Received: 26 January 2024 | Accepted: 19 June 2024

DOI: 10.1111/head.14817

RESEARCH SUBMISSION

Symptoms across the phases of the migraine cycle from the patient's perspective: Results of the MiCOAS qualitative study

James S. McGinley PhD[1] | Rikki Mangrum MLS[1] | Maya T. Gerstein DrPH[2] | Kelly P. McCarrier PhD[2] | Carrie R. Houts PhD[1] | Dawn C. Buse PhD[1,3] | Alexandra L. Bryant BS[1] | R. J. Wirth PhD[1] | Richard B. Lipton MD[3]

[1]Vector Psychometric Group, LLC, Chapel Hill, North Carolina, USA

[2]Patient Centered Outcomes, Open Health Group, Bethesda, Maryland, USA

[3]Neurology, Albert Einstein College of Medicine, Bronx, New York, USA

Correspondence
James S. McGinley, Vector Psychometric Group, LLC, 847 Emily Lane, Chapel Hill, NC 27516, USA.
Email: jim.mcginley@vpgcentral.com

Funding information
U.S. Department of Health and Human Services (HHS), Grant/Award Number: UH3FD006795

Abstract

Objective: To better understand the breadth and frequency of symptoms across the phases of the migraine cycle using data captured from qualitative patient interviews conducted through the Migraine Clinical Outcome Assessment System (MiCOAS) project.

Background: People living with migraine experience a range of symptoms across the pre-headache, headache, post-headache, and interictal phases of the migraine cycle. Although clinical diagnostic criteria and clinical trial endpoints focus largely on cardinal symptoms or monthly migraine days, migraine symptom profiles are far more complex. As a part of the MiCOAS project, semi-structured qualitative interviews were undertaken to better understand the migraine-related symptomology from the patient's viewpoint.

Methods: This concept elicitation study used iterative purposeful sampling to select 40 people with self-reported medical diagnosis of migraine for interviews that were conducted via audio-only web conferencing. Key topics related to migraine symptoms, including mood/emotion symptoms, were identified using content analysis. Interview transcripts were also coded to reflect the phase of migraine under discussion, so that patient experiences could be compared by phase.

Results: Forty participants (50%, $n=20$ episodic migraine; 50%, $n=20$ chronic migraine), aged from 21 to 70 years old reported a total of 60 unique symptoms, which were categorized into 30 broader symptom categories. Participants reported between 7 and 22 unique symptom categories across all phases. During pre-headache and headache, participants reported a median of 7.5 (interquartile range [IQR] = 5.5) and 8 (IQR = 4.0) different symptom categories compared to 4 (IQR = 3.0) and 1.5 (IQR = 2.5) for the post-headache and interictal periods, respectively. Head pain during the headache phase was the only universally reported symptom (100%, $n=40$). Pooling across all phases, the next most reported symptoms were light sensitivity

Abbreviations: CAS, cranial autonomic symptoms; CHAMP, Coalition for Headache and Migraine Patients; FDA, US Food and Drug Administration; IQR, interquartile range; MiCOAS, Migraine Clinical Outcome Assessment System; SD, standard deviation.

(93%, $n=37$), nausea (88%, $n=35$), irritability/impatience (83%, $n=24$), sound sensitivity (80%, $n=32$), and fatigue/exhaustion (80%, $n=32$). One or more interictal symptoms were reported by 73% ($n=29$) of participants and included mood/emotion symptoms, such as anxiety (30%, $n=12$), depression (18%, $n=7$), and anger (15%, $n=6$), as well as cardinal symptoms, such as light sensitivity (13%, $n=5$) and nausea (13%, $n=5$).

Conclusions: Patients experience a range of symptoms across the phases of the migraine cycle. Results often aligned with clinical expectations, but non-cardinal migraine-related symptoms were reported both inside and outside the headache phase, including between attacks. These discoveries highlight the importance of assessing a range of symptoms and timing when developing patient-reported outcome measures for migraine clinical trials.

Plain Language Summary

The Migraine Clinical Outcome Assessment System (MiCOAS) project aims to improve and standardize endpoints and the assessment of those endpoints in migraine clinical trials. As a part of MiCOAS, we conducted qualitative interviews to better understand which concepts matter most to patients with migraine. Our findings demonstrate the importance of assessing a range of symptoms across migraine phases (e.g., nausea, light sensitivity), and these symptoms should be considered when developing patient-reported outcome measures, and related endpoints, for migraine clinical trials.

KEYWORDS
migraine, qualitative research, quality of life, symptoms

BACKGROUND

Migraine is a chronic disease with episodic attacks that can be highly disabling, burdensome, and costly from both personal and economic perspectives.[1–6] Though it is one of the world's most common disorders, the diversity of migraine symptoms across individuals is still underrecognized, as evidenced by its underdiagnosis and misdiagnosis.[7,8] Migraine is largely defined by select cardinal symptoms (head pain, aura, light sensitivity, sound sensitivity, nausea/vomiting) and is characterized by multiple phases, including premonitory/pre-headache (time preceding head pain), headache (time of head pain), postdrome/post-headache (time after head pain), and interictal (time between attacks).[9,10]

The premonitory (or pre-headache) phase occurs hours to days before head pain, and a broad array of symptoms has been reported within neuropsychiatric, sensory, and gastrointestinal categories.[11,12] The headache phase can last between 4 and 72 h and has a defining characteristic of mild-to-severe head pain. The International Classification of Headache Disorders, 3rd edition further specifies that, to meet diagnostic criteria for migraine, each attack must include a combination of pain characteristics (unilateral location, pulsating quality, moderate to severe pain intensity, aggravation by routine physical activity) and specific associated symptoms (nausea and/or vomiting, light sensitivity, and sound sensitivity).[13] The postdrome (or post-headache) phase can last hours to days and characterizes the "hangover," or let down, period after the headache phase.[9]

In a large international survey, pre-headache symptoms were reported by 67%, while post-headache symptoms were reported by 60% of people with migraine.[14] Pre-headache and post-headache symptoms were common and disabling. Moderate-to-severe activity limitations occurred during the pre-headache and post-headache phases. Previously reported postdrome phase symptoms include cognitive difficulties, mood changes, gastrointestinal issues, and tiredness/weakness.[15,16] There is also growing interest in the interictal phase, or the period between migraine attacks. Although less well studied, an array of symptoms such as light sensitivity, sound sensitivity, allodynia, anxiety, and avoidance have been documented in this phase.[17–20]

Migraine treatment research focuses on a small number of outcomes and endpoints that were established with limited patient input and support. Preventive migraine clinical trials rely largely on changes in monthly migraine (or headache) days but ignore the potential impacts of symptoms persisting or arising in the interictal period between migraine (or headache) days.[21] Acute migraine clinical trials focus on the absence, or resolution, of pain (i.e., pain freedom or pain relief) along with the absence of most bothersome symptom (typically selected from light sensitivity, sound sensitivity, nausea/vomiting).[22] While these outcomes and endpoints provide valuable information for understanding the benefits of treatment, it

is possible that other outcomes that matter to people with migraine have been omitted from the clinical trial process. Consequently, it is essential to learn about patients' unique migraine symptom experiences.

The Migraine Clinical Outcome Assessment System (MiCOAS) is a multi-stage US Food and Drug Administration (FDA)-funded project focused on integrating the patient voice into the development of patient-reported outcome measures for use in clinical trials. The initial stage of the MiCOAS project involved gathering input from people living with migraine via qualitative interviews about their experiences and values. This article presents the results of the reporting and timing of migraine symptoms across all phases of the migraine attack and excludes study data on cognitive symptoms, COVID-19 impacts, and treatment priorities, which have been previously published.[23–25]

METHODS

Participants

Participants were recruited through the Coalition for Headache and Migraine Patients (CHAMP, https://headachemigraine.org/). CHAMP used its social media and partner platform communications to promote the study and invite potential participants. The study announcement directed interested people to a study-specific website where they could learn more about the planned research, fill out an online screening form, give their informed consent to participate (e.g., electronic informed consent), and provide other relevant information (e.g., sociodemographic information and headache history).

Eligible participants had to be US citizens with a self-reported medical diagnosis of migraine, screen positive for migraine with the ID-migraine screener,[26] be between the ages of 18 and 75 years old, be able to complete an interview in English, and agree to take part in a 90-minute recorded interview. The following were exclusion criteria: (1) self-report of a medical diagnosis of epilepsy, multiple sclerosis, schizophrenia, bipolar disorder, cognitive impairment, Alzheimer's disease, or another form of dementia; (2) screening positive for substance use over the preceding 3 months using the CAGE questionnaire[27]; or (3) self-report of a previous or current diagnosis, symptoms, or hospitalization related to COVID-19 infection at the time of screening.

Initially, 428 individuals screened eligible to take part in the study. Participants were selected using iterative purposive sampling aimed at achieving equal representation of episodic migraine and chronic migraine and diverse representation of characteristics such as gender, race, or ethnicity. Participants were enrolled in waves of 4 to 6 interviews and interview results were monitored for achievement of data saturation. Demographic characteristics from completed waves of interviews were used to determine priority characteristics for subsequent waves to ensure diversity in the participant sample. This study was reviewed and approved by the WCG Institutional Review Board.

Data collection and coding

In this concept elicitation study, 40 semi-structured qualitative interviews were conducted by trained interviewers. Broadly, concept elicitation refers to qualitative studies specifically designed to identify patient-reported outcomes, conducted as part of the development or evaluation of patient-reported outcome measures or clinical outcome assessments.[28] These studies do not have to consider meaningfulness or importance, but often do. Interviewers followed a semi-structured guide and used specific methods intended to elicit responses, such as open-ended exploratory questions followed by structured probes, a reconstruction of a migraine attack, and a visual ranking exercise. Interviews were conducted between July and November 2020. Each interview was conducted by audio-only web conferencing. With participant permission, interviews were audio-recorded and transcribed verbatim. Deidentified transcripts were then prepared for analysis (identifiers redacted from transcripts).

During interviews, participants were asked to describe a typical migraine attack and to describe the symptoms they experience in their "normal" pre-headache, headache, post-headache, and interictal phases. For the purposes of the interviews, these terms were defined as: (1) pre-headache: "the period of time between when your migraine attack begins up until the onset of your headache pain," (2) headache: "the period of time during your migraine attack when you experience headache pain," (3) post-headache: "the period immediately after your headache pain subsides," and (4) interictal: "the time period in between your migraine attacks." It is important to note that symptoms/concepts/terms were based on what participants said, which did not necessarily align with formal clinical/diagnostic definitions.

Using a hybrid deductive/inductive technique, all transcripts were coded using both an initial codebook created a priori, based on review of patient-centered migraine literature and expert clinical opinion, and open codes established iteratively at each interview wave to represent the verbatim responses of participants. Atlas.ti (v8.0) software was used to manage and code all interview data. Ten percent of the interview transcripts ($n=4$) were independently coded by two coders to test the consistency of the coding. Using the inter-rater agreement feature of Atlas.ti, the research team then compared passages of coded text. For codes with >80% agreement between the two coders regarding code attribution (i.e., which codes to ascribe to which text passages), flagged differences were examined and resolved by research team consensus. All coded passages were also reviewed by a senior member of the research team with significant experience in coding and analysis of qualitative data.

Data synthesis and analysis

Concept frequency counts based on content analysis were tabulated, and thematic analysis was used to identify patterns in the data. In the full MiCOAS qualitative study, the coded information was ultimately categorized into several domains (symptomology [cardinal/non-cardinal migraine symptoms], mood/emotions, cognition, daily

living, physical limitations, treatment priorities, migraine tracking, and COVID-19 impacts). Saturation was achieved across all domains based on constructed saturation grids. The current article focuses only on migraine-related symptomology (cardinal and non-cardinal symptoms), as well as mood/emotion symptoms reported by participants. The mood/emotion category includes symptoms generally related to either mood or emotions. Given the objectives of the current study, there was no attempt to distinguish these symptoms further. Results from other related MiCOAS qualitative work focused on domains of cognitive symptoms, COVID-19 impacts, and treatment priorities has been previously published.[23–25]

Participants reported a total of 60 unique symptoms, which were further categorized into 30 broad symptom categories by subject matter and qualitative experts (authors J.S.M., R.M., R.B.L., D.C.B.) to further synthesize the data to improve the presentation of the results. Table S1 in supporting information provides a complete list of the 60 symptoms and how they were condensed into the 30 broad categories.

Descriptive statistics, such as means, standard deviations (SDs), medians, interquartile range (IQR), and response frequency distributions (*n*, %) were calculated for demographic and symptom variables across the migraine phases using SAS 9.4. Pooled summary statistics (*n*, %) reflect the number and percent of participants reporting a given symptom in at least one migraine phase (i.e., pre-headache, headache, post-headache, interictal). The pooled *n* does not have to equal the sum of the phase-specific *n* because participants could endorse symptoms at multiple phases. Direct quotes from participants were extracted to illustrate the findings. All descriptive analyses in the current article focused on the 30 broad symptom categories, but the results for the complete list of 60 symptoms are available in Table S2 in supporting information. There were no missing data in the current study.

RESULTS

Sample characteristics

Participant demographic and clinical characteristics are summarized in Table 1. Participants were equally split between episodic and chronic migraine (50%, $n=20$ for each). The average age of participants was 44 years old (ranging from 21 to 70 years old), with 78% ($n=31$) being women, 68% ($n=27$) being White, and 23% ($n=9$) being Black or African American. About half of the participants had a college degree (48%, $n=19$), and more than half were employed (paid, part or full time; 55%, $n=22$). All participants (100%, $n=40$) reported using acute treatment(s), and 88% ($n=35$) used preventive treatment in the past year.

Symptoms overview

Pooling over all migraine phases, participants reported between 7 (minimum) and 22 (maximum) of the 30 possible symptom categories during any point of the migraine cycle (mean [SD] = 14.0

TABLE 1 Sample characteristics ($N=40$).

	n	%
Sociodemographic characteristics		
Age		
18–24 years old	5	13
25–44 years old	17	43
45–64 years old	13	33
65 years and older	5	13
Gender		
Women	31	78
Men	7	18
Genderqueer, non-binary, transgender	2	5
Race[a]		
White	27	68
Black or African American	9	23
American Indian or Alaskan Native	4	10
Asian	3	8
Native Hawaiian or other Pacific Islander	1	3
Other	1	3
Prefer not to answer	1	3
Ethnicity		
Hispanic	9	23
Non-Hispanic	31	78
Relationship status		
Married or partnered	19	48
Not married or partnered	21	53
Education		
Grade 12 or GED equivalent	3	8
Associates/technical/trade, some college	18	45
College degree or advanced degree	19	48
Employment[a]		
Paid employment	22	55
Student	8	20
Homemaker	3	8
Retired	6	15
Unemployed	2	5
Disabled	10	25
Other	1	3
Household income		
Under $22,000	8	20
$22,000 to $49,999	10	25
$50,000 to $99,999	10	25
$100,000 and over	8	20
Prefer not to answer	4	10
Migraine-related characteristics		
Migraine subtype[b]		
Episodic migraine (<15 headache days per month on average)	20	50

TABLE 1 (Continued)

	n	%
Chronic migraine (≥15 headache days per month on average)	20	50
Migraine with aura		
Yes	14	35
No	26	65
Average headache days per month		
0–1	0	0
2–3	6	15
4–7	8	20
8–14	6	15
15–23	18	45
24 or more	2	5
OTC or prescription acute treatment use (past year)		
Yes	40	100
No	0	0
OTC or prescription preventive treatment use (past year)		
Yes	35	88
No	5	13

Abbreviations: %, percent; Aura, use of the term "aura" or reporting aura symptoms; GED, general education diploma; *n*, number endorsed; OTC, over the counter.

[a]The total sample size for Race and Employment adds up to >40 because participants could select more than one response option.

[b]Chronic migraine was defined as an average monthly headache day frequency of ≥ 15 per month among people who meet criteria for migraine as per Silberstein–Lipton criteria and episodic migraine was the complement. It was not possible to assess the International Classification of Headache Disorders, 3rd edition criteria.

[3.8], median [IQR] = 13.5 [6.0]; Figure 1). Table 2 shows that six symptoms (head pain, light sensitivity, nausea, irritability/impatience, sound sensitivity, and fatigue) were reported by ≥ 80% of participants and seven symptoms were reported by 50% to 79% of participants (depression, anxiety, relief, changes in appetite, visual changes, numbness, and smell sensitivity). Less frequently endorsed were symptoms including thirst (8%, *n* = 3), diarrhea (8%, *n* = 3), tinnitus (8%, *n* = 3), and tremors (3%, *n* = 1). For reference, Table S2 provides the complete descriptive results for the full list of 60 symptoms. Notably, there were differences within the broader symptoms, such as how appetite was affected (both diminished and increased) and the range of specific symptoms representing head pain (e.g., eye, face, and temple pain), visual changes (e.g., blurred vision, eye floaters, vision loss), other pain locations (e.g., neck, back, and body pain), and tension locations (e.g., head, neck, shoulders).

Migraine phases

A unique component of the current work was the investigation of symptomatology across the migraine phases. Results showed the number of unique symptoms reported differed substantially depending on the timing of migraine cycle (Figure 2). For example, during pre-headache and headache, participants reported a median (IQR) of 7.5 (5.5) and 8.0 (4.0) different symptom categories, respectively. In contrast, the levels of symptom endorsement were lower during the post-headache and interictal periods with participants reporting median (IQR) of 4.0 (3.0) and 1.5 (2.5) symptoms, respectively. Findings showed that the number of endorsed symptoms differed across the migraine phases, as did the specific symptoms experienced.

Pre-headache

Table 2 provides a summary of the symptoms endorsed during pre-headache. Participants most often endorsed symptoms related to light sensitivity (75%, *n* = 30), nausea (63%, *n* = 25), sound sensitivity (60%, *n* = 24), visual changes (53%, *n* = 21), and head pain (50%, *n* = 20). There were frequent reports of symptoms related to numbness (43%, *n* = 17), tension (43%, *n* = 17), fatigue (40%, *n* = 16), anxiety (40%, *n* = 16), smell sensitivity (40%, n = 16), depression (35%, *n* = 14), appetite changes (33%, *n* = 13), aura (33%, *n* = 13), sleep issues (33%, *n* = 13), weakness (*n* = 28%, *n* = 10), and touch sensitivity (25%, *n* = 10). About 1 in 5 participants reported symptoms related to cranial autonomic symptoms (CAS; 23%, *n* = 9), non-head pain (20%, *n* = 8), anger (20%, *n* = 8), and vertigo (including dizziness, imbalance, motion; 20%, *n* = 8). Less frequently reported were symptoms such as vomiting and tinnitus (both 5%, *n* = 2). The first column of Table S2 provides further details on the specific symptoms experienced during the pre-headache phase.

Table 3 provides illustrative patient quotes describing the impact of sensory sensitivities and mood/emotion symptoms during the pre-headache phase. Participants frequently discussed how these types of sensory sensitivities worsened as they progressed into the headache phase.

Headache

The transition from the pre-headache to headache was described by one individual as:

> It's just like if you were to sit down in front of a stereo … the volume … you just cranked that to 11, if that was the symptom. So two being this is what I'm experiencing leading into it, and then you just turn that dial all the way up or push that button all the way up. It's just – you're just amplifying it.
>
> (00-14)

This statement aligns with other patient experiences expressing the "ramping up" process with regard to core associated migraine

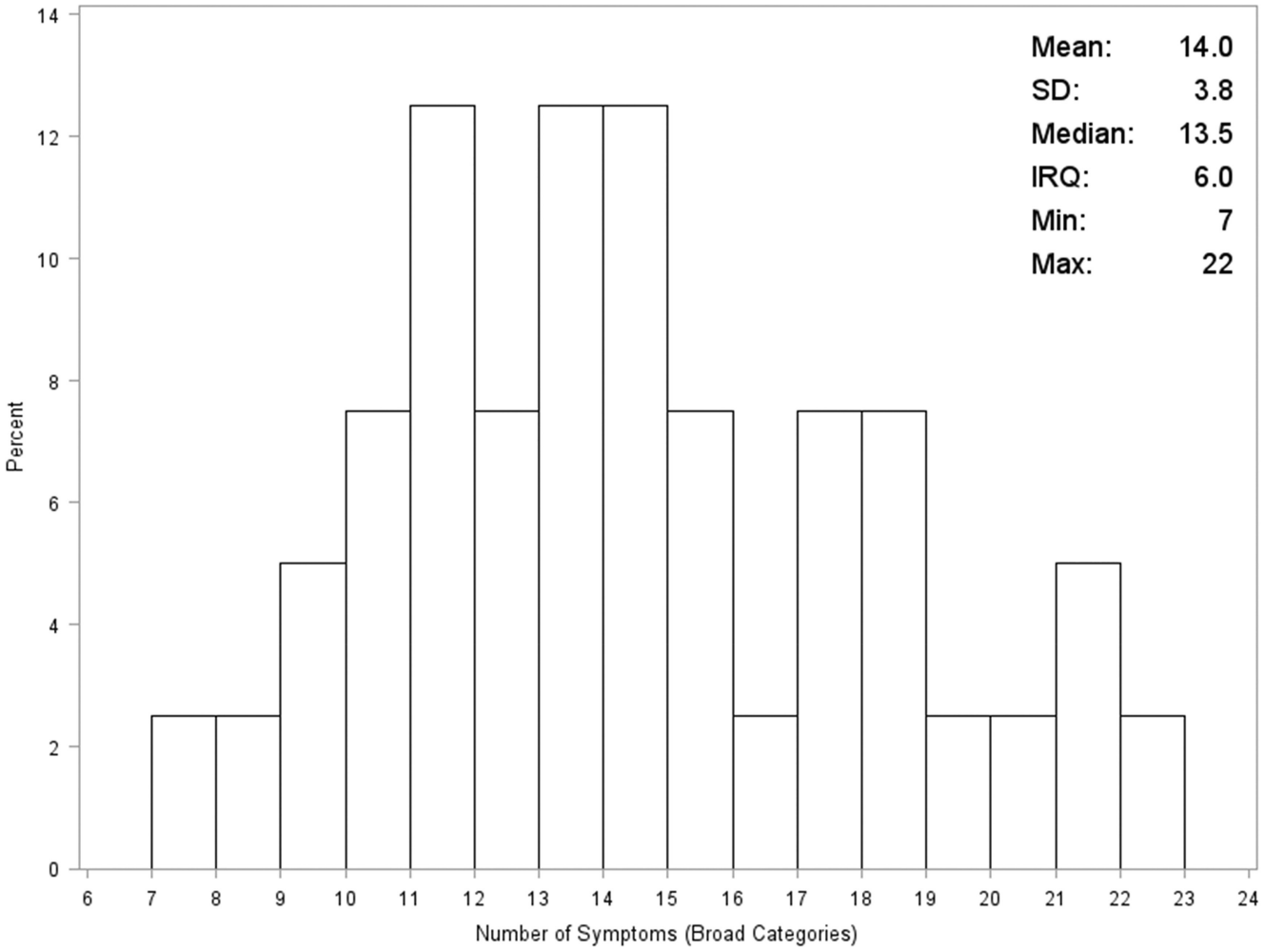

FIGURE 1 Histogram of number of unique symptoms (broad categories) reported across all phases. IQR, interquartile range; SD, standard deviation.

symptoms (Table 3). The most reported symptoms during the headache phase included head pain (100%, $n=40$), light sensitivity (80%, $n=32$), nausea (63%, $n=25$), and sound sensitivity (60%, $n=24$). Head pain in the headache phase was often described as completely debilitating (Table 3).

Other migraine-related symptoms reported often during the headache phase included irritability (65%, $n=26$), depression (50%, $n=20$), non-head pain (35%, $n=14$), smell sensitivity (35%, $n=14$), visual changes (30%, $n=12$), vertigo (30%, $n=12$), fatigue (28%, $n=11$), numbness (28%, $n=11$), and vomiting (28%, $n=11$; Table 2). Additional details regarding the specific symptoms identified through qualitative analysis are documented in Table S2.

Also of note was that not all symptoms worsened from pre-headache to headache. In many participants, symptoms like numbness, pins and needles, and clumsiness would either improve or become less noticeable in the context of increasingly debilitating head pain (Table 3). In the latter, participants described an attentional shift of focus to their head pain and thus, less ability to attend to other symptoms. As one individual put it:

> My focus is – like I said, it gets down to survival, so it's only on my pain and not really on anything else.
>
> (00-04)

Post-headache

During the post-headache phase, participants tended to report fewer symptoms compared to the pre-headache and headache phases (Figure 2). Positive emotions such as relief (60%, $n=24$) and euphoria/elation/happiness (28%, $n=11$) were often expressed, as were negative emotions such as depression (30%, $n=12$) and irritability/impatience (25%, $n=10$; Table 3).

Head pain (28%, $n=11$) and cardinal symptoms were often reported during the post-headache phase (light sensitivity: 30%, $n=12$; sound sensitivity: 25%, $n=10$; nausea: 15%, $n=6$). There were also high rates of fatigue (68%, $n=27$) and appetite change (38%, $n=15$), with most of these being increased appetite (30%, $n=12$). Fatigue and exhaustion were commonly cited during the post-headache

TABLE 2 Endorsement of broad symptom categories across migraine phases and pooled ($N = 40$).

	Pre-headache		Headache		Post-headache		Interictal		Pooled[a]	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%
Cardinal										
Aura	13	33	5	13	1	3	0	0	14	35
Head pain	20	50	40	100	11	28	2	5	40	100
Light sensitivity	30	75	32	80	12	30	5	13	37	93
Nausea	25	63	25	63	6	15	5	13	35	88
Sound sensitivity	24	60	24	60	10	25	3	8	32	80
Vomiting	2	5	11	28	0	0	0	0	11	28
Non-cardinal										
Appetite changes	13	33	9	23	15	38	0	0	23	58
CAS	9	23	6	15	0	0	1	3	12	30
Coordination difficulty	8	20	2	5	1	3	2	5	8	20
Being thirsty	0	0	0	0	3	8	0	0	3	8
Diarrhea	0	0	1	3	1	3	1	3	3	8
Fatigue/exhaustion	16	40	11	28	27	68	4	10	32	80
Visual changes	21	53	12	30	2	5	2	5	22	55
Numbness	17	43	11	28	2	5	1	3	22	55
Other pain	8	20	14	35	6	15	4	10	19	48
Insomnia	13	33	7	18	1	3	3	8	19	48
Smell sensitivity	16	40	14	35	3	8	1	3	20	50
Tension	17	43	4	10	2	5	1	3	18	45
Tinnitus	2	5	1	3	0	0	0	0	3	8
Touch sensitivity	10	25	9	23	3	8	0	0	15	38
Tremor	0	0	1	3	1	3	0	0	1	3
Vertigo	8	20	12	30	6	15	5	13	13	33
Weakness	11	28	8	20	5	13	0	0	16	40
Mood/emotion										
Anger	8	20	6	15	3	8	6	15	14	35
Anxiety	16	40	9	23	9	23	12	30	24	60
Depression	14	35	20	50	12	30	7	18	26	65
Euphoria/elation/ happiness	1	3	1	3	11	28	2	5	13	33
Guilt	0	0	5	13	3	8	2	5	6	15
Irritable/impatient	24	60	26	65	10	25	0	0	33	83
Relief	0	0	0	0	24	60	0	0	24	60

Note: In some cases, there were differences within the broader symptoms categories. For example, how appetite was affected (diminished or increased), the range of specific symptoms representing head pain (e.g., eye, face, and temple pain), visual changes (e.g., blurred vision, eye floaters, vision loss), other pain locations (e.g., neck, back, and body pain), and tension locations (e.g., head, neck, shoulders). Table S2 in supporting information provides summary statistics for the full list of 60 symptoms.

Abbreviations: %, percent; Aura, use of the term "aura" or reporting aura symptoms; CAS, cranial autonomic symptoms; *n*, number endorsed.

[a]Pooled *n* and % the number and percent of participants reporting a given symptom in at least one migraine phase (i.e., pre-headache, headache, post-headache, interictal). Pooled *n* does not have to equal the sum of the phase-specific *n* because participants could endorse symptoms at multiple phases. The Mood/Emotion category includes symptoms considered to be related to either mood or emotions.

period and, compared to other migraine attack stages, seemed to play a larger role in limiting participants' daily function.

Experiences with symptoms during post-headache were highly variable across participants and even within the same individual across attacks. Unlike pre-headache and headache phases, which participants found easier to describe in terms of typical experience, post-headache symptom experiences ranged from speedy and nearly symptom-free recovery to long-lingering residual symptoms

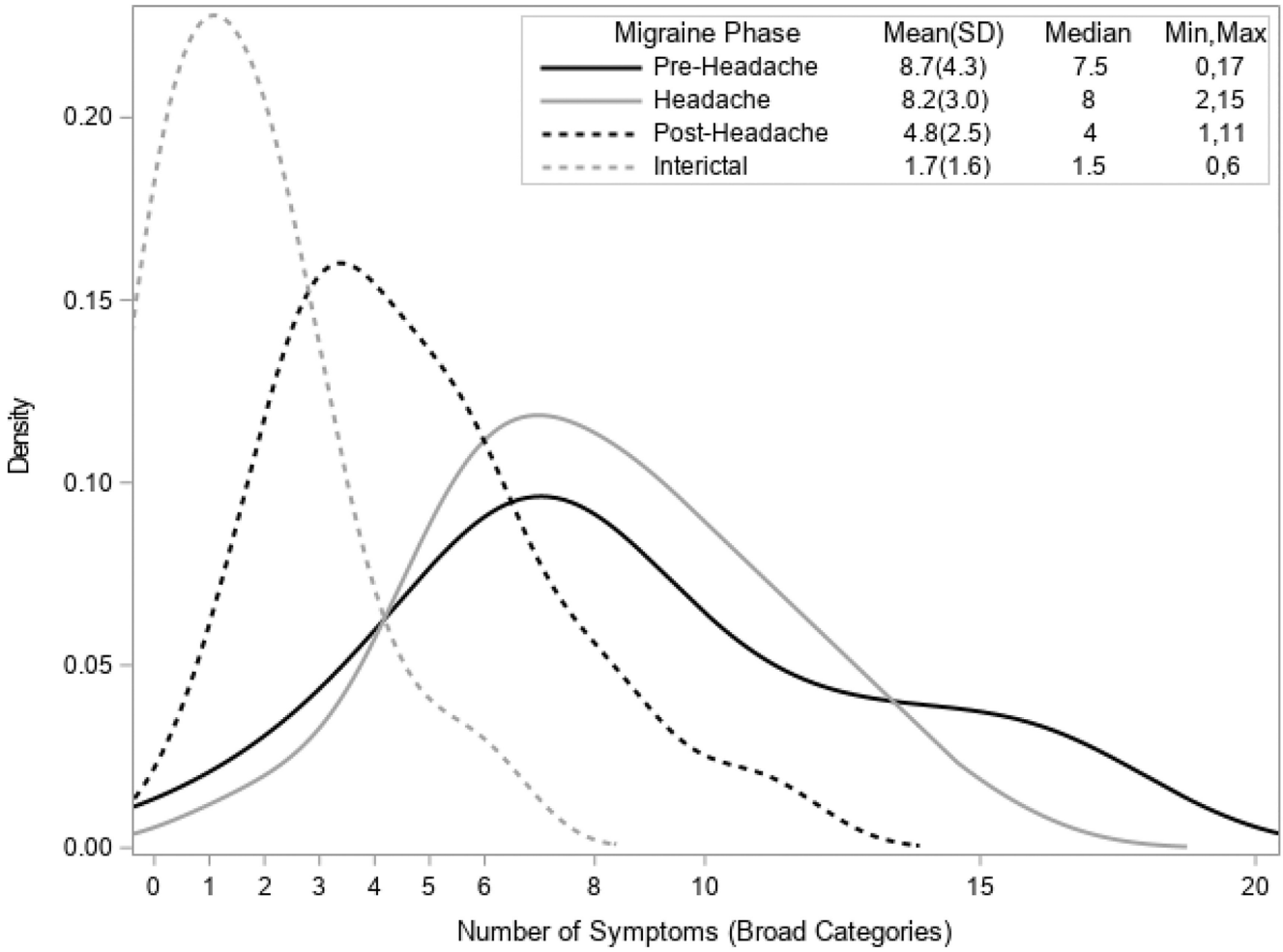

FIGURE 2 Distributions of number of unique symptoms (broad categories) reported within each phase. Information on the calculation of the kernal density (y-axis) can be obtained in the SAS® 9.4 ODS Graphics: Procedures Guide.[35] SD, standard deviation.

that take hours or days to resolve. For example, below are quotes from different participants regarding the experiences during the post-headache phase.

> I'm so relieved that I'm wired and I can dance a jig. And sometimes I'm – I will mop my whole apartment and go for a walk, because woo-hoo and hooray. But it's definitely relief.
>
> (00-18)

> And even recovering from that – you know, even after the pain goes away, it can affect me kind of in small ways, even after the headache. And the next day, I usually have some symptoms, too.
>
> (00-03)

Interictal period

Almost three quarters (73%, $n=29$) of the participants reported ≥ 1 symptom category during the interictal phase. Among those that reported symptoms between attacks, there were few similarities in symptom experiences (Table 2). The most frequently reported symptoms were anxiety (30%, $n=12$), depression (18%, $n=7$), and anger (15%, $n=6$). Some participants reported that exhaustion and fatigue (10%, $n=4$) are a key aspect of their interictal experience and a few individuals reported mild sensory sensitivities (light: 13%, $n=5$; sound: 8%, $n=3$) and nausea (13%, $n=5$) that lingered during interictal periods (Table 3).

Most individuals who experienced symptoms between migraine attacks had learned to cope with them, but both individuals with and without symptoms during the interictal period described an appreciation for their migraine-free days, which they used to catch up on work, household responsibilities, and social engagements disrupted by their migraine attacks. For example, one participant stated:

> I would say that if I'm headache-free in a day, I have a lot of energy. And what I do historically is if I'm having a good day, I have a list of things that I want to get done, like doing something out in the garden or going to the grocery store or cleaning out the garage. When I'm having a good day, I almost go nonstop, because I

TABLE 3 Symptoms and exemplary quotes by migraine phase.

Symptom	Exemplary quote
Pre-headache	
Light/sound sensitivity	And it looks like – I will tell him that the lights are too bright. Whether they are or not, all the lights are too bright. The TV is too bright. The lamp on dim is too bright. Everything is too bright. And all the sounds are too loud. His voice is too loud. Everything is too loud. (00-01)
Light sensitivity	It's not like I'm conscious of light sensitivity, but my body is reacting anyway and saying, don't look there, don't look there. (00-38)
Irritable/impatient	I'm just more like – I would say like easily, easily agitated, like I get more aggressive with my kids, like just leave and just – I'm not patient at all or my normal self. (00-32)
Anxiety	Yeah, one of the other things too is I start to feel anxious. Anxiety plays a part, because I know it's coming. And that just – it doesn't help. I guess, in that time where I know a migraine is coming, I start thinking about, OK, how bad is this migraine? What am I going to take for it? How long is it going to last? What do I have to tell people around me for the rest of the day or the night? All that anxiety, I guess, just makes it worse. (00-04)
Headache	
Light/sound sensitivity	It [sensitivity to light and sound] just becomes even more intense. (00-01)
Head pain	Where you can't even get up off the floor, that's where I was at with that kind of pain. (00-14)
Irritable/impatient	I get more moody, more snappy, I guess. More – oh – I take things wrong. It's like somebody's trying to joke, but it doesn't seem like a joke and it just irritates me and it's like, what? (00-35)
Multiple (improvement)	So for me, what happens is some of my other symptoms actually start to get better. The light sensitivity doesn't go away at all. Like I – light is a problem during the whole episode. But some of the other visual disruptions will gradually get a little bit better. The fogginess sometimes gets a little bit better, sometimes doesn't. But I will say that my vision actually improves. (00-03)
Post-headache	
Relief	Girl, absolute relief, because it's like, oh my God, it doesn't hurt anymore. It's like thank God. It is the best euphoria. It's like, oh my God, I'm not in pain. So it's like the reward. It is just total excitement, like yes, it's gone. Now I can function, so – yeah. (00-39)
Head pain	I have the – I guess it's called the residual headache. That's what I've been told by certain doctors, but I have the remnants of a headache. It's not that extreme pain, but it's achy. My head's achy in that area. But then my ability to do things and stuff comes back as my numbness and the pain and all goes away. (00-17)
Fatigue	Immediately after, I feel exhausted, completely worn down. It takes a lot out of me, which, I'm sure it does, having to push through and all. (00-17)
Interictal	
Fatigue/exhaustion	I'm exhausted. I'm very exhausted a lot. I'm fatigued. (00-02)
Nausea	Usually nausea. Sometimes just low-grade annoying. Putting lemon and mint in a lot of things, and that's enough. Minor headaches and then hypersensitivity, I think, would be just like the start of waiting for an attack. (00-18)

don't know what the next day's going to bring. So I do as much as I can.

(00-44)

DISCUSSION

Patient-centered research forms the foundation for understanding the unique experiences of persons with migraine. Recent qualitative work shows the diverse impacts of migraine and the need for integrating the patient voice into clinical research and practice.[29,30] The current study addresses this need by providing new insights on migraine-related symptom frequencies, intensities, and patterns of timing from the patient perspective while also complementing modern experimental studies focused on the phases of migraine.[31–33] Through qualitative analysis, numerous migraine-related symptoms and emotions/mood symptoms were identified. The pre-headache and headache phases were typically accompanied by the highest number of symptoms, followed by a reduction in symptoms for post-headache and interictal phases. Head pain and diagnosis-related associated symptoms (i.e., light and sound hypersensitivity and nausea) were frequently reported. However, results demonstrated that the presence of specific symptoms often differed across migraine phases and the range of possible symptoms reported by patients was larger than diagnostic criteria would suggest. During the pre-headache and headache phases, large percentages of participants consistently reported the same symptoms whereas, in the latter two phases, they tended to exhibit more heterogeneity in reported symptoms.

Head pain during the headache phase was the only universally reported symptom across all participants and it was endorsed by at least one participant in every phase, which was an unexpected

finding. Despite interviewers explicitly stating that headache pain is the definitive attribute of the headache phase, participants did not strictly follow this definition (i.e., individuals endorsed head pain outside of the headache phase). This phenomenon was not the product of collapsing symptoms into broader categories (e.g., in Table S2, the uncollapsed "head pain" symptom is endorsed at all attack phases). The interviewers did not interrupt, or correct, participants when describing their experiences with migraine, as the core purpose of this work was to document the unadulterated patient's perspective. In most cases, head pain descriptions during the headache phase qualitatively differed from the other phases. These differences are challenging to translate through summary statistics but can be highlighted through example quotes, descriptions, and word choices. Head pain during the headache phase was often described as completely debilitating, whereas, in other phases, it was mild/dull and often manageable. For instance, below is a patient quote about head pain during the interictal phase, which contrasts other patient descriptions of head pain provided in the "headache phase" subsection of the Results above and Table 3.

> I do have an overall pain level that exists always. So really, for me, instead of just having the before, during, and after, I have a baseline. And then it – there's the ramp-up period that's before it's really bad, the really badness, and then going back to baseline is probably more of how I would describe that process, just because I do have a baseline pain level that isn't none.
>
> (00-06)

Discrepancies between our a priori migraine phase definitions and participant reports highlight a potential misalignment between the traditional, clinically driven definitions for attack phases and what many patients actually experience (i.e., patients have difficulty describing their experiences within an assumed structure proposed by clinicians and researchers). Most participants were able to clearly differentiate among phases of their migraine attack, but for a subset of participants with chronic migraine or consistent/daily low-level migraine symptoms, differentiating among phases was difficult because attacks could go from a baseline level of dull pain and associated symptoms to a higher degree of intensity and back to their functional symptom baseline (i.e., never fully resolving; see above patient quote). This finding highlights a unique challenge of the heterogeneous migraine patient population and demonstrates how attempts to neatly categorize migraine experiences for clinical and research purposes may not directly translate to the experiences of people living with migraine. Of note, a similar theme was observed in a recent meta-analysis study that found inconclusive evidence to support the existence of a well-defined pre-headache phase.[34]

The current work has limitations. A relatively small number of participants was purposefully selected through CHAMP's network and it is unknown if the findings here generalize to the broader population or a different sample of individuals with migraine. However, it is important to note that the objective of the MiCOAS project is to develop outcomes and endpoints for use in migraine clinical trials, which also are not representative of the general population. In terms of severity and composition, it is possible that the sample recruited via CHAMP resembles those in clinical trials. The focus on collapsed symptom categories facilitated the presentation of results, but the reported frequency counts differed from those produced using the unaltered symptom codes. The non-collapsed results are available in the Supplemental Appendix in supporting information for interested readers.

It is important to reiterate that the symptoms discussed in the current work only cover a subset of domains from the larger MiCOAS qualitative study (e.g., cognitive symptoms and MiCOAS-related qualitative work have been previously published).[23–25] The other domains should also be considered if one wants to gather a more complete picture of the larger impact of migraine from the patient's perspective. The current results align with previous MiCOAS work focused on cognitive symptoms, which also documented a range of symptoms that were most common during the pre-headache and headache phases.[23] A future direction for MiCOAS research is synthesizing vast amounts of qualitative data to form a complete migraine conceptual model.

CONCLUSION

This analysis of qualitative data from the MiCOAS project demonstrated that a range of possible migraine-related symptoms appear throughout the migraine cycle, even interictally. Symptoms arise, wax and wane, or dissipate across the phases in ways that suggest complexity not captured in the traditional diagnostic framework. Consequently, measuring the benefits of treatment may require an enlarged view of the patient experience. Efforts to measure migraine as a symptom complex, and associated burden, should consider symptom profiles by stage and examine links between symptoms and measures of functional status. Current findings confirmed that core migraine symptoms, such as head pain and typical associated symptoms, are important to patients. However, focusing only on these select symptoms during the headache phase likely omits valuable information on the migraine patient experience that can support clinical and regulatory decision making. Based on the current findings, clinical research studies should consider broadening the range of potential outcomes to include a range of the identified symptoms. These studies should also attempt to implement research designs that reflect the differential patterns of symptom occurrence/co-occurrence across the respective migraine phases. Other future directions include further exploring the relationships between symptoms and functional impact and exploring the amount of impact associated with various symptoms. The insights gained from this work should be used in the development of new patient-reported outcome measures that can be readily used to define patient-supported endpoints in migraine clinical trial studies.

AUTHOR CONTRIBUTIONS

Study concept and design: James S. McGinley, Rikki Mangrum, Maya T. Gerstein, Kelly P. McCarrier, R. J. Wirth, Richard B. Lipton. *Acquisition of data*: Rikki Mangrum, Maya T. Gerstein, Kelly P. McCarrier, Alexandra L. Bryant. *Analysis and interpretation of data*: James S. McGinley, Rikki Mangrum, Maya T. Gerstein, Kelly P. McCarrier, Carrie R. Houts, Dawn C. Buse, Alexandra L. Bryant, R. J. Wirth, Richard B. Lipton. *Drafting of the manuscript*: James S. McGinley, Rikki Mangrum. *Revising it for intellectual content*: James S. McGinley, Rikki Mangrum, Maya T. Gerstein, Kelly P. McCarrier, Carrie R. Houts, Dawn C. Buse, Alexandra L. Bryant, R. J. Wirth, Richard B. Lipton. *Final approval of the completed manuscript*: James S. McGinley, Rikki Mangrum, Maya T. Gerstein, Kelly P. McCarrier, Carrie R. Houts, Dawn C. Buse, Alexandra L. Bryant, R. J. Wirth, Richard B. Lipton.

CONFLICT OF INTEREST STATEMENT

James S. McGinley is a full-time employee of Vector Psychometric Group, LLC, which in turn received funds from the FDA to conduct the research detailed in the manuscript. James S. McGinley has received honoraria/payment/reimbursement from the journal *Cephalalgia* (biostatistics editor). James S. McGinley has also received research grants/support from Amgen, Inc., and the National Headache Foundation. **Rikki Mangrum** is a full-time employee of Vector Psychometric Group, LLC, which in turn received funds from the FDA to conduct the research detailed in the manuscript. **Maya T. Gerstein** was a full-time employee of Pharmerit/OPEN Health, which in turn received funds from Vector Psychometric Group, LLC, and the FDA to conduct the research detailed in the manuscript. **Kelly P. McCarrier** is a full-time employee of Pharmerit/OPEN Health, which in turn received funds from Vector Psychometric Group, LLC, and the FDA to conduct the research detailed in the manuscript. **Carrie R. Houts** is a full-time employee of Vector Psychometric Group, LLC, which in turn received funds from the FDA to conduct the research detailed in the manuscript. **Dawn C. Buse** is a part-time employee of Vector Psychometric Group, LLC, which in turn received funds from the FDA to conduct the research detailed in the manuscript. In addition, she has been a consultant to Allergan/AbbVie, Amgen, Collegium, Lilly, Lundbeck, Theranica, and Teva Pharmaceuticals. **Alexandra L. Bryant** is a full-time employee of Vector Psychometric Group, LLC, which in turn received funds from the FDA to conduct the research detailed in the manuscript. **R. J. Wirth** is a full-time employee of Vector Psychometric Group, LLC, which in turn received funds from the FDA to conduct the research detailed in the manuscript. **Richard B. Lipton** received research support from the FDA on the MiCOAS project. In addition, he receives research funding from the NIH, the National Headache Foundation, and the Marx Foundation. He also receives research support from Allergan/AbbVie, Amgen, Biohaven, Eli Lilly, and electroCore. He receives personal fees as a consultant or advisor from Allergan/AbbVie, Amgen, Biohaven Holdings, Dr. Reddy's, GSK, Grifols, Eli Lilly, Lundbeck, Merck, Novartis, and Teva Pharmaceuticals. He holds stock or options in Biohaven Holdings and Ctrl M Health. In addition, he receives royalties for *Wolff's Headache*, 7th and 8th editions.

ORCID

Rikki Mangrum https://orcid.org/0000-0001-6231-5890
Maya T. Gerstein https://orcid.org/0000-0003-2035-0828
Richard B. Lipton https://orcid.org/0000-0003-2652-2897

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: McGinley JS, Mangrum R, Gerstein MT, et al. Symptoms across the phases of the migraine cycle from the patient's perspective: Results of the MiCOAS qualitative study. *Headache*. 2024;00:1-12. doi:10.1111/head.14817