Received: 28 October 2022 | Accepted: 22 February 2023
DOI: 10.1111/head.14521

RESEARCH SUBMISSIONS

Priority acute and preventive migraine treatment benefits: Results of the Migraine Clinical Outcome Assessment System (MiCOAS) qualitative study of people living with migraine

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Funding information
U.S. Food and Drug Administration, Grant/Award Number: UH3FD006795

Abstract

Background: There is renewed emphasis on including patients in determining, defining, and prioritizing outcomes for migraine treatment.

Objectives: To obtain insights directly from people living with migraine on their priorities for treatment.

Methods: A total of 40 qualitative interviews were conducted as part of the Migraine Clinical Outcome Assessment System project, a United States Food and Drug Administration grant-funded program to develop a core set of patient-centered outcome measures for migraine clinical trials. Interviews included a structured exercise in which participants rank-ordered pre-defined lists of potential benefits for acute and preventive migraine therapy. The 40 study participants who reported being diagnosed with migraine by a clinician ranked the benefits and explained their rationale.

Results: Study participants consistently ranked either pain relief or absence of pain as their top priority for acute treatment. Relief/absence of other migraine symptoms and improved functioning were also prioritized. For preventive treatment, participants prioritized reductions in migraine frequency, symptom severity, and attack duration. Few differences were found between participants with episodic migraine and those with chronic migraine. However, participants with chronic migraine ranked “increased predictability of attacks” much higher than those with episodic migraine. Participants' rankings were influenced by prior expectations and experiences of migraine treatments, which caused many participants to deprioritize desired benefits as unrealistic. Participants also identified several additional priorities, including limited side-effects and reliable treatment efficacy in both acute and preventive treatments.

Conclusion: The results showed the participants prioritized treatment benefits aligned with existing core clinical outcomes used in migraine research, but also valued benefits that are not typically assessed, such as predictability. Participants also

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Abbreviations: CHAMP, Coalition for Headache and Migraine Patients; CM, chronic migraine; EM, episodic migraine; FDA, United States Food and Drug Administration; MiCOAS, Migraine Clinical Outcome Assessment System.

deprioritized important benefits when they believed treatment was unlikely to deliver those outcomes.

KEYWORDS
migraine therapy, patient reported outcomes, qualitative research, quality of life

BACKGROUND

Migraine is one of the most common disabling diseases in the world,[1] but also remains underdiagnosed and undertreated.[2–4] Recent advances in migraine therapy contribute to a growing variety of available treatments and to variations in treatment benefits. Acute therapies focus on the rapid alleviation of symptoms once a migraine attack begins, while preventive treatments aim to reduce the overall frequency, duration, severity, and impact of migraine attacks.[5,6] Treatment aims have evolved over decades of clinical investigation driven by the characteristic features of migraine attacks (e.g., moderate–severe pain, nausea, photophobia, and phonophobia) and episodic or chronic occurrence. Although studies in the field of migraine often reference patient priorities or preferences for treatment,[7–11] published, systematic qualitative evaluation of treatment priorities directly by people living with migraine is limited. Prior studies that used qualitative methodology specifically to assess treatment priorities included a mix of stakeholders and found significant prioritization differences between people with migraine and other stakeholders.[12,13] Similarly, systematic reviews have been conducted to document the wide variety of outcomes that have been measured in migraine research, but these may or may not accurately reflect the treatment priorities of people living with migraine.[14–17] These reviews demonstrate that publications are inconsistent in reporting whether and how people with migraine have contributed to the selection and definition of these outcomes. Even when such information is summarized, it does not address whether patient participants engaged in any systematic prioritization of the relative importance of different outcomes or benefits of treatment.

The Migraine Clinical Outcome Assessment System (MiCOAS) project is a multi-stage project funded by the United States Food and Drug Administration (FDA) to develop a patient-centered core set of outcomes and endpoints for use in migraine clinical trials. As part of the project, the MiCOAS research team has gathered data from people living with migraine through qualitative interviews that explored experiences with migraine symptoms and burdens and inquired about perspectives on treatment through a ranking exercise.

OBJECTIVE

To address the gap in understanding regarding the treatment priorities of people with migraine, the MiCOAS team conducted qualitative interviews that included a structured exercise in which participants were asked to rank-order two pre-defined lists of potential treatment benefits or outcomes, one for acute treatments (eight benefits) and one for preventive treatments (11 benefits). Participants were asked to explain their rationale for each ranking and to describe any additional benefits they perceived that were not included in the pre-defined lists. This is a primary analysis of the data from the interviews.

METHODS

Participants with self-reported, medically diagnosed migraine were recruited through study announcements distributed by the Coalition for Headache and Migraine Patients (CHAMP, https://headachemigraine.org/) via newsletters and social media channels. CHAMP is a coalition of patient advocacy organizations focused on migraine and headache. CHAMP was selected because of its capacity to reach a large, diverse audience of people with migraine, as well as caregivers and clinicians who might share the announcement. Broad outreach also afforded an efficient way to reach people who have typically been underrepresented in migraine research, such as males and racial or ethnic minorities, while still permitting the selection of an overall sample that was representative of clinical trial participants and people who seek primary or specialty medical care for migraine.

The study announcement directed people to a dedicated study website that described the study and included a link to an electronic eligibility screening questionnaire. Participants who met the eligibility criteria were directed to an electronic informed consent form and those who e-signed the consent form were then directed to complete a health and demographic questionnaire.

Eligible participants were current US residents self-reporting a medical diagnosis of migraine and who screened positive for migraine on the ID-Migraine screener (endorsing two or more of the following: disability due to headache ≥1 day in the past 3 months, phonophobia, or nausea with headache),[18] were able to complete an interview in English, aged 18–75 years, and were willing to participate in a 90-min recorded interview. Exclusion criteria included (i) self-report of a medical diagnosis of multiple sclerosis, schizophrenia, bipolar disorder, cognitive impairment, Alzheimer's disease or dementia, or epilepsy, (ii) screening positive for alcohol or drug abuse over the past 3 months using the CAGE (Cutting down, Annoyance by criticism, Guilty feeling, and Eye-openers) questionnaire,[19] or (iii) self-reported diagnosis, symptoms, or hospitalization related to coronavirus disease 2019 infection. The study took place July–September 2020.

From the pool of 428 eligible individuals, 40 participants were selected using iterative purposive sampling aimed at achieving a balanced representation of episodic and chronic migraine (EM and CM, respectively) using enrollment targets for headache frequency

(Table 1). These targets were intended to ensure the inclusion of people with EM who experience different numbers of headaches and limit the inclusion of people with very low or very high frequency headaches who would be excluded in many clinical trials. In addition, sampling aimed to achieve a diverse representation of demographic characteristics such as sex, race, ethnicity, education, employment status, income, and use of acute and preventive treatments. Participants were enrolled in eight waves of four to six interviews each and the demographic characteristics of the sample of completed interviews was used to determine priority characteristics for the next wave. Interview results were also monitored for the achievement of data saturation.[20]

TABLE 1 Targeted sampling by headache frequency.

Headache frequency, headache days/month	Enrollment target
0–1	$n=2$
2–3	$n=6$
4–7	$n=6$
8–14	$n=6$
15–23	$n=18$
≥24	$n=2$
Total	$N=40$

Interviews focused primarily on topics related to migraine symptoms and impacts. During the last 15–25 min of the interview, a structured visual rank ordering exercise of acute and preventive treatment benefits was conducted. The interview guide, developed by the investigators, was piloted in the field with two volunteer participants prior to data collection. All interviewers were trained in the protocol and observed by senior members of the research team (M.T.G., K.M.). Interviews were conducted in 2020 via web-conferencing. Interviews were recorded with participant consent and transcribed verbatim for use in analysis (identifying details were redacted from transcripts).

For the rank ordering exercise, the interviewer displayed a prespecified list of acute and preventive pharmacologic treatment benefits using QuestionPRO and the Microsoft Teams screen-sharing function. Participants were asked to rank the items in order of importance while providing a verbal explanation of their rankings. The interviewer re-ordered items on the screen to match the participant's statements. Interviewers also asked probing questions about why participants ordered items as they did and inquired about any missing priorities that the participant believed should be included. Participants were not required to rank all items on the list but could choose items to rank and disregard the remainder.

The lists of treatment benefits (Figure 1) were developed through an iterative process that included consideration of

Acute Treatment Benefits

1. Pain relief: i.e., if pain is severe or moderate, it becomes mild due to treatment
2. Relief of other symptoms: Symptoms other than pain, e.g., nausea, vomiting, sensitivity to light
3. Absence of pain: i.e., if pain is severe or moderate, it becomes no pain due to treatment
4. Absence of other symptoms: Symptoms other than pain, e.g., nausea, vomiting, sensitivity to light
5. Greater ability to participate in your usual daily activities: e.g., work, school, family life, household responsibilities, social interactions
6. Greater ability to do physical things: e.g., climbing stairs, bending over, walking
7. Less "brain fog": e.g., improved ability to focus, think clearly, make plans and decisions, better memory
8. Improved feelings of well-being: e.g., less anxiety or worry, less depression, less irritability, anger, guilt, frustration
9. Less need for other medications or treatments

Preventive Treatment Benefits

1. Fewer days with migraine each month
2. Fewer migraine attacks each month
3. Longer periods of time in between your migraine attacks
4. More predictability: i.e., number and/or length of your migraine attacks
5. Less severe/intense pain when a migraine attack happens
6. Shorter attacks when they happen
7. Less severe symptoms when a migraine attack happens: e.g., nausea, vomiting, sensitivity to light
8. Greater ability to participate in usual daily activities: e.g., work, school, family life, household responsibilities, social interactions
9. Less "brain fog": e.g., improved ability to focus, think clearly, make plans and decisions, better memory
10. Improved emotional health: e.g., less anxiety or worry, less depression, less irritability, anger, guilt, frustration
11. Less need for acute migraine medications

FIGURE 1 Benefits of acute and preventive treatments provided to interview participants for ranking exercise.

four systematic reviews of migraine or headache endpoints and outcomes,[14–17] discussions with the MiCOAS study's External Technical Advisory Committee, and feedback from the FDA. The External Technical Advisory Committee included physicians who specialize in migraine, researchers, pharmaceutical industry representatives, and one patient advocate living with migraine. Iterative discussions focused on articulating treatment benefits in plain language and developing suitable definitions. Some benefits appeared on both lists and were labeled and defined in the same way, except for the benefit of improved emotional well-being. For acute treatment, this benefit was labeled as "improved feelings of well-being" to reflect the immediate mood benefits that may arise when an acute treatment relieves a migraine attack. For preventive treatment, this benefit was labeled as "improved emotional health" to reflect the broader, longer-term emotional benefits that successful preventive treatment may bring about in people's lives, including between attacks.

ETHICS REVIEW

This study was reviewed and approved by the WIRB IRB Institutional Review Board.

ANALYSES

Interview data were analyzed by computing mean, standard deviation, median, interquartile range, mode, and range of ranks; examining the number of participants selecting each rank for each benefit; and conducting content analysis to assess patterns and themes in participants' rationale for ranking. Content analysis was also conducted using Atlas.ti version 8.0 software to assess themes in participant responses regarding perceived additional benefits that were important.

RESULTS

Participants' characteristics

Table 2 provides a summary of participants' self-reported demographic and clinical characteristics. The mean (range) age of the participants was 44 (21–70) years. The sample was 78% (*n* = 31) female, 68% (*n* = 27) White, and 23% (*n* = 9) Black or African American. Just over half (47%, *n* = 19) of the study sample reported having received a college degree. The sample was composed of both currently employed (55%, *n* = 22) and unemployed (45%, *n* = 18) individuals. Most of the sample (70%, *n* = 28) reported an annual household income of <$100,000. Half of the participants (*n* = 20) reported experiencing ≥15 headache days/month, and half (*n* = 20) reported experiencing <15 headache days/month. All participants reported using acute treatment(s) and 88% (*n* = 35) reported using

TABLE 2 Demographic, headache, and treatment characteristics of the study sample.

Variable	Category	Total interview sample (N = 40)
Age, *n* (%)	18–24 years	5 (12)
	25–44 years	17 (43)
	45–64 years	13 (33)
	≥65 years	5 (12)
Gender, *n* (%)	Women	31 (77)
	Men	7 (18)
	Genderqueer/gender non-binary, transgender person	2 (5)
Race[a], *n* (%)	White	27 (67)
	Black or African American	9 (23)
	American Indian or Alaskan Native	4 (10)
	Asian	3 (7)
	Native Hawaiian or Other Pacific Islander	1 (2)
	Other[b]	1 (2)
	Prefer not to answer	1 (2)
Ethnicity/race[a], *n* (%)	Hispanic	9 (23)
	Non-Hispanic	31 (77)
Relationship status, *n* (%)	Married or partnered	19 (48)
	Not married or partnered	21 (52)
Number of other adults in household, *n* (%)	None	8 (20)
	1–2	27 (68)
	3–4	5 (12)
Number of children in household, *n* (%)	None	26 (65)
	1	5 (12)
	≥2	9 (23)
Education, *n* (%)	Grade 12 or GED equivalent	3 (8)
	Associate degree, technical school, or trade apprenticeship; some college (no degree awarded)	18 (45)
	College degree or advance degree	19 (47)
Employment[a], *n* (%)	Paid employment	22 (55)
	Student	8 (20)
	Homemaker	3 (8)
	Retired	6 (15)
	Unemployed	2 (5)
	Disabled (disability or leave of absence for any reason)	10 (25)
	Other	1 (2)

TABLE 2 (Continued)

Variable	Category	Total interview sample (*N* = 40)
Household income, *n* (%)	<$22,000	8 (20)
	$22,000–$49,999	10 (25)
	$50,000–$99,999	10 (25)
	≥$100,000	8 (20)
	Prefer not to answer	4 (10)
Migraine subtype by frequency, *n* (%)	<15 headache days/month on average (episodic migraine[c])	20 (50)
	≥15 headache days/month on average (chronic migraine[c])	20 (50)
	Migraine with aura	14 (35)
	Migraine without aura	26 (65)
Average number of headache days/month, *n* (%)	0–1	0
	2–3	6 (15)
	4–7	8 (20)
	8–14	6 (15)
	15–23	18 (45)
	≥24	2 (5)
Use of OTC or prescription acute pharmacologic treatment (within past year), *n* (%)	Yes	40 (100)
Use of OTC or prescription preventive pharmacologic treatment, *n* (%)	Yes	35 (88)

Abbreviations: GED, General Equivalency Diploma; OTC, over the counter.

[a] Total percentage exceeds 100% because participants were able to select more than one race and/or employment status category.

[b] Respondent reported races of "White, South American, and North African" and chose the label "Other".

[c] Chronic migraine was defined as an average monthly headache day frequency of ≥15 headache days/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 third edition of the *International Classification of Headache Disorders* criteria.

preventive treatment to reduce the frequency or severity of migraine during the past year. Participants selected from extensive lists of therapies that included prescription medications, over-the-counter treatments, and vitamin supplements, as well as an 'Other, please specify' option. Nine participants (22%) reported using non-prescription preventive treatments such as magnesium or riboflavin.

Benefit ranking results

The mean, median, mode, and range of ranks for each treatment benefit provided by participants are shown in Table 3. All participants completed the ranking exercise so there were no missing data. Most participants provided a ranking for all benefits on both lists. Three participants did not rank all items on both lists. One participant did not rank all acute treatment benefits, and another did not rank all preventive benefits. Removing these participants from analysis would have made small numeric differences in mean values but would not have altered the overall order of the mean, median, or mode rankings. Notably, the range of rankings shows that every treatment benefit was ranked at or near the bottom by at least one participant, as well as at or near the top by at least one person. Only three treatment benefits were ranked by all 40 participants: "greater ability to participate in usual daily activities," "fewer attacks," and "less severe intense pain."

Acute treatment benefits

Interview participants consistently ranked pain relief or absence of pain as their number one priority for acute treatment benefit (Figure 2). These two options each received 17 number one rankings (Table 4), with 85% of participants selecting one of these options as their top priority. The mean ranking for pain relief was considerably higher than the mean ranking for absence of pain because a substantial number of participants (*n* = 11) ranked pain relief second and few participants (*n* = 4) ranked it lower than fourth place. Rankings for absence of pain were more dispersed, with 12 participants selecting a ranking lower than fourth place.

As shown in Figure 2, average rankings for relief or absence of other migraine symptoms were similar and these were high priorities for many participants. Benefits related to functioning were ranked on average as the next highest priorities; while less need for other treatments was ranked last. These mean rankings generally aligned with the median and mode (Table 3), with the exception of "greater ability to participate in your usual daily activities." This benefit was ranked third by 12 participants compared with absence of other symptoms, which was ranked third by nine participants.

Preventive treatment benefits

Figure 3 shows the average rankings for benefits associated with preventive treatment. Interview participants prioritized reductions in migraine frequency, severity of symptoms, and the duration of attacks. Notably, 31 of the 40 participants (78%) selected fewer days, fewer attacks, and longer periods of time between attacks as their top three priorities (Table 5). Participants expressed that these benefits were interrelated: "*Because you're getting less migraines, so there's going to be longer periods of time in between them. And you're getting fewer [days] each month, and then fewer migraine attacks*" (00–14).

TABLE 3 Results of ranking of potential benefits by participants.

	Mean (SD)	Median (IQR)	Mode	Range
Acute treatment benefits				
Pain relief	2.2 (1.6)	2 (2)	1	0–8
Relief of other symptoms	4.0 (2.1)	4 (3)	4	0–8
Absence of pain	3.1 (2.7)	2 (4)	1	0–9
Absence of other symptoms	4.1 (2.3)	3.5 (3.2)	3	0–9
Greater ability to participate in your usual daily activities	5.0 (2.3)	5 (4)	3	1–9
Greater ability to do physical things	6.4 (2.5)	7 (3.2)	8	0–9
Less “brain fog”	5.5 (2.2)	5.5 (3)	5	0–9
Improved feelings of well-being	6.1 (2.3)	6 (3)	6	0–9
Less need for other medications or treatments	6.4 (2.4)	7 (4)	9	0–9
Preventive treatment benefits				
Fewer days with migraine each month	2.3 (1.7)	2 (2)	1	0–10
Fewer migraine attacks each month	2.7 (1.8)	2 (2.2)	2	1–9
Longer periods of time in-between your migraine attacks	4.6 (2.2)	4.5 (3)	3	0–10
More predictability	7.5 (3.3)	8 (4.2)	11	1–11
Less severe/intense pain when a migraine attack happens	3.8 (2.1)	3.5 (3)	4	0–9
Shorter attacks when they happen	5.1 (1.9)	5 (2)	4	0–9
Less severe symptoms when a migraine attack happens	5.2 (2.8)	5 (3)	5	0–11
Greater ability to participate in usual daily activities	7.2 (2.8)	7.5 (3)	7	0–11
Less “brain fog”	7.9 (3.1)	9 (3)	10	0–11
Improved emotional health	7.8 (3.4)	9 (4)	11	0–11
Less need for acute migraine medications	7.5 (3.5)	9 (4.5)	11	0–11

Note: A rank of 1 indicates the benefit was a top priority; a rank of 0 indicates that the participant did not rank the outcome.
Abbreviations: IQR, interquartile range; SD, standard deviation.

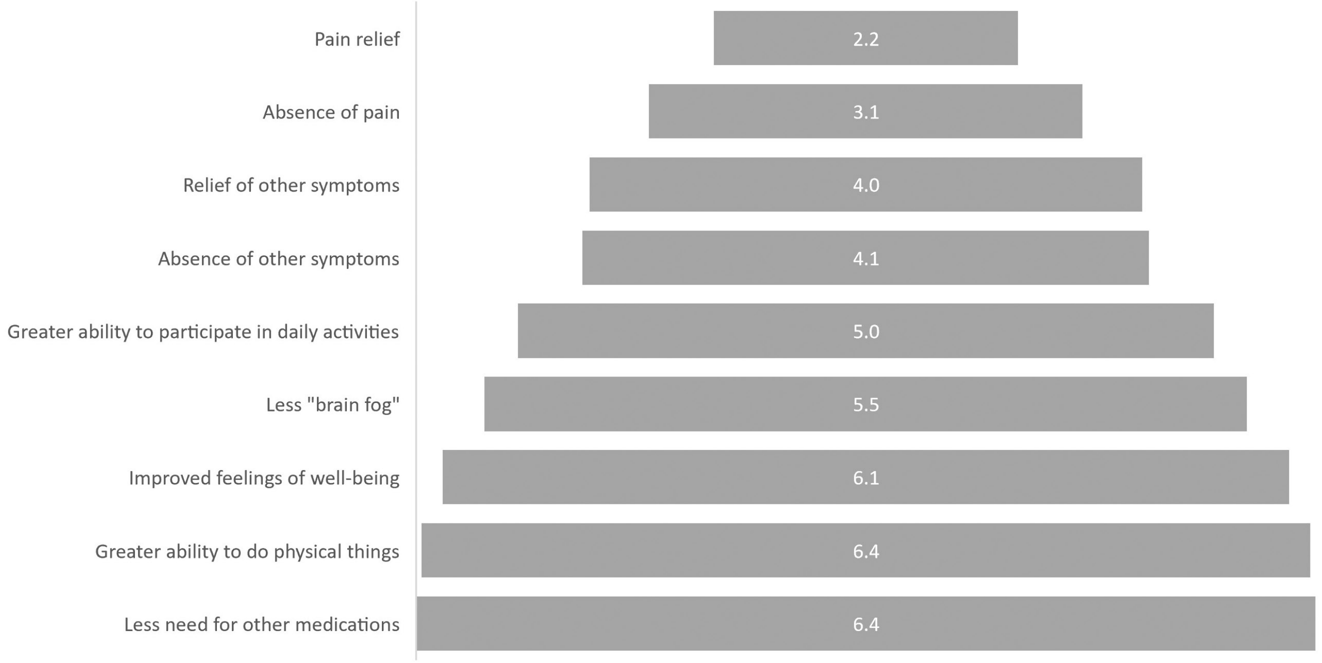

FIGURE 2 Average (mean) priority rankings for acute treatment benefits reported by interview participants ($N=40$) during virtual ranking exercise (lower value = higher ranking).

TABLE 4 Number of participants selecting each rank for each acute treatment benefit ($n = 40$).

	Rank									
Treatment benefit	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Pain relief	1	17	11	3	4	3	0	0	1	0
Relief of other symptoms	3	1	7	5	10	5	3	3	3	0
Absence of pain	1	17	6	3	1	3	2	3	2	2
Absence of other symptoms	2	1	8	9	6	4	2	3	4	1
Greater ability to participate	0	2	2	12	3	2	8	5	2	4
Greater ability to do physical things	2	0	1	2	5	3	4	5	10	8
Less "brain fog"	2	0	2	3	4	9	7	7	1	5
Improved feelings of well-being	1	2	0	3	2	5	8	7	7	5
Less need for other medications or treatments	1	0	3	0	5	5	4	5	6	11

Note: Gray shading indicates the mode; a rank of 1 indicates the benefit was the top priority; a rank of 0 indicates that the participant did not rank the item.

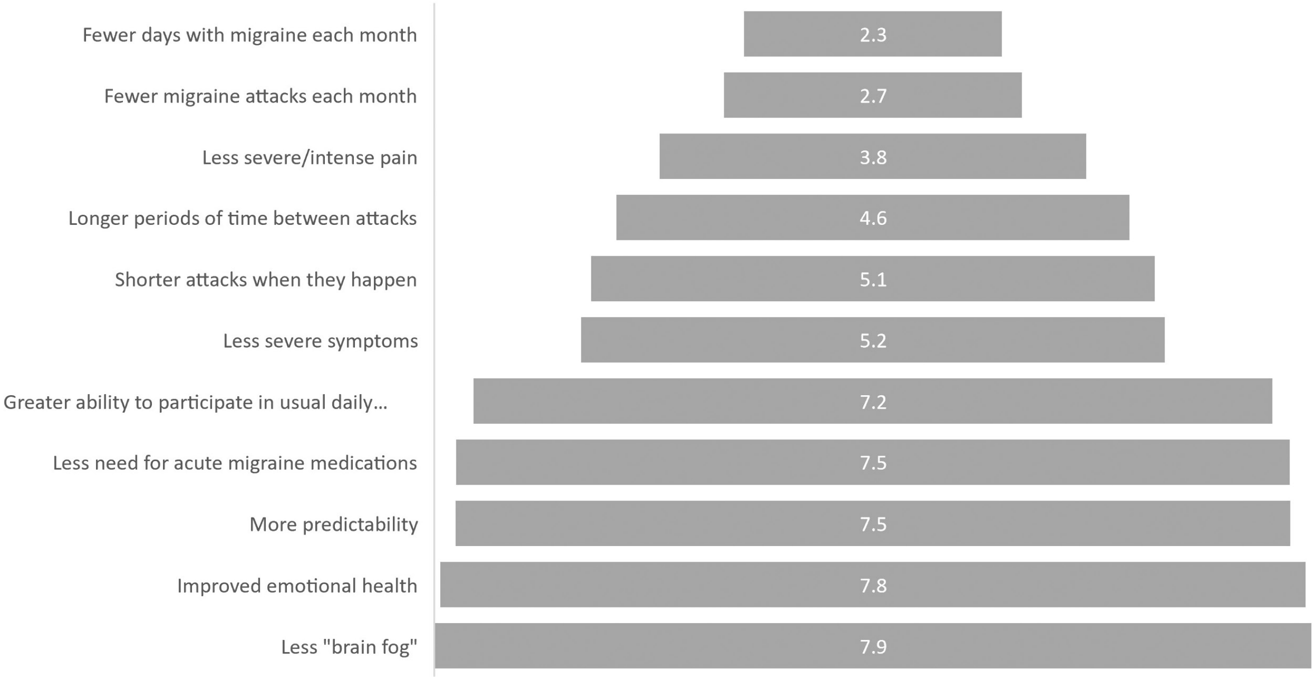

FIGURE 3 Average (mean) priority rankings for preventive treatment benefits reported by interview participants ($N = 40$) during virtual ranking exercise (lower value = higher ranking).

Difference in priorities for EM versus CM

Overall, the participants with EM and those with CM gave similar average rankings for acute treatment benefits (Figure 4). By contrast, the participants with CM on average ranked "more predictability" much higher than those with EM and gave a much lower average ranking for "greater ability to participate" (Figure 5). Conceptually, these benefits are related because the unpredictability of migraine attacks contributes substantially to impairments of daily life. For people with CM, the frequency of these unpredictable attacks results in a broad array of burdens, which may explain its higher ranking for this group. Unpredictability manifests in several ways as well: participants noted that migraine attacks can be unpredictable in when and how often they occur, but also in terms of which symptoms are present, how severe they are, and how long they last. The somewhat higher average rankings amongst those with CM for benefits such as shorter attacks, longer interictal periods, and less severe symptoms may reflect a desire for treatment that results in greater amounts of functional time over the course of a month. Importantly, the participants with CM often commented on the perceived tradeoffs of treatment and the ways this factored into their thinking. For example, one participant said, "*The main thing would probably be decreasing frequency. I think that's like the first. Second would be probably severity. Like if I can't have like less migraines, I'd rather them not be as bad. Those are like the two main things*" (00–29).

TABLE 5 Number of participants selecting each rank for each preventive treatment benefit ($n=40$).

	Rank											
Treatment benefit	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Fewer days with migraine	3	12	11	8	3	2	0	0	0	0	1	0
Fewer migraine attacks	0	11	13	6	5	2	1	1	0	1	0	0
Longer periods of time between attacks	1	2	3	8	6	7	5	4	2	1	1	0
More predictability	3	1	0	1	2	3	3	4	4	5	5	9
Less severe/intense pain	0	6	5	9	9	3	2	2	3	1	0	0
Shorter attacks	1	0	2	5	10	4	9	4	4	1	0	0
Less severe symptoms	4	3	3	0	2	9	7	5	1	4	1	1
Greater ability to participate in usual daily activities	3	0	1	0	1	4	2	9	7	4	6	3
Less "brain fog"	3	0	2	0	0	1	2	4	7	7	8	6
Improved emotional health	3	3	0	0	0	1	4	1	5	7	8	8
Less need for acute migraine medications	4	2	0	2	1	2	2	3	4	5	6	9

Note: Gray shading indicates the mode; a rank of 1 indicates the benefit was the top priority; a rank of 0 indicates the participant did not rank the item.

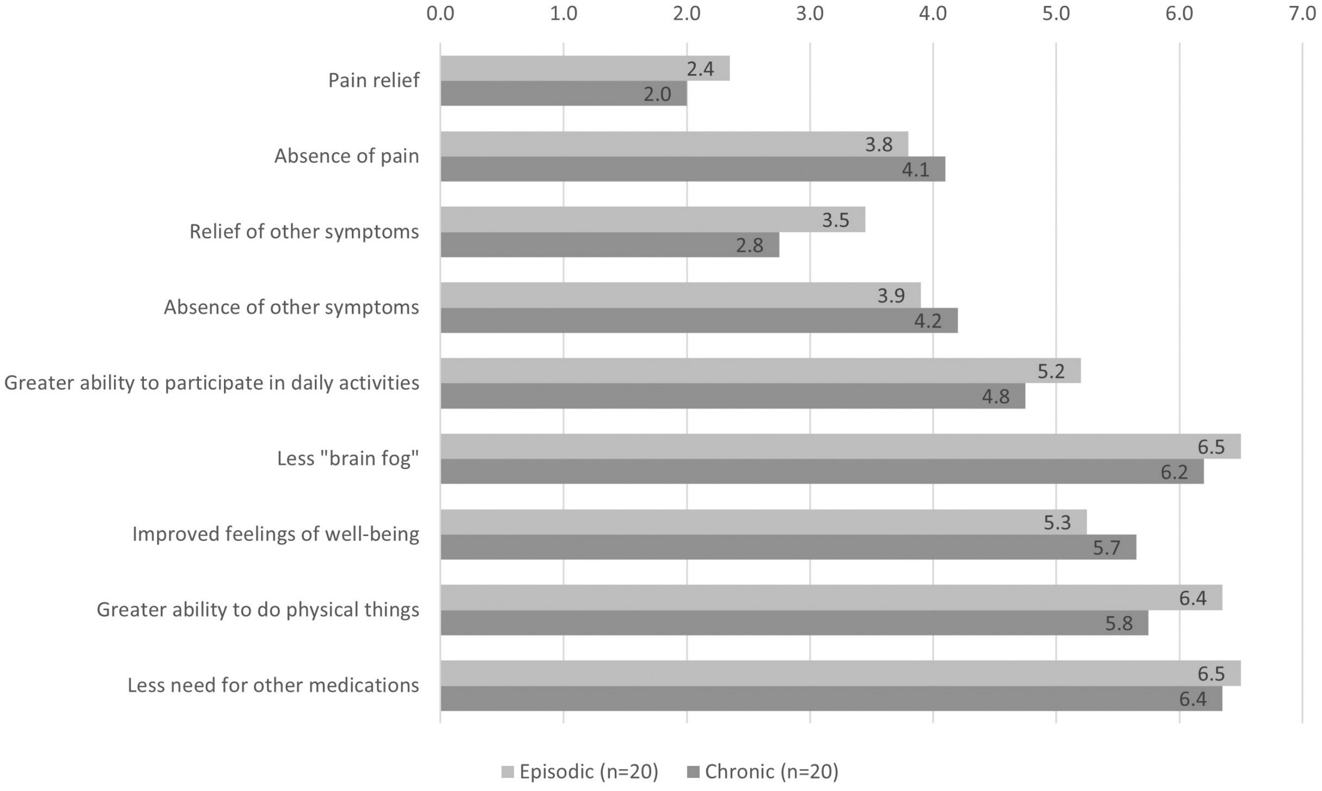

FIGURE 4 Comparison of average priority rankings for acute treatment benefits reported by participants with episodic ($n=20$) and chronic ($n=20$) migraine.

Themes in participant ranking rationales

A content analysis of participant comments during the ranking exercises demonstrated that several factors strongly influenced the ways that the participants prioritized benefits on each list. In all, 24 participants (60%) offered comments reflecting factors that influenced the way they ranked the outcomes provided.

Expectations about what treatment could achieve

About half of the participants ($n=21$) noted that their expectations about what medication could and could not do influenced their rankings. When participants believed that treatment could never achieve certain outcomes, they often ordered those benefits lower than their actual desire, including ranking them as lowest

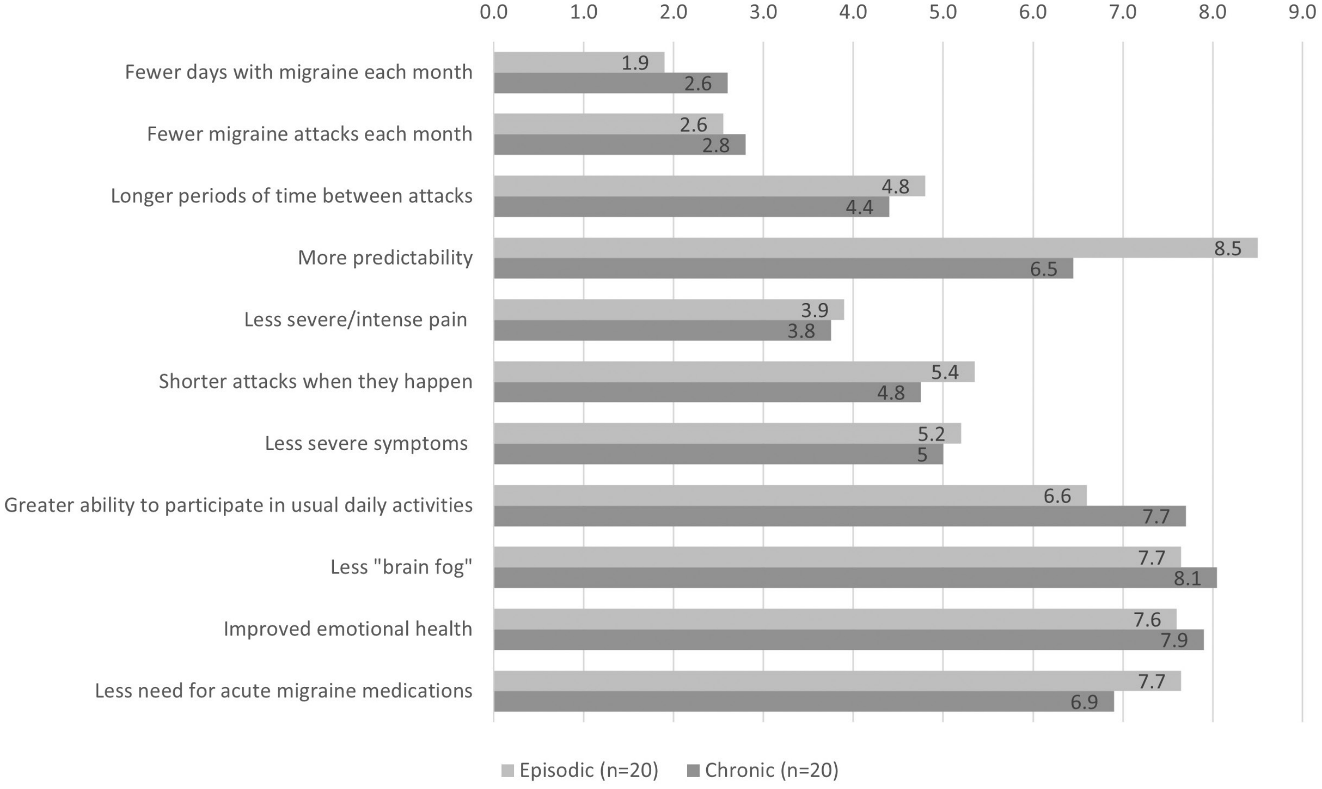

FIGURE 5 Comparison of average priority rankings for preventive treatment benefits reported by participants with episodic ($n = 20$) and chronic ($n = 20$) migraine.

priorities. As one participant observed, "[less need for medication, greater ability to do physical things] *those are the lowest priorities because I guess I'm always going to have a limitation to doing physical things. And I generally always needed some other form of medication or treatment. So, 90% of the time, those things I have to do anyway, so I wouldn't classify those are things that are important to me because, in 30 years or 40 years, there hasn't been a drug that has effectively gone through this whole list and changed all those items for me*" (00–04). For the acute treatment benefits, several participants noted that they selected a lower rank order for absence of pain because they did not believe it was a realistic outcome given their past experiences with treatment. One participant remarked, "*I think because ultimately that* [absence of pain] *would be the goal. I guess that would probably be better off first. But I guess being realistic about it, sometimes that's not always practical. Sometimes you don't get just 100% pain relief. But at the same time, it would be ideally absence of pain would be the goal*" (00–05). Another responded similarly, saying "*I guess I expect relief more than I expect absence of—like I think absence, of course, is the goal but not likely to happen*" (00–24). A third participant thought absence of pain "*just feels again like magically hypothetical*" (00–18).

Expectations about treatment side-effects influenced some rankings. One participant ranked less "brain fog" as a low priority and noted "*When you take something that messes with your CNS, you're never going to get something that cures the pain that doesn't create a side-effect. I just don't believe that's ever going to happen*" (00–04). By contrast, another participant ranked less "brain fog" second and explained "*Because a lot of times, when you do any medication, a side-effect is more brain focusing, or just a feeling of being drugged, and that's not fun*" (00–06).

Participants' expectations and beliefs about relationships among outcomes also influenced their rankings. For example, some participants who chose absence of pain as the most important benefit noted that they felt it was foundational and encompassed all other outcomes. As one participant said, "[With an absence of pain], *everything else will kind of take care of itself.*" (00–41). Another participant mentioned, "*If you ever have the pain, obviously absence of pain is the goal. So that's why I would put that at number one. And then relief of other symptoms. The other symptoms go hand in hand with pain based upon the descriptions, nausea, vomiting, sensitivity. Absence of pain is going to help with that*" (00–14).

Perceived tradeoffs and hierarchies of treatment benefits

Many participants were not simply ranking in order of pure importance but creating hierarchies or pathways amongst benefits, which then could result in a lower ranking for an ultimately desired benefit or a higher ranking for a benefit seen as a necessity. Seven participants (18%) ranked outcomes lower, including ranking them as lowest priorities, when they believed that achieving another high-ranked benefit would result in achievement of these outcomes. One participant commented, e.g., "*Greater ability to participate in daily activities. Put that one last. Yeah, because you're able to do—if you don't have them, I mean, you know, the less migraine attacks you have, you're going to be able to participate in everything. You'll be able to do your day-to-day activities at home, your day-to-day—be able to exercise, you're eating better, you're eating healthier*" (00–13). Four participants (10%) ranked less "brain fog" higher because cognitive function was important in their daily lives. One participant noted, e.g., "*I'm a software engineer, so I need to be able to think*" (00–42). Another said, "*If I've got brain fog, I'm not completely there, which would be the same reason to follow that with greater ability to participate in daily activities, because there's no point in me being there if I'm not mentally there*" (00–23).

The variability and unpredictability of migraine experiences made the exercise challenging for participants who wanted to consider layers of tradeoffs. For example, one participant mulled over how to order preventive treatment benefits to achieve better quality of life both during and between attacks: "*I'm just trying to think of what would be the best case scenario, if—like if something were working to prevent them from happening as frequently, it seems like the less severe pain would be the best of those three and then longer periods of time in between would mean higher quality of life on those days and then if I did have it, then less severe symptoms would be better.*" (00–08). Another participant (00–14) had difficulty deciding exactly how different acute benefits should be ordered to achieve the actual outcome they wanted, which was absence of pain and ability to get on with life, noting "*I think they all interrelate. […] you can't do daily activities without getting rid of the brain fog or the pain relief. So, you got to start with that and work your way through each one to get to the other.*" Another participant put it very succinctly: "*Dang. Like I said, all of these are like number one*" (00–16).

Additional potential treatment outcome priorities identified

Participants identified several other priorities related to the benefits of treatment that were important to them. These included benefits such as limited side-effects (53%, $n=21$ participants) and the reliability of the treatment's effectiveness (55%, $n=22$). One participant commented on their experience with several treatments saying, "*sometimes they worked and sometimes they didn't, and then you feel like you can't trust this drug and you're playing Russian roulette every time […] So if it's not somewhat consistent, it's worthless. For me, it has to be, like, at least 75% to 80% effective.*" Participants also mentioned mode of administration (63%, $n=25$) and availability or affordability of medication (13%, $n=5$) as important factors when considering treatment tradeoffs. One participant noted, e.g., "*I wish there was ones that I could take more often […] like if I have really bad migraines all week, I cannot take this abortive medication every day or anything. I have to really limit it. So, I guess it would be nice to have something that was more accommodative to that. The one thing that I do prefer about injections is that you don't have to swallow water or whatever you have to drink to take the pill because, when I'm so nauseous like that, it's very hard to swallow and drink*" (00–24).

Limitations

The way that "pain relief" and "absence of pain" were defined (Figure 1) may not have matched the way many participants thought about these concepts based on the label phrases alone, and this may have influenced rankings. Pain relief was defined as a lessening of pain after a dose of acute treatment, while absence of pain was defined as pain freedom after treatment. Interview transcripts suggest that some participants interpreted "absence of pain" as prevention of pain and ranked it lower because this outcome seemed less realistic.

The acute treatment benefits list was always offered first and benefits on both lists were always offered in the same order, which may have resulted in some primacy bias.

Participants could offer comments on other benefits of treatment but were not asked to rank them or to explain their relationship to the listed benefits. For example, although many people mentioned the reliability of treatment efficacy, the relationship between this benefit and other outcomes is unknown. This is of particular interest because the benefit of "more predictability" was included but not ranked highly by most participants, leaving an open question about how people with migraine think about the reliability of treatment efficacy relative to predictability in the number or length of attacks.

Finally, the size and composition of the sample was determined by the overall goals of the larger MiCOAS project. A larger or randomly selected sample may have produced different results from this structured ranking exercise.

CONCLUSION

Understanding the ways patients view and prioritize potential treatment benefits is critically important to therapy development, clinical trial design, and clinical practice. The existing clinical emphasis in acute treatment on migraine symptom prevention and relief aligns with overall priorities expressed by the overwhelming majority of the MiCOAS qualitative interview study participants; however, it is important to acknowledge that these priorities were frequently ranked highly with the assumption that they would necessarily lead to other benefits on the list. If a treatment offered pain relief, but no other benefits, it seems fair to say that these participants might find that treatment fell short of their needs. Similarly, clinical priorities for preventive treatment related to overall reduction in migraine attacks aligned with priorities selected by most study participants. Importantly, however, participants with CM—the population most likely to use and benefit from preventive treatments—also prioritized predictability. This, in turn, aligned with the identified gap in the pre-defined list of potential benefits: reliability of treatment efficacy. Put simply, people living with migraine want treatments that work consistently and provide them with a greater sense of confidence that they can make plans and live their lives.

The ranking exercise results appear to support the conclusion that clinical trial research and drug development are focusing on outcomes that are prioritized by people living with migraine. However, in this study, the numeric results do not give a fully accurate picture of what truly matters to people using these treatments. Rather, the ranking exercises revealed complexities that intervened and influenced the rankings offered by most participants. These complexities included assumptions about how outcomes lead to one another, assumptions about what migraine therapies can or ever will be able to achieve, and individual assessments of the tradeoffs or pathways among benefits.

From the standpoint of clinical outcomes assessment, these findings underscore the importance of taking a broader view of how treatment efficacy should be evaluated. Participants in this study expressed strong assumptions that addressing pain and reducing the number of days with migraine symptoms will necessarily lead to broader improvements, such as improved ability to carry out daily activities that require physical or cognitive functioning. Nevertheless, all the participants used prescription treatments with proven efficacy and all of them still reported substantial impairment of functioning. These impairments were related, at least in part, to the limitations of treatments that may not work every time, may cease to be effective over time, or may not deliver sufficient benefits quickly enough or for long enough. These features of migraine treatments could be assessed to develop a better understanding of the relationships between pain relief or attack prevention and the other outcomes that matter to patients. Similarly, consistent assessment of core functioning outcomes alongside measures of symptom severity and frequency could permit a better understanding of which symptoms must be relieved and to what degree to deliver improvements in function. Future migraine research would be improved by including these types of additional outcomes so that clinicians, scientists, regulatory agencies, and patients can better understand the benefits and drawbacks of available treatments.

AUTHOR CONTRIBUTIONS

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

ACKNOWLEDGMENTS

The authors would like to thank the FDA including Robyn Bent, MS; the CHAMP for assisting in recruitment; and Alyssa A. Uzumcu, BA, Alexis Cooke, PhD, Nancy M. Touba, MPH, David W. Dodick, MD, Walter F. Stewart, PhD, MPH, Elizabeth Nicki Bush, MHS, Roger Cady, MD, Katie M. Golden, BA, Peter Goadsby, MD, PhD.

FUNDING INFORMATION

This manuscript was supported by the FDA of the United States Department of Health and Human Services (HHS) as part of a financial assistance award (UH3FD006795) totaling $1,599,834 with 100% funded by the FDA/HHS. The contents are those of the authors and do not necessarily represent the official views of, nor an endorsement by, FDA/HHS or the United States Government.

CONFLICT OF INTEREST STATEMENT

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. **Calvin J. Hall, III**, was 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 receives research funding from the National Headache Foundation and Amgen. She has been a consultant to Allergan/Abbvie, Amgen, Lilly, Lundbeck, and Teva Pharmaceuticals. **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. **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. **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. **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 CtrlM Health. In addition, he receives royalties for Wolff's Headache, 7th and 8th editions. **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.

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How to cite this article: Mangrum R, Gerstein MT, Hall CJ III, et al. Priority acute and preventive migraine treatment benefits: Results of the Migraine Clinical Outcome Assessment System (MiCOAS) qualitative study of people living with migraine. *Headache*. 2023;63:953-964. doi:10.1111/head.14521