* Value
Total sample, n (%)	1697 (28.1)	2967 (49.1)	1381 (22.8)	6045 (100.0)		
Migraine-related disability,[a] n (%)						
Little or no	635 (37.4)	1136 (38.3)	481 (34.8)	2252 (37.3)	9.05	.171
Mild	304 (17.9)	513 (17.3)	270 (19.6)	1087 (18.0)		
Moderate	301 (17.7)	557 (18.8)	242 (17.5)	1100 (18.2)		
Severe	457 (26.9)	761 (25.6)	388 (28.1)	1606 (26.6)		
Headache frequency,[b] days per month, n (%)						
0-4	1015 (59.8)	1822 (61.4)	807 (58.4)	3644 (60.3)	9.85	.131
5-9	352 (20.7)	574 (19.3)	291 (21.1)	1217 (20.1)		
10-14	161 (9.5)	255 (8.6)	111 (8.0)	527 (8.7)		
≥15	169 (10.0)	316 (10.7)	172 (12.5)	657 (10.9)		
Cutaneous allodynia,[c] n (%)						
None	1094 (64.5)	1899 (64)	831 (60.2)	3824 (63.3)	10.30	.113
Mild	324 (19.1)	580 (19.5)	317 (23.0)	1221 (20.2)		
Moderate	174 (10.3)	293 (9.9)	138 (10.0)	605 (10.0)		
Severe	105 (6.2)	195 (6.6)	95 (6.9)	395 (6.5)		
Medication overuse,[d] yes, n (%)	315 (19.3)	527 (18.5)	277 (20.8)	1119 (19.2)	3.03	.220
Migraine symptom severity,[e] median (Q_1,Q_3)	18 (15,20)	18 (16,19)	17 (15,19)	18 (15,19)	19.59[f]	<.001
Pain interference,[g] median (Q_1,Q_3) 0-100	59.1 (53.8, 63.6)	58.1 (53.8, 63.6)	59.1 (55, 63.6)	59.1 (55,63.6)	8.28[f]	.016
Total pain,[h] median (Q_1,Q_3)	8.8 (4.2, 16.2)	8.45 (4.1, 15.3)	9.1 (4.9, 16.6)	8.7 (4.3, 15.9)	2.62[f]	.270
Anxiety,[i] n (%)	462 (27.2)	766 (25.8)	405 (29.3)	1633 (27.0)	5.94	.051
Depression,[i] n (%)	342 (20.2)	571 (19.2)	296 (21.4)	1209 (20.0)	2.86	.240
Past year visual aura, n (%)						
Absent	1348 (79.4)	2210 (74.5)	1108 (80.2)	4666 (77.2)	24.43	<.001
Present	349 (20.6)	757 (25.5)	273 (19.8)	1379 (22.8)		
Acute treatment optimization,[j] n (%)						
Very poor	85 (5.2)	97 (3.4)	62 (4.6)	244 (4.2)	16.63	.011
Poor	526 (32.3)	885 (31.1)	394 (29.5)	1805 (31.0)		
Moderate	409 (25.1)	680 (23.9)	322 (24.1)	1411 (24.3)		
Maximum	610 (37.4)	1188 (41.7)	556 (41.7)	2354 (40.5)		

[a]Based on MIDAS, sum of missed and reduced productivity days, categories: little or no (0-5), mild (6-10), moderate (11-20), and severe (≥21) disability.
[b]Monthly headache days over the past 90 days, divided by 3.
[c]Responses to 12 ASC questions scored as 0 (never or rarely), 1 (less than half the time), and 2 (half the time or more), and summed (range 0-24), categories: none (0-2), mild (3-5), moderate (6-8), and severe (9 or more).
[d]Among n=5814 respondents with medication overuse data.
[e]Based on MSSS of 7 items, range 0 to 21.
[f]Median test chi-square test statistic.
[g]Based on PROMIS pain interference scale, extent to which pain hinders engagement with social, cognitive, emotional, physical, and recreational activities, as well as sleep and enjoyment in life.
[h]Based on TPI, pain frequency and intensity in the head, face, neck/shoulder, back, arm/hand, legs/feet, and chest abdomen/pelvis.
[i]Based on PHQ-4, Depression and anxiety subscale sum scores (range 0-6), ≥3 considered positive for screening purposes.
[j]Based on mTOQ, responses to 4 questions scored as 0 (never or rarely), 1 (less than half the time), and 2 (half the time or more) and summed (range 0-8), categories: very poor (0), poor (1-5), moderate (6-7), or maximum (8) treatment optimization. Among n = 5814 respondents with mTOQ data.

Table 4.—Logistic Models Predicting Nausea, Photophobia and Phonophobia as the Most Bothersome Symptom Using Demographic and Headache Characteristics as Predictors (N = 6045)

	Nausea		Photophobia		Phonophobia	
	1697 (28.1)		2967 (49.1)		1381 (22.8)	
Total Sample, n (%)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)
Men†	<.001	.77 (.66, .89)	<.001	1.32 (1.16, 1.50)	.182	.90 (.77, 1.05)
Age,‡ years						
25-34	.584	1.10 (.77, 1.57)	.959	.99 (.72, 1.37)	.589	.90 (.61, 1.33)
35-44	.659	1.08 (.76, 1.54)	.255	.83 (.6, 1.15)	.394	1.18 (.80, 1.73)
45-54	.846	1.04 (.73, 1.47)	.501	.90 (.65, 1.24)	.568	1.12 (.76, 1.64)
55-64	.813	1.04 (.73, 1.50)	.967	1.01 (.72, 1.40)	.748	.94 (.63, 1.39)
≥65	.944	.99 (.68, 1.44)	.942	.99 (.70, 1.39)	.898	1.03 (.68, 1.55)
Annual household income§						
$25,000-$49,999	.026	.79 (.64, 97)	.089	1.18 (.97, 1.43)	.695	1.05 (.83, 1.32)
$50,000-$74,999	.159	.86 (.70, 1.06)	.601	1.05 (.87, 1.27)	.365	1.11 (.89, 1.39)
$75,000-$99,999	.001	.70 (.56, 87)	.008	1.31 (1.07, 1.6)	.784	1.03 (.82, 1.31)
>$100,000	.055	.82 (.67, 1.00)	.107	1.17 (.97, 1.41)	.870	1.02 (.82, 1.27)
Not white¶	.381	1.08 (.91, 1.27)	.192	.91 (.78, 1.05)	.550	1.05 (.89, 1.25)
BMI category††						
Underweight	.040	1.46 (1.02, 2.08)	.191	.79 (.55, 1.13)	.461	.85 (.55, 1.31)
Overweight	.012	.83 (.71, 96)	.113	1.11 (.97, 1.27)	.410	1.07 (.91, 1.25)
Obese	.003	.80 (.70, 93)	.012	1.18 (1.04, 1.35)	.859	1.01 (.87, 1.18)
Cutaneous allodynia‡‡	.066	.89 (.78, 1.01)	.311	.94 (.84, 1.06)	.002	1.24 (1.08, 1.41)
Past year visual aura§§	.005	.81 (.71, 94)	<.001	1.4 (1.24, 1.59)	.001	.78 (.67, 91)
Acute treatment optimization¶¶						
Moderate	.017	1.20 (1.03, 1.40)	.174	.91 (.79, 1.04)	.362	.93 (.79, 1.09)
Poor	.006	1.22 (1.06, 1.41)	.382	.94 (.83, 1.07)	.061	.86 (.74, 1.01)
Very poor	.007	1.49 (1.11, 1.99)	.010	.69 (.52, 92)	.850	1.03 (.75, 1.41)

†Women reference group.
‡18 to 24 years reference group.
§<$25,000 reference group.
¶White reference group.
††Normal reference group.
‡‡Allodynia present (mild, moderate, or severe); none reference group.
§§<2 times past year reference group.
¶¶Maximum treatment optimization reference group.
Several covariates that were included in initial models did not significantly contribute and were trimmed from final models: MIDAS, MHDs, medication overuse, MSSS, PROMIS pain interference, TPI, PHQ-2 anxiety, PHQ-2 depression.
BMI = body mass index.

maximum treatment optimization, those in the very poor category were 31% less likely to designate photophobia as the MBS (OR .69, 95% CI .52, .92); the ORs for the other categories were nonsignificant (Table 4).

In the model for phonophobia as the MBS, sex, age, household income, race, BMI, and treatment optimization were not significant predictors. The presence of cutaneous allodynia was associated with a 24% increase in the likelihood of designating phonophobia as the MBS (OR 1.24, 95% CI 1.08, 1.41), and the presence of aura was associated with a 22% decrease in the likelihood of designating phonophobia as the MBS (OR .78, 95% CI .67, .91) (Table 4).

DISCUSSION

This study was conducted to determine the relative rates of reporting nausea, photophobia, and phonophobia overall and in identifying a single MBS in a

representative US sample of persons with migraine, as well as to identify the sociodemographic characteristics and headache features associated with designating these cardinal symptoms as the MBS. Among respondents with migraine in the MAST sample, almost two-thirds (64.9%, 3921/6045) reported all 3 associated symptoms, 30.8% (1862/6045) experienced 2 cardinal symptoms, and 4.3% (262/6045) experienced nausea as the sole cardinal symptom. The most commonly designated most bothersome symptom was photophobia (49.1%, 2967/6045), followed by nausea (28.1%, 1697/6045) and phonophobia (22.8%, 1381/6045). This result differs somewhat from other observational research,[32] where nausea (plus vomiting in the same response option) was selected as "... the MBS during a migraine attack" by 39.5% of men and 48.4% of women. Vomiting is less common than nausea but may be debilitating. We hypothesize that combining nausea and vomiting in the same response option may have inflated reporting of nausea symptom bothersomeness in this earlier work.

Findings from the current study align with results of clinical trials using MBS as a coprimary efficacy endpoint. In many trials, the most common MBS was photophobia, occurring in roughly half of respondents.[5-17] It should be noted that clinical trials have taken 2 approaches to determining MBS; some determine MBS during a clinic visit,[6,14,15] while others determine MBS immediately prior to taking study medication.[7,9,10,12,13,16] The MAST survey used a recall-based question about MBS with headache attacks over the last 3 months. When study respondents report their MBS prior to treatment, several factors may influence their response. These include which symptoms are present at the time of reporting, symptom severity at the time of reporting, trait variability or vulnerability to a particular symptom, and environmental factors that might make a symptom more bothersome. For example, nausea might be particularly bothersome to someone who is at a dinner party, while photophobia could be especially bothersome for someone working in a brightly lit office, and phonophobia could be particularly bothersome for someone on a noisy subway. Alignment on the relative frequency of the candidate MBS suggests that lessons from trials and surveys may be mutually reinforcing.

In the univariate analysis, there were several differences in unadjusted sociodemographics and respondent attack characteristics seen across MBS groups. Differences were seen in sex, mean age, household income, mean BMI, BMI category, symptom severity, pain interference, visual aura, and treatment optimization. No differences were observed for race, disability category, MHD frequency category, cutaneous allodynia, rates of medication overuse, and noncephalic pain.

Based on the individual logistic models predicting each cardinal symptom as MBS, there were fewer significant variables. In the model for nausea as MBS, compared with those designating either photophobia or phonophobia as MBS, respondents were more likely to be women, to have lower incomes, and to report lower levels of treatment optimization. Whether people with migraine and prominent nausea are less likely to have their treatment optimized because they are difficult to treat, or whether nausea is most likely to be designated the MBS when treatment is suboptimal, cannot be determined from these data. If nausea becomes the MBS due to suboptimal treatment effects, then treatment options that bypass the gastrointestinal tract (injections or nasal sprays, for example) or the addition of an antiemetic to the acute treatment may prove beneficial. While the burden of persistent frequent nausea with migraine has been studied,[33] less is known about the biological origins of this symptom among those who report nausea as the MBS.

Of the 1381 respondents who designated phonophobia as the MBS, the modeling found a 24% increase in the presence of cutaneous allodynia and a 22% decrease in the likelihood of visual aura. Phonophobia may be mediated by connections between the auditory pathways, auditory thalamus, and sensory cortex, but these pathways are not well characterized.

Respondents designating photophobia as the MBS (N = 2967) were more likely to be men, more likely to be obese, and 40% more likely to have visual aura associated with their attacks. Our results suggest that aura is associated with photophobia, a form of visual hypersensitivity. Neuroimaging studies demonstrate that in comparison to patients with migraine without aura those with aura have increased interictal stimulus–induced activation of the visual

cortex and increased visual network connectivity.[34-36] Previous studies assessing photosensitivity symptoms in migraine with and without aura have generated conflicting results; most do not demonstrate between-group differences.[17,37-39] There may be visual processing differences among individuals with and without visual aura.[40] Previous research has suggested neurophysiological links between visual disturbances and visual migraine symptoms, such as photophobia.[17] The exacerbation of headache by light affects about 90% of people with migraine who have normal eyesight.[41-43] Blind patients with retinal degenerative diseases (ie, retinitis pigmentosa) experience photophobia. Noseda and Burstein have proposed that these findings, together with those from animal studies, indicate that photophobia may arise from the convergence of photic signals from retinal ganglion cells and trigeminovascular neurons on cells in the posterior thalamus.[44,45] The visual cortex appears to be hyperexcitable in people with migraine even in the prodromal phase and may be the neural substrate of abnormal processing of light sensitivity.[46,47] Some studies have suggested that visual cortex hyperexcitability is greater in migraine with aura than migraine without aura.[17,36,37] This could provide a link between the visual cortex hyperexcitability, symptoms of photophobia, and the propensity to develop cortical spreading depression and aura.[45]

The strengths of this study include the large representative nature of the sample, which matches US Census for the total screened sample and previous AMPP Study data for the migraine sample. Modified ICHD-3 beta symptom criteria were used to identify persons with migraine using a validated diagnostic screener, and missing data are limited due to the online data collection methods. The assessment also included validated tools and scales where possible. Limitations include the low response rate typical of online data collection (adjusted for in part by matching to Census) and reliance of retrospective self-report of symptoms and medication usage, which may be subject to recall bias. In addition, the case definition of migraine results in the inclusion and exclusion of specific associated symptom profiles. Eligible respondents had to have either nausea or both photophobia and phonophobia to be included in the study. Question wording for designating the MBS also differed somewhat from that used in clinical trials. While each respondent meets symptom criteria for migraine, we cannot confirm all reported MHDs were migraine headache days. We also do not know if the choice of MBS is a stable within-person characteristic or varies across attacks. Rates of medication overuse may be conservative due to overlapping days of medication use that could not be detected with the survey methodology. It should also be noted that these are not independent analyses; based on ICHD symptom criteria, if a respondent did not report nausea, then they had to report both photophobia and phonophobia to be included in the migraine cohort.

CONCLUSIONS

Among MAST Study respondents, 95.7% had at least 2 cardinal associated symptoms, and most (64.9%) reported all 3 cardinal migraine-associated symptoms. As in clinical trials, the most frequent MBS was photophobia, followed by nausea and phonophobia. There were striking differences in MBS reporting related to demographics, migraine features, and treatment features. Nausea as the MBS was more common in women and among respondents with lower incomes and less optimal acute treatment optimization. Photophobia as the MBS was more common in men, obese respondents, and those reporting visual aura. Phonophobia as the MBS was associated with allodynia and lower rates of visual aura. These results may inform clinical trial design and may also help clinicians identify and treat the symptoms considered most bothersome in their patients with migraine.

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