MiCOAS- A Qualitative Study of Migraine Experience and Treatment Priorities Among People Living with Migraine: Final Report

Date and Version	January 27, 2021; Version 3.0
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Funding Source	The research detailed in this report was supported by the FDA's Center for Drug Evaluation and Research pilot grant program "*Development of Standard Core Clinical Outcomes Assessments (COAs) and Endpoints*" (RFA-FD-19-006).

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1 Executive Summary

1.1 Study Goals and Objectives

Migraine is a highly prevalent and potentially severely disabling neurological disease that is associated with significant economic, social, and personal burden. Treatments for migraine fall under 2 broad categories, acute and preventive. The field of migraine is currently experiencing an explosion in new treatment development; in recent years, the U.S. Food and Drug Administration (FDA) has approved several new acute and preventive pharmacologic treatments for migraine as well as a number of devices. s. FDA has also recently begun to focus on ensuring that outcomes and endpoints in clinicial trials are patient-focused which includes “identifying information that is most important to patients related to treatment benefit, risks, and burden [...].”

To work towards meeting the goal of patient-focused outcomes and endpoints, Vector Psychometric Group, LLC in collaboration with Albert Einstein College of Medicine was awarded U.S. Food and Drug Administration (FDA) Grant # 1UG3FD006795-01 to support the development of a patient-informed and publicly available standard core set of COAs for migraine to be known as the *Migraine Clinical Outcome Assessment System* (MiCOAS). A key component of MiCOAS is the collection of qualitative data about the migraine experience via interviews with persons living with the condition. This report describes findings from the first phase of these qualitative interviews.

1.2 Methods

Exploratory, semi-structured qualitative interviews (N=40) were conducted in order to capture the experiences of persons living with migraine, with a specific focus on understanding the potential treatment benefits that persons with this disease value most. Individuals with migraine were recruited through a study announcement disseminated by the Coalition for Headache and Migraine Patients (CHAMP), a patient advocacy organization for migraine, headache, and cluster diseases. A total of N=428 individuals responded to the announcement and were eligible for participation, from which 40 participants were selected through iterative purposeful sampling. Interviews were coded using a hybrid deductive/inductive approach informed by both a preliminary codebook constructed a-priori and open codes developed iteratively at each interview wave. Case counts, average treatment priority rankings, and thematic content analysis were used to identify key concepts and themes within multiple domains of interest. An examination of saturation in full and stratified (chronic, episodic) samples was conducted. A review of saturation grids suggests that concept saturation was reached in both total and stratified groups.

1.3 Results

Analysis of interview data from total and stratified samples identified a set of findings across multiple key domains. A summary of these key findings is provided below:

- Cognitive Interference: Participants described disruptive, migraine-related deficits in sustained attention, executive function, language/speech production, receptive language, and memory.
- Treatment Priorities: Participants’ desire to function at home, school, work, and in social settings seemed to motivate their expressed priorities for acute/preventive treatment including rapid pain/symptom relief, substantial reduction in migraine frequency, and improved cognition.

- Symptom Burden: Participants experienced a very wide range of symptoms that occured in and varied across multiple phases of their migraine attacks. With such substantial variation in symptom presentation across and within subjects, there does not appear to be a single, or even several, universal symptom profiles emerging from the qualitative descriptions of participants' migraine experiences.
- Changes in Mood/Emotions: Irritability/impatience was the most frequently cited attack-related negative emotion/mood change, followed by anxiety and depression. Although anxiety and depression are experienced less frequently, they may hold greater implications for the health and wellness of individuals with migraine both during and in the period in-between attacks.
- Impact on Daily Living: The headache phase of the migraine attack was equated with essentially zero function defined by the complete absence of activities, both physical and cognitive. Daily function during pre-headache, post-headache, and inter-ictal periods were marked by greater variation within and across participants.
- Physical Limitations: Migraine-related physical limitations were largely attributed to experiences with worsening pain due to movement.
- Migraine Tracking: Participants reported using a variety of mediums to track their migraine attacks and cited both benefits (e.g., identifying triggers and effectiveness of treatment) and considerable barriers (e.g., logging during attacks, pinpointing symptom patterns/triggers) to consistent migraine tracking.
- COVID-19 Impacts: COVID-19-related impacts centered on changes to care access and treatments (disruptions and benefits), daily life, and frequency and severity of migraine attacks. However, symptom profiles, disease impacts, and treatment priorities did not fundamentally change as a result of the pandemic.
- Aura v. No Aura: Across most concepts/domains migraine experience among participants with aura did not appear to differ in a substantial way from the total sample. Some participants with aura did express an increased focus on associated symptom relief relative to others.
- Chronic v Episodic: A stratified analysis of chronic v. episodic interview participant data found, in large part, more commonalities than differences between groups. However, this comparative analysis did identify some distinctions worthy of future consideration. This includes a higher inter-ictal symptom burden despite less time spent in the inter-ictal state, more frequently reported pain during pre-headache, and more experiences with lingering cognitive deficits during post-headache among participants with chronic migraine when compared to those with episodic migraine.

1.4 Conclusion

This exploratory qualitative inquiry established a complex constellation of migraine symptoms and impacts that together, motivate patient priorities for treatment. Findings from this study will be examined alongside results from an exhaustive literature review, input from the study expert technical advisory committee, and additional discussions with the MiCOAS project team and FDA to a identify a list of potential/preliminary outcomes of interest and target areas of focus for the next phase of qualitative work. The next phase of qualitative interviews will be designed to further inform identification of a core outcome set, construction of new items/instruments (as needed), and content validation of existing measures.

2 Introduction/Background

Migraine is a highly prevalent and potentially severely disabling neurological disease that is associated with significant economic, social, and personal burden.[1-3] It is a chronic disorder characterized by episodic attacks, which can impact the functioning of the individual in multiple roles and settings including occupational, academic, social, familial, and personal. [2-8] The 2016 Global Burden of Disease analysis reported that migraine is the second most disabling disease worldwide, second only to low back pain, and that migraine caused 45.1 million years lived with disability in 2016 alone.[9]

There are many subtypes of migraine. One important distinction is between episodic migraine and chronic migraine.[10] These groups are largely distinguished by the number of headache days that occur each month; chronic migraine requires 15 or more headache days per month or more than 3 months with at least 8 days/month having features of migraine headache. Treatments for migraine fall under 2 broad categories, acute and preventive.[4,6] Acute migraine treatments aim to resolve migraine symptoms when an attack occurs and return individuals to a "normal" level of functioning as quickly as possible.[11] Preventive migraine treatments aim "to reduce the frequency, duration, or severity of attacks".[12] Both acute and preventive migraine treatments have broader aims to increase individuals' health-related quality of life by decreasing disability, impact, and burden associated with migraine.

In recent years, the FDA has approved several new acute and preventive migraine treatments and the field of migraine is currently experiencing an explosion in new treatment developments. However, there is limited evidence of content validity for some of the existing clinical outcome assessments (COAs) used in acute and preventive migraine treatment trials, particularly for legacy patient-reported outcome measures (PROMs) that were developed prior to the FDA's directive that outcomes and endpoints should be patient-focused. Most notably, several of these assessments were developed with limited explicit input from people with migraine.

In recent acute migraine trials, common coprimary endpoints are pain freedom and absence of the individual's designated most bothersome symptom (MBS) at 2 hours post-dose. In evaluation of preventive treatment efficacy, the standard primary endpoint has been reduction in mean migraine (or headache) days per month. The current study was designed, in part, to understand the extent to which these endpoints fully capture what people with migraine value most in terms of treatment efficacy. Further, it is unclear if commonly used single- and multi-item patient-reported instruments that assess broader quality of life, functional impact, and disability do so in a manner that is relevant to individuals with migraine and comprehensive. Taken together, these trends demonstrate a clear need to better understand the experiences of people with migraine and incorporate this information in the development of a core set of migraine therapy endpoints.

2.1 Study Goals and Objectives

To work towards meeting the goal of patient-focused outcomes and endpoints, Vector Psychometric Group, LLC in collaboration with Albert Einstein College of Medicine was awarded U.S. Food and Drug Administration (FDA) Grant # 1UG3FD006795-01 to support the development of a patient-informed and publicly available standard core set of COAs for migraine. This project to develop the *Migraine Clinical Outcome Assessment System* (MiCOAS) focuses on incorporating the experience of people living with migraine and feedback regarding outcomes most meaningful to them.

A key component of this work is the conduct of qualitative research interviews to capture the experiences of persons living with migraine, with a specific focus on understanding the treatment benefits that persons with this disease value most. The MiCOAS team has partnered with Pharmerit to provide support for the qualitative data collection and analysis components of the project, This report describes findings from these qualitative interviews, outlining key insights on people's experience living with migraine and their priorities for acute and preventive treatment.

3 Methods

3.1 Recruitment and Sampling

A study announcement and invitation to participate was distributed to individuals living with migraine via the Coalition for Headache and Migraine Patients (CHAMP, https://headachemigraine.org/) through their social media and partner platforms and communications. CHAMP is a coalition of patient advocacy organzations and is comprised of many advocacy groups and individuals. They focus on identifying the unmet needs of those with headache, migraine, and cluster headache diseases, and continuously work to better support people with migraine and their caregivers. As such, our collaboration with CHAMP provided a unique opportunity for people with migraine to be informed about and participate in this patient-centered research effort.

The study announcement directed individuals interested in participating to a designated study website where they received more detailed information on the study, completed an electronic screening questionnaire, provided their informed consent to participate, and answered additional questions about their sociodemographic data and headache history . Screen shots from the e-screening, consent, and data collection platform used to capture this information can be found in Appendix A.

Through this recruitment mechanism we received interest and information on N=428 self-selected individuals who were deemed eligible to participate based on their responses to the study screener. This self-report study screener was structured to assess alignment with the below inclusion/exclusion criteria.

3.1.1 Inclusion Criteria

To be eligible for <u>inclusion</u> in the study, at the time of screening, a person needed to:

- Be a resident of the US
- Be between 18 and 75 years of age
- Report being diagnosed with migraine by a healthcare professional
- Report experiencing any two out of the three below clinical criteria for migraine:
    - Limited activities on at least 1 day over the last 3 months because of their headaches (disabilty)

    - Bothered by lights when having a headache (photophobia)
    - Gets sick to their stomach or nauseated with their headache (nausea with or without vomiting)
- Be able to distinguish between a migraine day and other types of headache days
- Be proficient in the English language (i.e., ability to read, write, speak, and understand English well enough to complete informed consent process and take part in the interview).
- Provide informed consent to participate in the study and complete the web-based informed consent documentation
- Be willing to have their interview audio-recorded for the purpose of transcription and data analysis

3.1.2 Exclusion Criteria

An individual reporting any of the following at the time of screening was excluded from this study:

- Self-report of a medical diagnosis of a pain disorder, or any other clinically significant disease(s) that might interfere with the person's ability to provide non-confounded descriptions of their experience with migraine symptoms and impacts. These include:
    - Multiple Sclerosis
    - Epilepsy
- Self-report of a medical diagnosis of severe mental illness, cognitive impairment, or any other disorder that compromises the ability to give informed consent. These include:
    - Schizophrenia
    - Bi-polar disorder
    - Cognitive impairment
    - Alzheimer's disease or dementia
- Self-reported alcohol or drug abuse over the past 3 months
- Self-reported symptoms or hospitalization related to COVID-19 infection

From this large potential participant pool, we conducted iterative purposeful sampling to target variation in our sample and ensure the data represents a wide range of experiences. This included specific quotas around headache days per month (Table 1), but also efforts to diversify the sample by gender, race, ethnicity, age, education, employment status, income, clinical characteristics, and acute and preventive medication use. Before each interview wave (N=4-6 interviews/wave), the qualitative research team reviewed and prioritized participants for sampling based on these considerations as well as emerging concepts that the team felt should be further explored through information-rich cases.

Table 1. Targeted Sampling Stratification by Headache Frequency

Headache Frequency	Approximate Targeted Sample
0-1 headache day a month	n=2
2-3 headache days a month	n=6
4-7 headache days a month	n=6
8-14 headache days a month	n=6
15-23 headache days a month	n=18
24 or more headache days a month	n=2
TOTAL	**N=40**

3.2 Data Collection

In a strategic effort to assess the interview guide's function and evaluate the implications of COVID-19 on the study team's ability to collect usable data before initiating full scale data collection, we conducted an initial set of four pilot interviews (n=4) and one group practice interview with patient advocates who also live with migraine (n=2 participants). Following these interviews, the qualitative research team paused to review the collected data and discuss the initial observations with the broader research team and FDA. Based on these initial interviews and minor interview guide revisions to reduce observed redundancy and clarify question language, the research team and FDA felt comfortable moving forward with full scale qualitative data collection.

The MiCOAS research team conducted N=40 semi-structured qualitative interviews as part of this qualitative exploratory phase. Qualitative interviews utilized a combination of techniques to elicit rich responses including broad exploratory questions followed by structured probes as needed, a migraine attack reconstruction, and a web-based visual exercise to rank treatment priorities. The interview guide for this study can be found in Appendix B. In the virtual ranking exercise, participants were shown a pre-specified list of possible acute and preventive pharmacologic treatment benefits/outcomes using QuestionPRO and the Microsoft Teams screen sharing function and asked to rank those items in order of importance to the participant while providing a "think aloud" explanation of their rankings. Screen shots of the virtual ranking exercise can be found in Appendix C-D.

3.3 Data Analysis

All interviews (N=40) were coded using a hybrid deductive/inductive approach, where codes are informed both by a preliminary codebook constructed a-priori and open codes developed iteratively at each interview wave to reflect the verbatim words of participants. During this process, all codes were reconciled through team consensus. All interview data were managed using Atlas.ti (v8.0) software.

Where appropriate, frequency counts and average treatment rankings were utilized to offer a high-level overview of coded content and provide the research team a starting point for additional analyses. Frequency counts and treatment rankings were also stratified on migraine phases (where appropriate) and migraine classifications (e.g., episodic vs. chronic). Concept frequencies, case counts, and priority rankings alone do not provide a full picture of the experience of individuals living with migraine as was reflected through their thoughtful insights and observations. Thus, thematic content analysis was undertaken to identify key patterns within the data and to categorize coded information into recurrent themes.

3.3.1 Concept Saturation

Nearly 400 context and content codes were identified during the coding process representing a wide range of domains including symptoms, emotions/mood, cognitive interference, daily living, physical limitations, acute and preventive treatment priorities, COVID-19 impacts, barriers to care, migraine tracking, and migraine disease history. Concepts endorsed in each interview wave were measured against previous interviews waves to identify the appearance of novel concepts. This process continued through a total of eight interview waves. All domains were assessed for saturation in the total (N=40) interview sample as well as in stratified chronic (n=20), and episodic (n=20) interview samples. Saturation results are summarized in saturation grids appended to this report (Appendix E). Saturation grids allow for an examination of first coding appearance by transcript and interview group and To determine point of saturation, codes were sorted within each domain by first reported appearance. The research team then examined the sorted codes for natural cut-off points indicative of a shift in the pace in which subsequent new codes appeared. For example, within the physical limitation domain, 19 out of 21 codes (90%) appeared for the first time within the first three interview groups. After the third interview group, only two additional codes were cited in interview groups 4 and 5, suggesting that saturation of concepts for this domain was largely achieved by interview group 3 (Table 2).

An examination of all saturation grids and related metrics demonstrates increasingly fewer newly cited codes in later stages of interview and no new cited concepts after interview group 6 (out of 8). Together, this suggests that data collection has reached concept saturation across all domains in both total and stratified (chronic, episodic) samples. A high-level summary of saturation metrics by domain for total, episodic, and chronic interview samples can be found in Table 2. A comparison of stratified saturation metrics did not identify any notable patterns of variation in saturation between migraine subgroups.

Table 2. Concept Saturation Summary: Total and Stratified Samples

Domain	Code Volume	Saturation Metrics (N=40)	Episodic Metrics (n=20)	Chronic Metrics (n=20)
Symptoms*	~121 codes	89% of codes within first 73% of interviews (Group 6)	94% of codes within first 80% of interviews (Group 6)	94% of codes within first 80% of interviews (Group 6)
Emotions/Mood*	~47 codes	85% of codes within first 35% of interviews (Group 3)	78% of codes within first 35% of interviews (Group 3)	78% of codes within first 20% of interviews (Group 2)
Cognitive Interference*	~36 codes	84% of codes within first 30% of interviews (Group 3)	80% of codes within first 50% of interviews (Group 4)	82% of codes within first 35% of interviews (Group 3)
Daily Living*	~39 codes	100% of codes within first 35% of interviews (Group 3)	100% of codes within first 45% of interviews (Group 4)	86% of codes within first 45% of interviews (Group 4)
Physical Limitations*	~21 codes	90% of codes within first 35% of interviews (Group 3)	75% of codes within first 35% of interviews (Group 3)	78% of codes within first 55% of interviews (Group 5)
Treatment Priorities	~40 codes	100% of codes within first 40% of interviews (Group 4)	97% of codes within first 40% of interviews (Group 4)	95% of codes within first 35% of interviews (Group 3)
COVID-19	~23 codes	96% of codes within first 55% of interviews (Group 5)	100% of codes within first 65% of interviews (Group 5)	95% of codes within first 70% of interviews (Group 6)
Other Content/Context	~72 codes	96% of codes within first 45% of interviews (Group 4)	85% of codes within first 40% of interviews (Group 4)	86% of codes within first 35% of interviews (Group 3)

*Among later reported first time codes, majority of concepts were previously identified and attributed through coding to other phases of the migraine attack

A comparison of code frequency across episodic and chronic migraine interview sub-samples is provided in Appendix F.

4 Characteristics of Study Participants

A summary of participant characteristics across interviewed and eligible sample populations can be found in Table 3. A comparison between interviewed and eligible samples for this study demonstrates efforts to oversample on certain demographic characteristics including gender (i.e., male), race/ethnicity (i.e., Non-White and Hispanic), education (i.e., less than college degree), income (i.e., lower income brackets), and migraine frequency (i.e., episodic). Most targeted quotas around headache days per month were met. However, the research team was unable to identify available participants in the 0-1 headache day per month range.

Table 3. Comparison of Interview and Eligible Participant Characteristics

Variable	Category	Total Interview Sample (N=40)	Total Eligible Sample (N=428)
Age, n (%)	18-24 years old	5 (12.5)	18 (4.2)
	25-34 years old	5 (12.5)	61 (14.3)
	35-44 years old	12 (30.0)	113 (26.4)
	45-54 years old	9 (22.5)	125 (29.2)
	55-64 years old	4 (10.0)	83 (19.4)
	65 years and older	5 (12.5)	28 (6.5)

Variable	Category	Total Interview Sample (N=40)	Total Eligible Sample (N=428)
Gender, n (%)	Women	31 (77.5)	401 (93.7)
	Men	7 (17.5)	22 (5.1)
	Trans Man	1 (2.5)	1 (0.2)
	Genderqueer/Gender Non-Binary	1 (2.5)	4 (0.9)
Race*, n (%)	American Indian or Alaskan Native	4 (10.0)	9 (2.1)
	Asian	3 (7.5)	8 (1.9)
	Black or African American	9 (22.5)	18 (4.2)
	Native Hawaiian or Other Pacific Islander	1 (2.5)	1 (0.2)
	White	27 (67.5)	396 (92.5)
	Other	1 (2.5)	6 (1.4)
	Prefer not to answer	1 (2.5)	8 (1.9)
Ethnicity/race*, n (%)	Hispanic	9 (22.5)	21 (4.9)
	American Indian or Alaskan Native	1 (0.2)	2 (0.5)
	White	7 (17.5)	17 (4.0)
	Other	1 (0.2)	2 (0.5)
	Prefer not to answer	1 (0.2)	2 (0.5)
	Non-Hispanic	31 (77.5)	407 (95.1)
Relationship Status, n (%)	Married or partnered	19 (47.5)	277 (64.7)
	Not married or partnered	21 (52.5)	151 (35.3)
Adults in Household, n (%)	None	8 (20.0)	70 (16.4)
	1	16 (40.0)	230 (53.7)
	2	11 (27.5)	91 (21.3)
	3	4 (10.0)	27 (6.3)
	4	1 (2.5)	9 (2.1)
	5 or more	-	1 (0.2)
Children in Household, n (%)	None	12 (65.0)	296 (69.2)
	1	5 (12.5)	57 (13.3)
	2	5 (12.5)	52 (12.1)
	3	2 (5.0)	16 (3.7)
	4	1 (2.5)	4 (0.9)
	5 or more	1 (2.5)	3 (0.7)
Education, n(%)	Grade 12 or GED equivalent	3 (7.5)	11 (2.6)
	Associates degree, technical school, or trade apprenticeship	8 (20.0)	70 (16.4)
	Some college (No degree awarded)	10 (25.0)	60 (14.0)
	College Degree (BA, BS, or similar)	11 (27.5)	155 (36.2)

Variable	Category	Total Interview Sample (N=40)	Total Eligible Sample (N=428)
	Advanced or graduate/post-graduate degree (PhD, MD, JD, PharmD, or similar)	8 (20.0)	130 (30.4)
	Prefer not to answer	-	2 (0.5)
Employment*, n (%)	Paid employment	22 (55.0)	209 (48.8)
	Student	8 (20.0)	28 (6.5)
	Homemaker	3 (7.5)	34 (7.9)
	Retired	6 (15.0)	47 (11.0)
	Unemployed	2 (5.0)	27 (6.3)
	Disabled (or on disability or leave of absence)	10 (25.0)	127 (29.7)
	Other	1 (2.5)	13 (3.0)
	Prefer not to answer	-	2 (0.5)
Household Income, n (%)	Under $12,999	2 (5.0)	19 (4.4)
	$13,000 to $21,999	6 (15.0)	33 (7.7)
	$22,000 to $49,999	10 (25.0)	82 (19.2)
	$50,000 to $74,999	6 (15.0)	76 (17.8)
	$75,000 to $99,999	4 (10.0)	59 (13.8)
	$100,000 and over	8 (20.0)	118 (27.6)
	Prefer not to answer	4 (10.0)	41 (9.6)
Migraine Subtype by Frequency, n (%)	Chronic Migraine	20 (50.0)	254 (59.3)
	Episodic Migraine	20 (50.0)	174 (40.7)
Average Number of Headache Days per Month, n (%)	0-1	-	1 (0.2)
	2-3	6 (15.0)	13 (3.0)
	4-7	8 (20.0)	55 (12.9)
	8-14	6 (15.0)	105 (24.5)
	15-23	18 (45.0)	98 (22.9)
	24 or more	2 (5.0)	156 (36.4)
Acute Pharmacologic Treatments (within past year), n (%)	Yes	40 (100)	424 (99.1)
	No	-	4 (0.9)
Current Preventive Pharmacologic Treatments, n (%)	Yes	35 (87.5)	372 (86.9)
	No	5 (12.5)	56 (13.1)
Current Opioid and Barbiturate Use, n(%)	Yes	3 (7.5)	24 (5.6)
	No	37 (92.5)	404 (94.4)
Current Opioid Use, n (%)	Yes	8 (20.0)	86 (20.1)

Variable	Category	Total Interview Sample (N=40)	Total Eligible Sample (N=428)
	No	32 (80.0)	342 (79.9)
Current Barbiturate Use, n (%)	Yes	7 (17.5)	72 (16.8)
	No	33 (82.5)	356 (83.2)

*Total percent exceeds 100 because participants are able to identify with more than one race and/or employment status category

A summary of self-reported acute and preventive medication, herbal, and vitamin treatment use among the interviewed sample is provided in Table 4 below. This summary reflects a wide range of utilized therapeutics. Neurostimulation and Biobehavioral treatment are not reported here.

Table 4. Self-Reported Acute (Within Past Year) and Preventive (Current) Medication Use Among Interview Participants (OTC and Prescription) (N=40)

Variable	Category	Total Sample (N=40)
Type of Acute Pharmacologic Treatment, n (%)	Acetaminophen, aspirin, caffeine (generic)	10 (25.0)
	Acetaminophen with codeine (generic)	1 (2.5)
	Aleve/Naproxen Sodium*	12 (30.0)
	Aleve (naproxen sodium)	8 (20.0)
	Naproxen sodium (generic)	6 (15.0)
	Almotriptan (generic)	1 (2.5)
	Anaprox (naproxen)	1 (2.5)
	Aspirin	3 (7.5)
	Butorphanol tartrate (generic)	1 (2.5)
	Cambia/Diclofenac*	4 (10.0)
	Cambia (diclofenac)	2 (5.0)
	Diclofenac (generic)	3 (7.5)
	Celebrex (celecoxib)	1 (2.5)
	Compazine/Prochlorperazine*	6 (15.0)
	Compazine (prochlorperazine)	6 (15.0)
	Prochlorperazine (generic)	2 (5.0)
	Demerol (meperidine)	1 (2.5)
	DHE-45 injection (dihydroergotamine)	1 (2.5)
	Dihydroergotamine (generic)	1 (2.5)
	Excedrin*	7 (17.5)
	Excedrin (acetaminophen + aspirin + caffeine)	4 (10.0)
	Excedrin “Generic” (acetaminophen + aspirin + caffeine)	2 (5.0)
	Excedrin Migraine (acetaminophen + aspirin + caffeine)	7 (17.5)
	Fioricet or Esgic (butalbital + caffeine + acetaminophen) with or without codeine	6 (15)
	Fiorinal (butalbital + caffeine + aspirin) with or without codeine	1 (2.5)

Variable	Category	Total Sample (N=40)
	Flurbiprofen (generic)	1 (2.5)
	Frova/Frovatriptan*	5 (12.5)
	Frova (frovatriptan)	2 (5.0)
	Frovatriptan (generic)	4 (10.0)
	Hydrocodone with or without acetaminophen (generic)	3 (7.5)
	Imitrex (sumatriptan) nasal spray	2 (5.0)
	Imitrex (sumatriptan) pills or tablets/capsules	8 (20.0)
	Inodcin (indomethacin)	1 (2.5)
	Maxalt/Rizatriptan*	15 (37.5)
	Maxalt (rizatriptan)	13 (32.5)
	Rizatriptan (generic)	6 (15.0)
	Meloxicam (generic)	2 (5.0)
	Midrin (Isometheptene + dichloralphenazone + acetaminophen)	2 (5.0)
	Migranal nasal spray (dihydroergotamine)	1 (2.5)
	Mobic (meloxicam)	1 (2.5)
	Motrin/Advil/Ibuprofen*	19 (47.5)
	Motrin (including prescription Motrin) (ibuprofen)	3 (7.5)
	Advil (ibuprofen)	13 (32.5)
	Ibuprofen (generic)	11 (27.5)
	Naprosyn/Naproxen*	6 (15.0)
	Naprosyn (naproxen)	2 (7.5)
	Naproxen (generic)	4 (10.0)
	Naratriptan (generic)	2 (5.0)
	Nasal spray (non-prescription, flonase)	2 (5.0)
	Percocet, Percodan (oxycodone)	2 (5.0)
	Phenegran/Promethazine*	5 (12.5)
	Phenergan (promethazine)	3 (7.5)
	Promethazine (generic)	4 (10.0)
	Reglan (metoclopramide)	1 (2.0)
	Relpax/Eletriptan*	7 (17.5)
	Relpax (eletriptan)	4 (10.0)
	Eletriptan (generic)	3 (7.5)
	Reywow (lasmiditan)	1 (2.5)
	Sinus or allergy medications	5 (12.5)
	Sumatriptan (generic)	8 (20.0)
	Toradol/Ketorolac*	10 (25.0)
	Toradol (ketorolac)	8 (20.0)
	Ketorolac (generic)	4 (10.0)
	Tramadol compound (generic)	5 (12.5)

Variable	**Category**	**Total Sample (N=40)**
	Tylenol/Acetaminophen*	19 (47.5)
	Tylenol (acetaminophen)	11 (27.5)
	Acetaminophen (generic)	17 (42.5)
	Ubrelvy (Ubrogepant)	5 (12.5)
	Vicodin (acetaminophen and hydrocodone or other hydrocodone compound)	1 (2.5)
	Voltaren/Diclofenac*	5 (12.5)
	Voltaren (diclofenac) pills or tablets/capsules	1 (2.5)
	Voltaren (diclofenac) topical gel	2 (5.0)
	Diclofenac (generic)	3 (7.5)
	Zolmitriptan (generic)	1 (2.5)
	Zomig (zolmitriptan) pills or tablets/capsules	2 (5.0)
	Zomig (zolmitriptan) nasal spray	4 (10.0)
	Other prescription injection	13 (32.5)
	Other prescription medication (pills or tablets/capsules)	6 (15.0)
	Other prescription nasal spray	2 (5.0)
Type of Preventive Pharmacologic Treatment, n (%)	Aimovig (erenumab)	7 (17.5)
	Ajovy (fremanezumab)	4 (10.0)
	Amitriptyline (generic)	4 (10.0)
	Aspirin	1 (2.5)
	Botox (onabotulinumtoxin A)	7 (17.5)
	Candesartan (generic)	1 (2.5)
	Coenzyme Q10	3 (7.5)
	Cymbalta (duloxetine)	2 (5.0)
	Effexor (venlafaxine)	1 (2.5)
	Emgality (galcanezumab)	9 (22.5)
	Gabapentin (generic)	4 (10.0)
	Lexapro (escitalopram oxalate)	2 (5.0)
	Lisinopril (generic)	2 (5.0)
	Lopressor/Metoprolol*	2 (5.0)
	Lopressor (metoprolol)	1 (2.5)
	Metoprolol (generic)	2 (5.0)
	Magnesium	8 (20.0)
	Namenda/Memantine*	2 (5.0)
	Namenda (memantine)	1 (2.5)
	Memantine (generic)	1 (2.5)
	Nortriptyline (generic)	1 (2.5)
	Propranolol (generic)	2 (5.0)
	Riboflavin/Vitamin B2*	5 (12.5)
	Riboflavin (vitamin B2)	2 (5.0)

Variable	Category	Total Sample (N=40)
	Vitamin B2	3 (7.5)
	Sertraline (generic)	1 (2.5)
	Topamax/Topiramate*	9 (22.5)
	Topamax (topiramate)	5 (12.5)
	Topiramate (generic)	5 (12.5)
	Venlafaxine (generic)	1 (2.5)
	Verapamil (generic)	3 (7.5)
	Zoloft (sertraline)	1 (2.5)
	Other	5 (12.5)

*Represents the total number of individuals who endorsed the brand or generic drug treatment

5 Key Findings from Qualitative Analyses

The next several sections highlight findings from the total and stratified analysis of N=40 interviews. Results are organized by the following key domains:

- Cognitive Interference
- Treatment Priorities
- Symptom Burden
- Changes in Mood/Emotions
- Impact on Daily Living
- Physical Limitations
- Migraine Tracking
- COVID-19 Impacts
- Stratified Observations
    - Aura v. No Aura
    - Chronic v. Episodic

For purposes of this qualitative analysis, migraine phases are discussed in terms of pre-headache, headache, post-headache, and inter-ictal periods.

5.1 Impact of Migraine-Related Cognitive Interference

Table 5 summarizes the frequency with which various migraine related cognitive changes were reported to occur within the interview sample. The table presents cognitive impact frequencies across phases of the attack according to interview participants' descriptions of typical migraine attack experiences. The figures presented in each table cell represent the number of interview cases that reported experiencing the associated cognitive change within the 40 conducted and coded interviews for this study.

Table 5. Frequency of migraine related cognitive changes reported by interview participants (N=40) across pre-headache, headache, post-headache, and inter-ictal phases of their typical migraine attacks

Cognitive Interference	Pre-Headache	Headache	Post-Headache	Inter-Ictal
Trouble with concentration/focus	25	25	11	0
Confusion/disorientation	4	3	2	0
Avoid making decisions	17	18	6	0
Fogginess	18	9	17	0
Losing words/speech	24	12	9	2
Memory	12	15	11	12
General	3	5	7	9
Learning	9	7	5	6
Retrieval/recall	3	10	4	1
Slurred words/speech	1	3	0	0
Difficulty processing information	14	11	7	1

A high-level overview of Table 5 frequencies suggest that migraine attack-related cognitive changes often manifest at pre-headache, carry into headache, and may resolve or linger during the post-headache period, depending on the individual. Interestingly, experiences with fogginess, losing words/speech, and difficulty processing information reported during pre-headache were not universally observed during headache. This may be due to debilitating and distracting pain during headache that dominates the experience, using up all attentional resources and thus, reducing bandwidth to focus on/identify cognitive changes. For example, one participant described the headache phase of their migraine as follows:

> *00-12: I have no activities, no talking. I'm just laying there, I'm in pain. It's not – nothing else is happening. Everything is focused on my body and how it's reacting to it.*

An overview of the proportion of individuals reporting any cognitive changes in the pre-headache, headache, post-headache and inter-ictal phases of their migraine suggest that cognitive interference is a common burden in pre-headache, headache, and post-headache periods. In the pre-headache phase, 36 out of 40 (90%) participants reported experiencing one or more cognitive feature. During headache, this number remained relatively stagnate with 35 out of 40 (87.5%) participants reporting one or more issues with cognition. In post-headache, the number of individuals reporting cognitive interference declined to 27 out of 40 (67.5%), which still represents the majority of our sample. In the inter-ictal period, the number of participants reporting one or more cognitive feature declined further to 13 out of 40 (32.5%) participants. The distribution of the number of cognitive interference concepts endorsed by interview participants across pre-headache, headache, post-headache, and inter-ictal phases is provided in Table 6. Among participants reporting cognitive interference during pre-headache and/or headache, the vast majority endorsed two to five cognitive features, suggesting that co-occurence of cognitive deficits during these phases may be common. In contrast, during post headache and inter-ictal periods, the majority of participants reporting cognitive interference endorsed only one or two cognitive features.

Table 6. Proportion of participants (N=40) reporting occurence and co-occurence of migraine-related cognitive interference features across pre-headache, headache, post-headache, and inter-ictal phases

# of Endorsed CI Features	Pre-headache	Headache	Post-headache	Inter-ictal
0	10.0%	12.5%	32.5%	67.5%
1	10.0%	7.5%	22.5%	22.5%
2	22.5%	22.5%	20.0%	5.0%
3	15.0%	22.5%	7.5%	5.0%
4	20.0%	10.0%	7.5%	0.0%
5	15.0%	15.0%	5.0%	0.0%
6	7.5%	5.0%	5.0%	0.0%
7	0.0%	0.0%	0.0%	0.0%
8	0.0%	2.5%	0.0%	0.0%
9	0.0%	2.5%	0.0%	0.0%

Concept frequencies and case counts alone do not provide a full picture of migraine-related cognition as was reflected through the thoughtful insights of our interview participants. Thus, below we outline additional observations on the impact of cognitive interference among people living with migraine based on the analysis of coded content from N=40 interview transcripts.

It is important to note that, at times, it was difficult to differentiate between problems with sustained attention (Section 5.1.2), language (5.1.1), and memory (5.1.4) based only on the verbatim words of participants. However, there is a distinction between assessing subjective cognition (i.e., patient self-report) and objective cognition (i.e., measures obtained using cognitive tests known to assess particular cognitive domains). For purposes of this study, we are interested in the domain of subjective cognition and thus, use participants' perceptions of cognitive change to drive our categorization of cognitive impacts/features.

5.1.1 Impacts on Receptive Language, Language Production, and Speech Production

Migraine-related cognitive impacts on language and speech were reported during at least one phase of the migraine attack among the majority (29/40;72.5%) of participants in our interview sample. Language and speech problems included impairments to 1) receptive language, 2) language production, and 3) speech production. It was not uncommon for individuals to report challenges in two or more of these areas of language and speech production and processing.

Very few participants reported continued challenges with language and speech in the inter-ictal period. Rather, language and speech-related cognitive changes most often initiated during pre-headache, held significant implications for daily life and function during the migraine attack itself, and resolved by or during the post-headache period. These changes also served, for some in the sample, as an early indicator of migraine attack onset and a tool for others in their life to identify that a migraine headache was imminent or had already begun. One participant said the following about issues with language and speech production as an early indicator during pre-headache:

> *00-17: I'll even get to where I'm trying to speak with you right now and words just aren't coming out right. I'm stuttering on my words, I'm trying to think of what word I'm trying to use, stuff like that. And then I'm like, OK, I know I'm fixing to get a migraine because I can't even speak properly.* [pre-headache]

5.1.1.1 Impacts on Receptive Language

Participants reported challenges in understanding/processing verbal communication during their migraine attacks. For these individuals, information may need to be repeated multiple times to promote comprehension. Participants often described "hearing" the words others were saying but struggling to understand them (Box 1a-c).

Box 1: Receptive Language	
1a	00-23: I can't tell you how many times I've looked someone straight in the face, tried to read their lips and still didn't catch everything that they said. And I'm like, sorry, can you repeat that? But it's like at least two times that I have to ask them for – to repeat it. [post-headache]
1b	00-28: Can you say that one more time? Like, I'll say exactly what the person said, and then it doesn't register. So sometimes I'll be like, can you say that one more time? I'll literally hear you say the question, but it almost feels like I wasn't listening, like a kid. Like, they're looking right at you, and they're not listening. [pre-headache]
1c	00-35: I can't do it. I – it's very sl – like my brain is very sluggish. Sometimes things are repeated several times before I comprehend what they're saying. Even carrying on a conversation gets really hard. [headache]

5.1.1.2 Impacts on Language Production

Issues around language production were common in our sample. Patients described jumbling words (Box 2a-b), struggling to form words (Box 2c-e), and difficulty finding words (Box 2f-g). Many participants described knowing what they want to convey while being unable to find or form words to reflect their thoughts (Box 2h). These problems with language production can be particularly harmful during migraine attacks when individuals are unable to express their basic needs or describe the sensations they are feeling to others (Box 2i-j). Language production issues were also reported to cause deep frustration, fear, and panic in some who experience it (Box 2k-l).

Box 2: Language Production	
2a	00-09: The other effect of it is that sometimes the words get kind of jumbled up…I'm trying to say – an example – at the start of it, in my house, there's running joke with my family – everything is the dishwasher. Every appliance in my house is the dishwasher – the stove, the microwave, the refrigerator is always the dishwasher. So it's things like that. [pre-headache]
2b	00-42: I remember, once at work, I was leaving – because I knew I was getting a migraine – and I called a tissue box a toothbrush in front of all my coworkers. And no one really paid attention, but I was like, oh man, it is way past time for me to go home. [headache]
2c	00-17: I can't form my words. the word is there. I see the word in my head, but when I try to say it, it just does not come out. I can't – I'll say, help me – like, help me think of the word I'm trying to say. I say that all the time to my husband or to my kids – I'll pretty much describe it to them, what I'm trying to say. [pre-headache]

Box 2: Language Production

2d 00-36: I feel like I have peanut butter in my mouth…And the only way that – or one of the only ways that I feel like I can communicate is I'll just text people. Especially if somebody's standing right beside me, I'll just try and either write it down on some paper or text it all out. It's like, hey, look, I don't know how to describe it but I can't form words right now. [pre-headache]

2e 00-42: And I open my mouth to say something, and either something random comes out or I can't get my word out at all. [pre-headache]

2f 00-06: So if I was trying to think of a bookshelf, I might think of the thing that holds the books, or the thing with things on it, but there's a bunch of things with things on it all on top of each other and – or I might try to like…It's almost like buffering, so it's like there's a – like in the middle of a sentence, just have to stop and do video buffering on your thoughts. [pre-headache]

2g 00-05: So I worked in registration at a hospital and everything, and I would notice that as far as – we basically repeat the same thing over and over every day. And so just the normal things… I'm getting ready to maybe have them sign a HIPAA document and everything, but I can't figure out what's this document called? This important document? And I'm like – so I have to – it takes me a minute for it to click. I know what I'm trying to say, but I don't know what I'm trying to say. [pre-headache]

2h 00-06: It's like the connection between knowing what I'm trying to say and my mouth is just broken. Which is really frustrating, and that ends up just making things worse, because then I frustrate myself, and the frustration makes the pain worse. [pre-headache]

2i 00-01: Inside me, I'm super aware. So that's the problem is that I can't tell anybody how everything feels because I can barely talk. And everything they – when they touch me, it's hypersensitive. But people are thinking that I'm not aware. [pre-headache]

2j 00-36: Anyways – but yeah, during the attack, if I haven't already communicated what I need or what I need to do, it's normally like a no-go, because I just can't really do much else. [headache]

2k 00-01: Well, if – you know, my speech – it's not so much the reading, because I'm pretty assured in my reading that I will have decent comprehension. But if words don't come to me quickly in my speech, I can get panicked. Why can't I fill in the blanks fast? I'm a writer. I'm a poet. I've been a professor at the university level. Why isn't that word there? [post-headache]

2l 00-27: Yeah. It's – that's the biggest frustration, because of my career, because I've worked all my life towards being an academic. I've based my identity on, if not being smart, at least being educated. And honestly, it's all – when there's a migraine coming…I'm not capable of doing or thinking or focusing not just like I used to be able to, but like a person with a kindergarten education, I don't think. And that's embarrassing when you lecture for a living. I couldn't remember the word head the other day. I said neck-ball. And it's like, if I were lecturing a class of 500 college students – ugh. So it's – that's the – I would deal with the pain every day if it would just not leave me so stupid. [pre-headache]

5.1.1.3 Impacts on Speech Production

Although distinct, issues with speech production often co-occurred with the language production deficits described above. Common experiences reported with speech included stuttering, slurring and garbled verbal expression (Box 3a-c).

Box 3: Speech Production	
3a	00-23: And good luck understanding the words coming out of my mouth if you ask me a question, because it's probably just going to sound like the gibberish out of a toddler. [headache]
3b	00-04: And like I said before, my speech gets slurred or paused or hesitant – or kind of get the – I can't string cohee – coherent thoughts together. And if someone's talking to me, I'll just want to not – I' like to keep it as short as possible. [headache]
3c	00-09: I have started to – depending on the severity of the migraine, I – my speech becomes slow, or I start to stutter. [headache]

5.1.2 Sustained Attention

Participants in our sample described changes in their ability to sustain attention during their migraine attacks including a general and overwhelming sense of "fogginess" or "brain fog" (Box 4a-b), vivid descriptions of confusion/disorientation (Box 4c), and substantial trouble maintaining their concentration or focus (Box 4d). For participants in our sample, issues with sustained attention did not seem to linger into the inter-ictal period between migraine attacks, but rather, played a prominent role in cognitive interference during the attack itself. Although these cognitive changes were reported throughout all phases of the migraine attack, the negative implications of deteriorations in sustained attention were most prominent during the early stages of attack onset (i.e., pre-headache) when individuals may still be attempting to maintain some level of function at work, home, school, or social settings (Box 4e-f).

Box 4:Sustained Attention	
4a	00-18: Sometimes it really – I just say that I'm thinking through cotton or that my brain feels foggy. [pre-headache]
4b	00-06: So brain fog feels like – it's almost – if you were to think about – if you're in like a pool and you're trying to walk through waist-high water, it's a lot more difficult to reach your destination, even if it's only a couple feet away. It's like that but with your thoughts. So it's right there but it's a lot farther than it seems. [pre-headache]
4c	00-12: I'll have a list and everything, I'm not – I'm just randomly walking around the grocery store like a complete idiot, like somebody the other day in XXXX, somebody just walked up to me and said are you OK, because I feel – you looked like you were confused? I was like oh – and I was like no, I'm just looking for some vegetables. She's like can I help you and then she was able to help me, but – so other people notice it too. [pre-headache]
4d	00-10: It becomes very difficult to concentrate. Even focusing's very difficult as well. And I think those are also standards in regards – oh, something's happening…it's like all of a sudden, it's like it comes out of nowhere, and you can be completely involved in a conversation or in a task or – whether it be work or home or friends or whatever, and it's just one of those things where you kind of get this glazed look on your eyes, and you're just really kind of like – you're there, but you're not all there to a certain degree. [pre-headache]

Box 4:Sustained Attention

4e 00-36: Quite a bit, because the brain fog comes in. And also, it goes back to that emotional state, where all I can focus on is, if I'm at work, trying not to cry again at work or, if I'm in the grocery store, trying not to let anybody see my face getting really red because I'm trying not to freak out, so it's almost this no focus on anything else, other than crisis mode, essentially. So it's – and also not being able to get work done, but it's more so taking the focus off of anything else and just strictly putting it on what's going on inside my body, what I feel right now and how to stop it, how to get help. So – because I feel like, most of the time, if I have any task to do, I will try my hardest to get that done. [pre-headache]

4f 00-38: Before the headache pain really sets in, a lot of times I'll be at work and I'll notice that I'm gritting my teeth and that it's starting to h – get hard to concentrate, and it's getting hard to s – I don't feel like I want to look at the screen. 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. And so, I'll be trying to plan out my work for the day and I'll feel like this is too hard. I don't want to do it now. And then I'll realize it's the migraine talking, that it hurts to think basically. [pre-headache]

5.1.3 Executive Function

Deficits in executive function, including difficulty making decisions and processing information, were commonly reported during, but not in-between, migraine attacks. Many participants described mistrust in their own capacity for planning or decision-making during pre-headache and headache phases (Box 5a-c). Some described struggling to make treatment decisions in the midst of their migraine attacks and a heavy reliance on others to manage their medication and health care utilization in these circumstances (Box 5d-f). This is an important implication of executive function loss that is further complicated by co-occurring language/speech production problems that hinder communication to others involved in their medical decision-making (Box 5g).

Box 5: Executive Function

5a 00-13: Don't ask me to sign nothing because I don't know what I'm signing. And don't ask me to read nothing. Don't ask me to think about it because I'm not in my right frame of mind. It's like you're asking somebody who's in the hospital to sign something and you done gave them drugs. Why would you? It's like asking somebody against their will to do something and you know that they can't, but you still want them to sign some paper? No. [pre-headache]

5b 00-01: I wouldn't say that I'm thinking clearly. What I'm aware of is that I wouldn't say that my executive function is high – is working properly…I wouldn't say that my thinking faculties are working properly. I couldn't make an executive decision. I used to run an architectural firm with 100 people. I wouldn't want to be the CEO in charge, making decisions then. [pre-headache]

5c 00-38: Well, like if I'm trying to plan out what I'm going to do at work. It'll – it'll be kind of obsessive. It won't be natural. It won't be like, oh, I should do this first. It'll be like, oh, should I do this or that? Or, what about this? What about that? I'll just – my thinking will be more unhealthy. So it'll be harder to make decisions because I'll be doing the what ifs. [pre-headache]

5d 00-09: When they're really, really bad, I can't – things doesn't make sense to me. I can't function enough to make sense. And because now I'm only dealing with half a vision, it's just not wise for me to try to do things like make major decisions. I've put safeguards into place that during an attack, my father is my power of attorney. So that's how bad they can be, especially if I only have half eyesight. So it's just not safe. [headache]

Box 5: Executive Function	
5e	00-27: I can't do it at all. I – the – yeah. When – I've had my husband basically forcibly take me to the emergency room when it was bad enough. He'd ask me, do you want to go to the emergency room, and I can't even decide yes or no. [headache]
5f	00-41: But I will say, my husband will ask me, do you need to go to the emergency room? And normally, my answer's no. But I'll have to say do I want to go to the emergency room, like let me try to process what he just asked me…For me, it feels like I'm processing this information so slow in that – during that timeframe. [headache]
5g	00-36: Like my sister and I live together, and she's really great in so many other aspects, but sometimes her caretaking skills are a little slackened, and she knows this, and we talk about it, and it's fine. But I just know that, if I don't communicate that to her before of what I need during the attack, when I can't maybe articulate it as well or even really know exactly what I need, she's not going to be that much help. [headache]

5.1.4 Memory

Issues with memory were discussed across all phases of the migraine attack and as a key cognitive impact in the inter-ictal period in between attacks. Participants distinguished between issues related to learning (i.e., forming new memories) and retrieval (i.e., recalling previously learned information).

5.1.4.1 Impact on Learning

Disruptions to learning during the migraine attack itself were often characterized as a complete black or partial brown out of events and interactions (Box 6a-b). This differed from disruptions to learning during the inter-ictal period, which were described as less dramatic deficiencies in short-term memory including forgetting recently made plans/responsibilities or conversations (Box 6c-d).

5.1.4.2 Impact on Retrieval/Recall

Problems with retrieval/recall manifested during migraine attacks as temporary disruptions to long-term memories like the names of well-known friends and acquaintances and important, long-held household or family responsibilities (Box 6e-f). Issues with retrieval/recall were most frequently reported during the headache phase of the attack among participants in our sample, suggesting a relationship between head pain and a deterioration in the focus required to recall/retrieve important memories (Box 6g).

5.1.4.3 Memory in Inter-Ictal Periods

Participants have various theories about the cause of deficiencies in memory during inter-ictal periods. Some participants believe that issues with the formation of new memories and other general concerns about memory loss in-between attacks are directly related to chronic cognitive deterioration made worse by each migraine attack (Box 6h-i). Others drew connections to migraine medications whose cognitive side effects made remembering things more challenging (Box 6j). Regardless of the reason behind inter-ictal impacts on memory, participants who experienced problems with memory outside the context of the migraine attack itself viewed this as a highly concerning aspect of their migraine disease and/or treatment (Box 6k).

Box 6: Memory

Learning

6a 00-06: It’s harder to process memory, so it may be harder for me to form new memories. I know that there have been times where I don’t really remember what happens during a migraine peak or it’s just like a block. If I’m – like I know that changed the way that I did school in college because, if I went to class on a day that was – where the pain levels were too high, anything that I learned during that period I wouldn’t remember any of it of and I had a lot of trouble relearning, because there was a block connecting that information because there was so much pain that my brain’s not letting me remember the information that was there. [headache]

6b 00-10: It’s awful. It’s – there is absolutely – there’s no memory. There’s – I mean, there’s memory of me going through this and of dealing with it, and you’re like, my God, I just want to chop my head off. But as far as everything else, it’s just a very – it’s like snippets of what may have – what’s gone on during that time. [headache]

6c 00-09: Long-term memory – I tell people all the time, long – you cannot get me on my long-term memory. I can remember what you wore, where you were standing, what was said. I can be very detailed with long-term memory. But if you say to me, you know, tomorrow we’re going to go ahead and go out, and we’re going to do so-and-so, if I didn’t write that down, I promise you I will not remember. [inter-ictal]

6d 00-41: So if I made a plan or I set a date for something, I immediately have to put it in my calendar. If I don’t, I will completely forget about it. Like I didn’t have this meeting in my calendar, and I actually forgot about it. And the only reason I remembered last night was because I came across the e-mail. So I was just like, oh my God, I didn’t put that in the calendar. (laughter) And that’s second nature to me these days, because as soon as I – I don’t even let the doctor’s office give me cards. I am just like this with my phone, putting it in as we’re making the appointment, because if I don’t, I’ll never show up. I have missed so many appointments. [inter-ictal]

Retrieval/Recall

6e 00-08: Like our dog has to take a lot of medicine. He’s 17 years old and so when I have a headache, sometimes I forget to give him his medicine at the time or I'll accidentally give him the wrong medicine at that time, so that he got a double dose or something. So – and I just feel really guilty after. [headache]

6f 00-12: I’ll forget their names. I see these people almost every day. So it’s like instead of saying whoever that I'm going to see, I don’t remember their name. I know them and I'm walking on my – they’ll – say somebody will engage in a conversation with me, I'm pretty much looking at them, they're like a stranger, and that’s a bad feeling too, because you're trying to connect with me, which is probably what I need. You know what I mean? [pre-headache/headache]

6g 00-40: I can’t remember things at all when I’m in the middle of a migraine. They’ll ask me – somebody will ask me a question. And I – for the life of me, I can’t remember what it is. [headache]

Inter-Ictal Memory

6h 00-09: Oh, my memory is bad all the time now because of so many migraine attacks. It didn’t – it’s just – it gets worse as time goes on...Long-term memory – I tell people all the time, long – you cannot get me on my long-term memory. I can remember what you wore, where you were standing, what was said. I can be very detailed with long-term memory. But if you say to me, you know, tomorrow we’re going to go ahead and go out, and we’re going to do so-and-so, if I didn’t write that down, I promise you I will not remember….It’s just too many bad attacks too many times too long. My brain is literally fried. It can’t even recover the way it’s supposed to. [inter-ictal]

Box 6: Memory

6i 00-01: Well, you don't notice it until there's a need for something, where you – if, that day after the migraine, there's a need for that memory, even if it's short-term memory, and you can't access it, then it's very noticeable – something that happened two days before the migraine and it's not immediately available but you sort of know it. You can't talk about it, but it's like what's this? That's uncomfortable…I end up – some – it varies between anxious and depressed….It's like this underlying thing of, you know, is this age or Alzheimer's or is this the side effects from migraine or these little white dots on the MRI? Is this – what is this? [inter-ictal]

6j 00-26: Well, I know that one of the side effects of the medication that I do take is the memory. That's why I write a lot – that's why I write stuff down. [inter-ictal]

6k 00-17: My memory has been affected bad, and I think it has to do with the migraines. But they're not really sure because I'm only 33. I should not be having memory problems the way I do…. I've noticed long-term, as well, I have memory issues, and it's scary because I shouldn't…. My husband has traumatic brain injury from being injured in Afghanistan. He has a reason to be 33 and have memory issues. I don't see where I do unless it's the migraines or whatever that's causing the issues. I shouldn't be having issues he does with memory. [inter-ictal]

5.1.5 Cognitive Interference Across Phases and its Relationship to Pain

Cognitive changes related to language/speech production and processing, sustained attention, executive function, and memory can manifest across all phases of the attack. For many individuals in our sample, changes to cognition that interfere with their daily life begin in pre-headache and increase in severity as headache pain intensifies (Box 7a). Many participants viewed cognitive interference as having a direct relationship to head pain (i.e., as head pain gets worse, cognition declines. In turn, as head pain resolves, so do the cognitive effects) (Box 7b-e). For some participants however, cognitive interference as a result of migraine is noticeable outside the context of head pain (i.e., begins before onset of pain and/or lingers after pain resolves) (Box 7f-h).

Of all the phases of the migraine attack, post-headache was observed to have the greatest variability in presence and manifestation of cognitive interference both across and within our participant sample. For some, cognitive changes resolved rapidly early in the the post-headache period (Box 7i-j). For others, cognitive impacts lingered well beyond head pain into the post-headache period with a more gradual return to a cognitive "baseline" (Box 7k-l). Variable experiences with cognitive interference during post-headache could even occur from attack-to-attack within the same individual (Box 7m).

Box 7: Cognitive Interference Across Phases and its Relationship to Pain

7a 00-16: Pretty much brain fog. Like there's three stages – like a little bit of brain fog, a good bit of brain fog, and then just ridiculous brain fog.

7b 00-14: The worst the pain gets, the harder it is to stay focused because your mind is kind of not focusing on the pain. But it makes it harder to concentrate because the pain is – becomes the, I don't want to say the leader of your – it's not controlling your thoughts. But it's overwhelming your – the control of your thoughts I should say. You want to focus, but the pain is taking away your focus at times the worse it gets. [headache]

7c 00-06: I always notice that, as pain increases, cognitive function goes down. It's directly related. But as pain levels are really high, I sometimes get stuck in a circular pattern of thinking, where I'll just say the same thing over and over and I don't know what's going on. [headache]

Box 7: Cognitive Interference Across Phases and its Relationship to Pain

7d 00-20: The brain fog, I – that's only caused by the pain

7e 00-17: And the brain fog, I think that’s more caused by the symptoms

7f 00-03: I get kind of a mental fogginess. I can still operate and function, but I just feel kind of – I mean, I don’t have any technical term, but just kind of feel slightly out of it – just kind of slightly – kind of almost one step behind where everybody else is, in a way. [pre-headache]

7g 00-03: The fogginess sometimes gets a little bit better, sometimes doesn’t. [headache]

7h 00-06: Sometimes brain fog will continue, but it’s a different brain fog. So the pain brain fog is more like wading through water trying to get there, versus the after-pain brain fog is less like fog and more like brain jumble. So if you’re looking at a subway map and there’s all the lines crossing over each other and you’re trying to go on the blue line, and the blue line, at one station, intersects with yellow and green, it may be like you’re going down the blue line and you’re trying to get to the end of the blue line, but you end up getting to the end of the green line instead. So things get more jumbled rather than they do lost and harder to find. They’re there. They’re just in the wrong order. [post-headache]

7i 00-07: I can think a lot more clearly. I could process things. I could retain information. That’s when I’m like, OK, you can explain to me now – how do we do this? How do I – I can listen to you now. So it’s just – yeah – processing is just a lot better. [post-headache]

7j 00-14: It’s gotten more back – it was I would say more back to normal because I didn’t have that pain that would distract my focus, take away from my focus…definitely my focus came back together because I didn’t have that intense pain. [post-headache]

7k 00-41: I’ll still have brain fog. I actually will still have brain fog for days. And I won’t realize it until later. I could be completely fine, have ba – brain fog and work on my report, like my budget or whatever, and come back a couple days later without brain fog and be like, OK, that makes no sense. I don’t know why I did that. I must have had brain fog. And I’ll have to fix it. [post-headache]

7l 00-04: The brain fog or the mental acuity – I just don’t – I have a hard time thinking intensely or making sense of something or speech, I guess – memory – those kinds – those cognitive things are the things I really notice that will linger and linger. [post-headache]

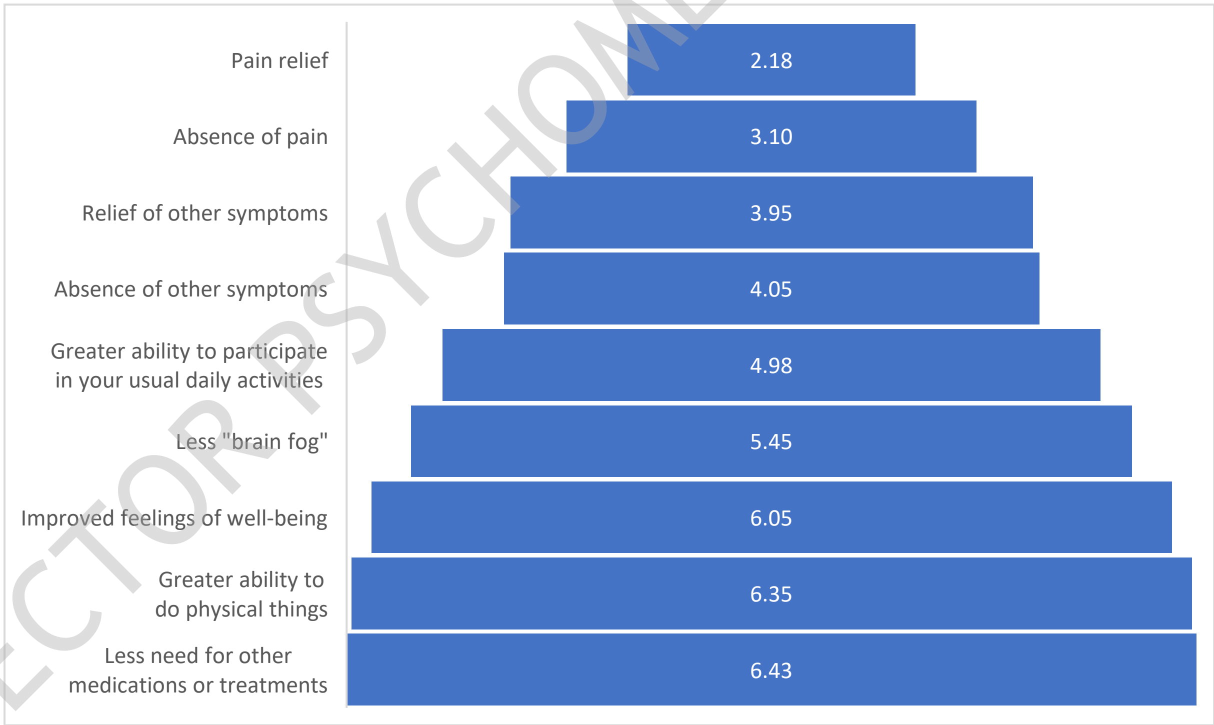
7m 00-08: I think it also kind of is situational. So I can think of some times where right after I had a migraine, I was still in that kind of fogginess and confusion or not being able to concentrate and then other times, it seems like I can bounce back quickly and feel like more of a – immediately jumping back into normal life. I don't know that it’s – it definitely not always one or the other. [post-headache]

*Quotes that are not attributed to a specific phase of the attack were extracted from participants’ general descriptions of cognitive impact

5.2 Acute and Preventive Migraine Treatment Priorities

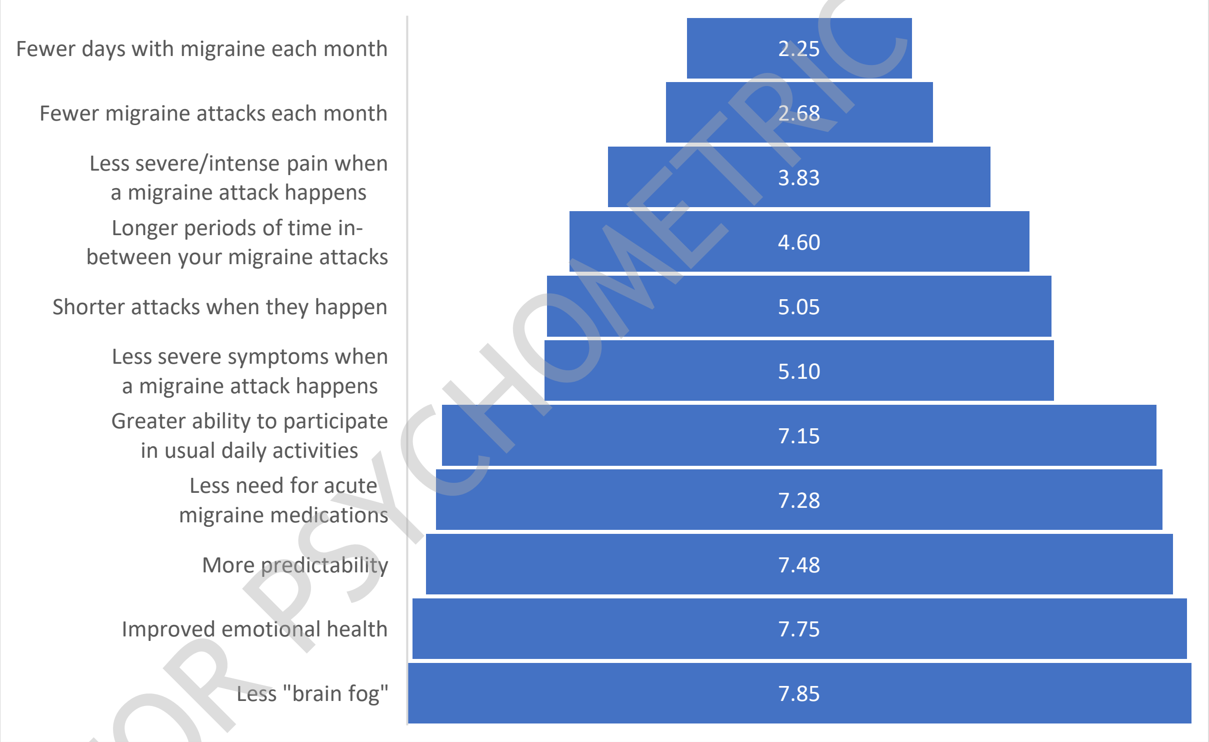
Figure 1 and Figure 2 provide average acute and preventive pharmacologic treatment priority rankings derived from interview subjects' (N=40) participation in two think-aloud treatment outcome/benefit ranking exercises. A high-level overview of Figure 1 suggests that pain and associated symptoms were consistently cited as a top priority for acute treatment among the individuals we interviewed; indeed, the first four highest rankings are related to desired changes in pain and associated symptoms. While pain and associated symptom relief was, on average, ranked higher than absence of pain and associated symptoms as a priority for treatment, in this sample, mean values of relief and freedom (presented in Figure 1) were generally close. The median value for absence of pain ranking differed somewhat from the mean value reported in Figure 1 (median=2; mean=3.1; SD=2.7). This difference between median and mean values is likely due to a large proportion (n=12) of individuals who listed absence of pain in the bottom half of their priority rankings (≥5) and greater variability around the mean ranking for absence of pain compared to other ranked outcomes/benefits. A more detailed discussion of the circumstances and rationale that led many in the sample to prioritize relief over absence is provided in section 5.2.2. Median rankings for other acute treatment priorities closely aligned with the means presented in Figure 1.

Figure 1. Average priority rankings for acute treatment benefits/outcomes reported by interview participants (N=40) during virtual ranking exercise (rank of 1 reflects highest priority/most desired outcome)



A high-level overview of Figure 2 suggests that preventive treatment benefits/outcomes related to migraine attack/headache frequency reduction were consistently ranked as a top priority among participants in the sample, with reductions in pain and symptom severity as a highly ranked, secondary objective of preventive treatment. Fewer days with migraine, fewer migraine attacks, longer periods of time in-between migraine attacks, and shorter attacks when they happen were viewed by most participants as different means to a similar end. That is to say, all contributing factors to an overall reduction in the burden of migraine frequency and thus, prioritized above other potential preventive treatment outcomes like greater ability to participate in usual daily activities, less need for acute migraine medication, more predictability, improved emotional health, and less "brain fog". . Median rankings for preventive treatment priorities largely aligned with the means presented in Figure 2.

Figure 2. Average priority rankings for preventive treatment benefits/outcomes reported by interview participants (N=40) during virtual ranking exercise (rank of 1 reflects highest priority/most desired outcome)



Average rankings alone do not provide a full picture of treatment priorities as they were reflected through the thoughtful insights and observations from interview participants. Thus, below we outline additional observations on acute and preventive treatment priorities among people living with migraine based on our analysis of coded content from N=40 interview transcripts.

5.2.1 Cognitive Interference as a Treatment Priority

Most participants in the interview sample experienced cognitive impacts from migraine that interfered with their daily life. Despite this, we observed variation in how much priority participants placed on addressing cognitive interference through acute and/or preventive migraine treatments relative to other potential benefits like pain and symptom relief. Among the participants who viewed cognitive interference as a high priority for migraine treatment, most desired a reduction in cognitive impacts so that they could better accommodate daily responsibilities and activities like work, school, family, and friends (Box 8a-d). However, some participants who did not view cognitive interference as a high priority for migraine treatment, de-prioritized it not because they did not perceive cognitive impact on their life but because they viewed the resolution of cognitive impacts as a potential extension of pain and symptom relief (Box 8d-f). Others did not believe migraine treatments could effectively address cognitive interference and may even compound it (Box 8g).

Box 8: Cognitive Interference as a Treatment Priority

8a 00-05: I want to be able to enjoy myself and hang out with friends and everything. But while also I want to be able to participate, I also want to be – make sure I'm there – like my cognitive ability is also there. I don't want to be there but then just taking up space, like I have nothing to contribute because I'm trying to get through a migraine.

8b 00-09: Only because of the fact that – you know, two kids, two dogs, a senior father, and then I work in finance, I got to have at least some of my mental capacity to function properly with that stuff.

8c 00-23: I'd follow that [previously ranked item] with less brain fog, just because, even if I'm able to participate in daily activities, 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.

8d 00-42: I'm a software engineer, so I need to be able to think.

8e 00-08: I guess – I think I just was thinking like if I wasn't having as many headaches or wasn't having as severe of headaches, then those [reduction in cognitive impacts] would kind of happen automatically, so that's why they seemed less important.

8f 00-14: And then less brain fog, goes with all six of those [previously ranked treatment priorities] because that's kind of an after effect of all that.

8g 00-20: I would say, from an – if I'm in enough pain, it's more or less that it breaks my train of thought. You know, it – when the headache – when it turns into a migraine, I – it's like almost every blood pump seems to give another shock of pain. So it's really hard to formulate a full sentence, not because I'm missing my words. It's more or less, I'm just getting interrupted by, like, someone hitting with a bat, essentially, so…It's not like cognitive impairment.

8h 00-04: I think the brain fog – that always happens when I have migraines, so I just don't – like I said, it's one of those things I just don't think it's ever not going to happen. 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.

5.2.2 Pragmatic Prioritization of Relief Over Absence of Pain/Symptoms

Interview participants frequently ranked pain and symptom relief as an acute migraine treatment priority over absence, citing practical reasons for this determination. Although complete freedom from pain and symptoms is likely an ideal outcome for acute treatment, based on their experiences with previous treatments, many participants did not believe pain freedom was a realistic expectation and thus, viewed reliable pain and symptom relief as an acceptable and more pragmatic alternative outcome (Box 9a-g). This observation is further supported by the results of our treatment benefits/outcomes ranking exercise, in which pain and symptom relief was, on average, ranked as a higher priority than absence of pain and symptoms (Figure 1). Even among participants that ultimately ranked absence of pain/symptoms higher than pain/symptom relief, there was a commonly held view that absence may not be a realistic outcome of treatment. This pragmatic view of relief over absence seemed to be driven by participants' treatment histories. Individuals with a moderate to long history of treatment with acute migraine medications developed a practical view of potential benefits and limitations that framed their current prioritization of pain/symptom relief over absence (Box 9l).

A meaningful threshold for pain and symptom relief was defined by many individuals in terms of their ability to return to some level of daily function (e.g., continue working, parenting, completing household tasks, socializing) (Box 9h-k).

Box 9: Pragmatic Prioritization of Relief Over Absence of Pain/Symptoms

9a 00-01: Well, if I have pain relief as opposed to – you know, absence of pain, in this life – I'm not even looking for that. It would be nice, but it's like a philosophical thing. OK? I don't ask for that ever. But pain relief would be almost 99% of my quest. And it really is a philosophical thing for me.

9b 00-03: As far as realistic outcomes, I don't think – you know, I'm going to rate absence of lower, just because I'd be happy for relief, honestly.

9c 00-06: Absence of pain – I don't ever expect that to be a reality for me, so it's not important to me.

9d 00-18: Because I don't really – even with new treatments, I don't – does anybody really expect a total absence of pain and symptoms? Yeah. So I think if it's there on the list, I will totally take it, but I think my expectation is always just like pain relief and relief of other symptoms is like fabulous. Yeah.

9e 00-17: I definitely need pain relief, but it's – I don't think you're ever going to be in absence of pain…To be a realistic thing, pain relief is more realistic to me.

9f 00-24: So pain relief – I think probably obvious that pain is the most debilitating and horrible. And 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, so I'm trying to be reasonable in my approach.

9g 00-42: Obviously, I would like something that, I take it, and maybe 10 minutes later, it's totally gone and I'm back to normal. But that doesn't exist. And I don't think it will.

9h 00-05: At least if it can – it would be awesome to get it 100% back to normal. But I guess to kind of be reasonable, 50% at least, cut in half. Or at least to the point where I can function with it. I can continue my day. I can continue my activities. My work is not going to be impacted to get me back to that point.

9i 00-17: The threshold of some pain relief, like I said. It might only be 50% relieved, but it might also – and that being said, help me to where I'm seeing again and can walk again – have more function to be able to do more things.

9j 00-18: I mean, ideally it would be a lot, but the – I think enough would just be manageable, like to let you function, so to go from like unbearable, I cannot stand up, and keep my eyes open to just a normal headache, to like OK, I can either get myself home or sit down until it passes. I think functional – just to be a functional human.

9k 00-35: Like 50 to 75% less…Just because I'd be able to function better, rest, if I need to, and just not be in as much pain. It – the less pain, the better. If it could completely take it away, it would be nice, but I don't think I've done anything that is like 100%.

9l 00-09: Because absence of pain – I've been at this a very long time, and I know that sometimes that's just not a realistic expectation. If you lessen it, you get some relief from it, I would rather – I would be OK with that as opposed to the absence of it, where I've yet to ever experience that right away. You know, so I have to be realistic in my expectations of what I expect. And so to say like absence of pain – I haven't found that medication yet, and I've been on a bunch of them.

5.2.3 Pain as Universal Priority

Individuals within our interview sample expressed varied views on the role of treatment in addressing other migraine symptoms and impacts outside of pain. This was highly dependent on the types of associated symptoms they experience and the level of disruption the associated symptoms cause. However, head pain was the one universal treatment priority that could be identified across all participants in the sample (Box 10a-c). For some of these participants, head pain was seen as a gateway to a cascade of other symptoms and impacts that they believe would resolve if the pain was addressed (Box 10d-f). Although this sentiment was common, it was not a universally held perspective on the relationship between pain, associated symptoms, and impacts on functional status. Other participants within the sample described symptoms and impacts, including but not limited to vertigo, visual disruptions, and issues with cognition, as equally disruptive as head pain and as occurring both within and outside the context of their head pain. In these circumstances, associated symptoms and impacts were often prioritized for treatment on equal or close to equal ground with head pain (Box 10g-i).

Box 10: Pain as Universal Priority

10a 00-09: Pain relief is the most important, because with that pain, you just can't – sometimes you just can't get it together. You know, I can handle the less vision. I can handle my – the weakness on one side. But that pain, it's like a jackhammer sometimes.

10b 00-35: As the most important thing, I just would love to be pain free. It would be nice.

10c 00-44: Because migraine pain is the ultimate killer. It just – you know, you want to be – have relief of the pain. What goes along with it, the other symptoms, like you have nausea or the sensitivity to light, those are not my main concerns. I mean, it's really just the pain that I want to get rid of.

10d 00-02: I think the pain is what controls every other factor around a migraine – is the pain.

10e 00-08: Well, I guess I was just thinking if out of all of those, I could only have one, absence of pain would then hopefully make all the other things (inaudible) place.

10f 00-14: Absence of pain. So if that goes away, then that helps the other things.

10g 00-03: Yeah, I think it's just because I hate the visual disruptions and the mental fog so much that in a weird way, as I said, there are times, particularly when the headache itself isn't as severe, where those symptoms have been more disruptive to me in recent years – not every time, but there are times – they are consistently disruptive. Let me put it that way. The other symptoms are always disruptive for me, whereas sometimes the pain I can kind of work through. So if I had something that could magically clear up my visual disruptions and stuff, that would be lovely.

10h 00-11: Sure. Well, first of all, those are the most bothersome things to me, either the throbbing or, when I say relief of other symptoms, the motion sensitivity. So those would be, from a treatment, the most important outcomes. Now, as to why I say they're the same – because it depends, in a particular migraine, which is worse. You know, at some point, if the motion sensitivity's worse, obviously I'd want that to be number one. If the pain is the worst, then that's the one. You see, once again, in a complex thing, it's hard to say – like, if you were to ask me right now which one's more important, the pain relief is, because right now I've got a lot of the throbbing going on and not as much motion sensitivity.

10i 00-24: And then [symptom] relief is second because those other side dishes, as I refer to them, can be just as debilitating as the pain. And they also last a long time. They often last before, during and a long time after.

5.2.4 Meaningful Change for Acute Treatment: Quick Relief Defined by Daily Function/Productivity

Quickly achieved pain relief was consistently cited by interview participants as a key priority for acute migraine treatment. Definitions of meaningful “quick” pain relief varied across participants in the sample but rarely exceeded a timeframe of 1 hour. It was not uncommon for individuals to desire some level of pain relief within 15-30 minutes (Box 11a-c). Meaningful pain relief was often defined by interview participants in terms of daily function. Most participants sought a level of relief that would allow them to maintain productivity while engaging in their daily work, school, family, and social obligations, even at reduced capacity (Box 11d).

Several participants noted that the longer severe head pain lingered, the more likely their day would be consumed by their migraine attack and remarked that even a 2-hour period of intense head pain with no function would derail daily life and hinder their ability to participate productively in work, school, home, social, and family duties for the rest of the day (Box 11e-g).

Box 11: Quick Relief Defined by Daily Function/Productivity

11a 00-07: Ideally, I would like within the half hour. And rarely does it happen within a half hour, hour. Usually, it happens after. And I really, really wish it would happen faster, before – especially before I get to that point, so I could take it at the beginning of a migraine and then prevent it from getting worse. But it – I don’t feel like medication does that for me…It’s just the time limit I want to give my migraines. It’s like that’s all you have

11b 00-10: At least between 10 to 15 minutes. After that, all sh** hits the fan again….I mean, after that amount of period of time, you just get into a position where it – you just – there’s – you can’t stop it. It just continues no matter what you try. So I mean, if it can’t be less than 30 minutes, I don’t have 30 minutes.

11c 00-20: Thirty minutes or less, honestly. I'd like it that way. Any – if I'm going more than 30 minutes where I'm – where I've actually had to take a Soma, man, that's rough. I'm panicking at that point. Because I'm, at that point, wondering, OK, did I just kill 30 minutes and make this exponentially worse, and it's just not going to work? So, ideally, I would – when I – for a while, I had the gel kind, and they work in like 10 minutes. That was fantastic. But – I would say in an ideal world, 10 minutes would be fantastic, but I wouldn't expect that. I would expect at least 30 minutes maximum, with some relief along the way, knowing that it's coming to full strength.

11d 00-12: They have to happen fast and have to last, because (inaudible) when you get up and go to work, you can't wait half an hour for relief. It has to work and you have to be able to be functional at work….because I don’t have pain relief right away, I'm not getting out of bed when it’s breakfast. I'm getting out of bed when it’s 1:00 PM and that’s kind – that really messes up your – just your day schedule, your sleep schedule, all – and then you're not getting deep sleep and it just progresses just – that that becomes just part of the syndrome, not – just being antisocial kind of thing and not being able to get the – get any work done.

Box 11: Quick Relief Defined by Daily Function/Productivity

11e 00-10: Again, I don't have time for any more to wait around for it to work. It's really important, both of them, because speed-wise as well as the decrease in pain makes a big difference in what the quality of life will look for me for that day and for the days after.

11f 00-05: Considering I work fulltime and I'm also a student, so usually within an hour – you could take a nap in an hour. An hour is not much time that's gone from your day. But then when you start taking like two hours and three hours, it's like, I got stuff to do, I can't be down like that. And even in terms of work, working with the migraine and trying to not go home. I could see my boss letting me rest for maybe 30 minutes to an hour. But like two hours? They're probably going to send me home.

11g 00-41: And to not take too long. To me, two hours is a long time. But like with my Nurtec, it's about an hour – sometimes 30 minutes, depending on how quickly I can get to it before it gets worse. So if I know really early, like if I take it as soon as I get that little sixth sense, I can probably be OK within 30 to 45 minutes. But if I don't, sometimes it takes like that whole two hours. And to me, that's still a long time. That still pretty much stops your day…So it would be nice if it was in that 30-minute timeframe. I could be – like if I had a job, I could be at work, take my Nurtec, go take a break or even say, oh, I'm going to take my lunch or whatever, and then come back and be OK. That is what I think we all would like to have. If we're going to have an attack, then we want a medication that will do that.

5.2.5 Meaningful Change for Preventive Treatment: Reduction in Number of Migraine Headache Days

When asked to reflect on their goals for preventive migraine treatment, most participants defined meaningful change for preventive therapeutics in terms of a percent reduction in the number of migraine headache days they typically experienced. Participants cited a wide range of acceptable reductions with expectations ranging from a 10 to 100 percent decrease in number of days with migraine headache. Across this range, a "50% reduction" or "reduction of half of more" was most commonly cited by participants as the threshold needed to motivate use of a preventive treatment and to perceive their preventive medications as effective or worthwhile (Box 12a-e). This threshold seemed to be especially relevant when discussing preventive treatments that place a greater burden and/or perceived risk to the participant like provider administered Botox injections (Box 12f-g).

It is also important to note that headache days and migraine headache days may not be viewed synonymously by all individuals living with migraine, especially among those with low-level or dull baseline head pain in between attacks or during pre-headache/post-headache periods. It may be helpful to revisit the distinction between migraine days and headache days to better understand how participants interpret these concepts and to explore frequency metrics that resonate best with patient definitions/priorities.

Box 12: % Reduction in Number of Migraine Headache Days

12a 00-08: I would ideally like for it to mean that I don't have any migraines in the month, but failing that, that at least that they would be less than half the time, like maybe 25% of the days instead of 75%....At least a 50% reduction, I guess.

12b 00-11: I mean, I would say, once again, I would look for it – for me to consider it to be successful, I would need a f – let's say a 50% or more decrease…In totally migr – remember at the beginning

Box 12: % Reduction in Number of Migraine Headache Days

I said to you, so far in August, Migraine Buddy tells me I have 23 migraine days? Well, let's take that number, and I'd like to reduce – OK, I'll be a little more generous. Let's say 40 to 50% or more of a reduction. So would consider that about 11 days or more, I guess, it was successful.

12c 00-21: I chose this number because that is what the medicines out there are saying they do, so – and I feel that that's a good number, because if they can't do – if they can't do half, then the – I don't see the point. I mean, if they're going to do it by one, I don't – if it could give me one migraine less a month, I don't see the point in taking it. So I think half is a good number. If they can beat half, that's great. But all the research out – everything I've heard of, it's been a half. So I'm not expecting them to do any more than that, but if they can, that's awesome.

12d 00-28: Either cut by half or more, because when you see 20 and 30%, it's like, I could have done that with eating better or trying – no. It should be cutting it at a drastic rate.

12e 00-44: 50% would be good…Well, because I know there's no cure, but if I have 12 migraine days a month, that's almost half the month. If I can reduce that to six migraine days, that's a benefit to me. That's good.

12f 00-17: Botox is scary to me. That's a toxin I'm putting in my body. So it scares me every time I go get it done. But it helps, so I take that into consideration, too. So – from 15 to – in half, I mean –

12g 00-18: But the Botox – it would – I think that was – I think it was supposed to cut it down by half and that was – I think that makes sense, because you're going every three weeks. It's a whole bunch of needles. It's potentially making your forehead numb. So – and you have to fight with your insurance company, so that was like – I was good with the cutting down by half, if that worked.

5.2.6 Other Treatment Priorities

5.2.6.1 Limiting Side Effects

In addition to the acute and preventive treatment benefits prioritized by our interview sample, participants also highlighted side effects as a key concern and consideration when selecting migraine therapy. Multiple participants reported hesitating to utilize their medication or discontinuing prescription drugs in favor of over-the-counter options due to unmanageable physical and/or cognitive side effects (Box 13a-c, f). Participants commonly described their medication side effects as a general, unspecified, but intense feeling of being unwell (Box 13b-c). Many participants also mentioned concerns about the long-term implications of therapeutic side effects, citing this as a common reason they may hesitate to utilize a new therapy or reduce their utilization of acute and preventive treatments even when faced with debilitating and/or frequent migraine attacks (Box 13d-e). While participants expressed a strong desire for effective migraine therapy, they also carefully weigh known and/or perceived risks of available treatments and may abandon therapeutics whose effects they believe may be worse than the migraine disease itself (Box 13f).

Box 13: Limiting Side Effects

13a 00-03: I don't like things that are going to make me nauseous, because I'm already dealing with the other stuff. And again, I remember taking a prescription a number of years ago the doctor recommended, but I felt worse in some ways, so it just didn't seem like it was worth the effort, honestly. So I take mostly over-the-counter stuff now – and a combination of over-the-counter

Box 13: Limiting Side Effects

things at the same time that don't seem to give me any sort of nauseous feelings or anything like that.

13b 00-39: Whenever I had to take the sumatriptan, I was always afraid to take it because I knew how bad I was going to feel afterwards. And my husband was like, well, you'd rather just be in pain than take the medicine? I said the way that medicine makes me feel, if my pain is a three or a four, I'd rather just try to ride it out, because that medicine made me feel so bad.

13c 00-38: I tried one a long time ago. I don't know if it was a beta blocker or what, but it made me feel horrible and I wouldn't – I was not going to feel horrible every day to prevent something that might happen. So I went off that pretty quickly.

13d 00-28: But I'm not big on medication, and it might be one of the reasons why my migraines last so long, because I could pop two 800s and be OK, but in 10 years, what is that going to do to my liver? So I'm always worried about the side effects of what is going to happen long-term, not even now, just long-term, when I get older. You know, oh, I don't have use of my right hand, because I pumped myself with so many ibuprofens, or just weird things like that.

13e 00-02: The thing that I worry about with Botox is the long-term effects. So that's one thing that I want to note is that I'm really concerned about the length of time I'm going to take it, because there's just so much of a gray area about it. You never know. I told my doctor, if I lose a limb someday – you just don't know. So I don't know how long that that's going to be an option for me. I think about that often. Do I want to continue this treatment?

13f 00-42: The epilepsy drugs like Topamax, which is nicknamed Dopamax on some of the forums I frequent – those that cause sluggishness and brain fog or weight gain – those are completely out of the question. There's just no way I could take something like that and function every day in what I do, which is basically like solving puzzles all day, so I have to have my brain function…. And – yeah – side effects – the side effects just are unacceptable at this point in time with the preventives – just totally, totally unacceptable. I don't know why anyone takes them. I guess it must be that bad that they are willing to risk that. And I see all kinds of horror stories that this person started Dopamax and gained 100 pounds, and that's just crazy to me. That's just insane.

5.2.6.2 Efficacy over Modality

Participants expressed a range of preferences for different modalities of medication administration. For example, many preferred tasteless, orally administered pills (Box 14a-b) while others found nasal sprays to be convenient and more easily tolerated irrespective of taste (Box 14c-d). Despite various opinions on medication modality, participants generally prioritized medication efficacy over mode of administration. For example, multiple participants reported aversions to injectable treatment but would gladly utilize injections if they reliably and quickly resolved pain and/or substantially reduced migraine attack frequency (Box 14e-f).

Box 14: Efficacy over Modality

14a 00-03: I would say the – I had, at various points, been given a sample for one with – that I – would have been administered by needle, and I've been less warm to using that than I would have been a pill. So that, I guess, would be one that did have a impact. Partially, I would say, in – just because of the mode of delivery and everything and not wanting to waste it on a minor headache and not knowing if it was going to be a minor headache, I just ended up not using it at all, essentially. So I would be more likely to probably do something in pill form in that sense.

Box 14: Efficacy over Modality

14b 00-02: I recently tried a preventative medication, I tried Ajovy, and I tried Aimovig, and they're both administered by shot, subcutaneous, I guess you call it, and I'm very, very – I don't like shots, especially after getting 41 at a time of Botox, I just – I can't handle shots…I cannot handle injections, they're very hard for me to administer, especially for myself. I had to bring it into my doctor when I had my treatment to have her do it. I just couldn't.

14c 00-18: So aiming a spray up my nostril is so much easier than being dexterous and having the manual dexterity to put my thumb on this injector, shove it down hard and hold. That just felt so difficult.

14d 00-07: Well, I know, with the nasal sprays that I did, like the Imitrex nasal and also – oh, and Zomig – that's the other medication that I was on, so right before this one – just it creates sort of like a weird postnasal drip kind of taste in your mouth, so that's just – there's just that after thing. But I will take it if it helps my migraine. So it's – but it's not a preferred – actually, it might be a preferred form because it's just the easiest. But I wish that taste wasn't there.

14e 00-11: I look at it as – first of all, I probably look at it in – using a business kind of way, as a cost-benefit analysis, and when I say cost, I don't necessarily mean the amount of money it costs per se, but I look at – and most of these, it's – not to not answer that question – are a kind of lesser of all evils. Well, would I rather have some momentary discomfort of the needle sticking into my leg, or would I rather have another 20 migraines? So, so far, I've opted to, I'll stick myself once a month, as much as I don't like it.

14f 00-04: But here's the thing – like even – you go get a Toradol injection, the injection hurts. But the pain relief that comes in 30 minutes to 40 minutes is well worth the short-term pain. I guess that's where you decide, if you need to go to urgent care, if you really want to go through the extra – I mean it's kind of crazy to think that you have to have more pain to get rid of pain, so – yeah – that's part of the decision making. Am I going to be able to stomach or deal with more pain to get rid of the pain that I'm currently in?...Like if I had a more effective drug that was more painful that I could do myself, I would take it more often than the less effective drug that's less painful. I think it gets back to my end goal. My end goal is to not feel pain. And if I can – if 30 seconds of intense pain will cure four hours of intense pain, that's well worth it. The tradeoff is well worth it.

5.2.6.3 Challenges with Oral Medications

Many participants expressed a preference for acute oral medications to injections, nasal sprays, or suppositories but several also mentioned challenges around administering oral treatment that may be an important consideration for individuals with certain migraine symptom profiles. Specifically, for individuals who experience nausea and/or vomiting during migraine attacks, medication in pill form was less ideal as they may have difficulty swallowing oral treatment and/or keeping medicine down (Box 15a-c). These individuals discussed a range of alternative preferences to existing oral medications including injections, liquids, quick dissolve treatments, and smaller pills (Box 15d-f).

Box 15: Challenges with Oral Medications

15a 00-24: The only – 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 and do anything

Box 15: Challenges with Oral Medications

15b 00-36: So I would say taste – and even sometimes when you're just taking it with water, you can still taste stuff in your mouth. And like I said, being so intertwined with nausea and digestive issues with migraine, I think taste – taste and size, I guess.

15c 00-05: I think the taste is a big thing. Nobody wants to take some medicine that's horrible tasting. And also if you're nauseous, you're more likely to upchuck your med. So I like something that's quick. So even though I don't like shots, it would be nice if it was just like a patch. You could just throw it on your arm and be done.

15d 00-16: Honestly, flavored liquid is the best for me, just because I have a hard time swallowing pills. But if it was a pill, I'd prefer it to be like coated, so it doesn't melt in your mouth as soon as you put it in there, and smaller.

15e 00-38: Mostly I'm more concerned with is it effective? But if I can't swallow and hold things down, it's not going to be effective, if it's a tablet. So for example, (inaudible) is usually a shot and I don't have to worry about vomiting it back up. And that's a good thing, even though I don't really like needles, but it's much better than throwing up. So for migraines, for people like me, who really can't hold things down, the method is really important. If you can absorb it through your skin or through your mouth, that's so much better than having to swallow it.

15f 00-42: Well, now, with my experience with the Rimegepant and the BC powder, I would say that I definitely prefer powdered medications or things that dissolve quickly or things that don't have to go through such a laborious digestive process, just in case the gastroparesis is what's preventing the medication from even getting into my blood stream.

5.2.6.4 Sufficient Acute Treatment Supply

Participants, especially those living with chronic migraine, also cited concerns over what they viewed as an insufficient supply of prescription acute treatments (Box 16a). These individuals often discussed rationing their acute migraine medication due to concerns about exceeding the allowable monthly amount and dosage determined by their healthare professional and by their insurance provider (Box 16a-c). In the context of limited medication supply, some participants were confused by instructions to treat migraine symptoms quickly but not too often and struggled with the choice to treat or not to treat at migraine onset. Hesitancy to treat with acute medications led some interview participants to deviate from their treatment plan, "miss the boat", and thus, compromise the efficacy of their acute therapy (Box 16d-e).

Box 16: Sufficient Treatment Supply

16a 00-02: No. The doctor cannot request any more than that. I'm at the highest milligram and the highest quantity, because they'll only distribute – the insurance company will only distribute so many in a 30-day or 90-day period – I forget how they do it – but – and I don't even know if I'm answering your question, but if I could change one thing for my treatment, that's what I would do. I would say they need to do a better job to really analyze – come on. Is 12 pills enough for a chronic migraine sufferer? It's not enough.

16b 00-09: I tend to try to wait like a little teeny bit before I take the abortives, because they're limited. So the total abortives I have for the month is 22. So if I have to take one of them twice a day – you know, twice in – during an attack – that's not going to last me very long. So I have to be creative on how I use the abortives.

Box 16: Sufficient Treatment Supply

16c 00-24: I wish there was ones that I could take more often that were – like I have a very small window, limitation of what I can take – or how many I can take in a period, in the daytime or how many – like if I have a mi – 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.

16d 00-25: Migraine – medication management's another issue maybe we'll get to. But – so if I get to this phase, I reach for my meds for sure. And unless I've had – yeah, that's another issue – too many in a week, because you're only supposed to take – they say two to three meds a week, which is really hard if you're having four migraines. So that's a balance I have to find.

16e 00-42: It's just really hard, because every single migraine medication that's out there – and non-medical treatments like the neurostimulators – they all say to use it at the first sign of migraine, that they don't really work if you wait too long into the attack. And it's – I just don't know. I don't know enough to know if I'm taking the medication at the correct time. Am I taking it too soon? Was this a regular headache that would have gone away on its own that I'm now medicating, and now that means that, if I use the medication now, I won't be able to take it for the next couple of days if I get a real migraine, when I really need it? So it's always a lot of agony and drama…I do feel like I miss the boat a lot.

5.3 Migraine Symptom Burden

Table 7 summarizes the frequency with which various migraine symptoms were reported to occur within the interview sample. The table compares symptom frequencies across phases of the attack and the inter-ictal period according to interview participants' descriptions of typical migraine experience. The figures presented in each table cell represent the number of interview cases that reported experiencing the symptom within the 40 conducted and coded interviews for this study.

Table 7. Frequency of migraine related symptoms reported by interview participants (N=40) across pre-headache, headache, post-headache, and inter-ictal phases of their typical migraine attacks

Symptom	Pre-Headache	Headache	Post-Headache	Inter-Ictal
Aura	13	5	1	0
Changes in appetite	13	9	15	0
Diminished appetite	13	9	3	0
Increased appetite	0	0	12	0
Changes in sleep patterns	13	9	2	3
Insomnia	13	7	1	3
Sleep during the day	0	3	1	0
Clumsiness/lack of coordination	8	2	1	2
Dehydration	0	0	3	0
Diarrhea	0	1	1	1
Fatigue/exhaustion	16	9	27	4
Hot feeling/flushed	6	6	0	1
Nausea	25	25	6	5
Numbness	12	7	2	1
Pain	23	40	16	5
Back pain	2	3	0	1
Body pain	1	5	2	1
Dull head pain	3	0	6	0
Eye pain	6	9	1	0
Face pain	2	7	0	0
Head pain	13	40	6	2
Jaw pain	0	3	0	0
Neck/shoulder pain	8	9	4	3
Temple pain	3	7	0	0
Pressure	3	0	0	0
Eye pressure	2	0	0	0
Ear pressure	1	0	0	0
Pins and needles	11	6	0	0
Sensitivity	31	34	19	6
Light sensitivity	30	32	12	5
Smell sensitivity	16	14	3	1
Sound sensitivity	24	24	10	3
Touch sensitivity	10	9	3	0
Tension	17	4	2	1
Head tension	6	0	0	0
Leg/arm tension	1	0	0	0
Neck tension	10	4	2	1
Shoulder tension	7	1	1	0
Tinnitus	2	1	0	0
Throbbing with no pain	0	0	1	0
Tremor	0	1	1	0
Vertigo (dizziness, imbalance, motion sensitivity)	8	12	6	5
Visual change	22	12	2	2
Vision loss	5	3	1	0
Blurred vision	11	7	0	0
Eye floaters	8	3	1	2
Eye strain	1	1	0	0
Peripheral vision loss	3	1	0	0
Teary eye	2	0	0	0
Vomiting	2	11	0	0
Weakness	11	8	5	0

*Aura frequencies represent the number of participants in the sample who utilized the term "aura" to describe their symptom experience.

A high-level overview of Table 7 suggests that participants living with migraine experience a very wide range of symptoms across all phases of their migraine attacks. Some of the most commonly reported symptoms within our interview sample included various sensitivities (light, sound, etc), nausea, visual changes, tension, and pain. While it is possible to identify the most common symptoms within our sample by examining frequency of symptom report, it is not possible to identify one or even several universal symptom profiles.

Thus, symptom frequencies and case counts alone do not provide a full picture of migraine-related symptom burden as was reflected through the insights and observations of interview participants. Below, we outline additional observations on symptom burden among people living with migraine based on our analysis of coded content from N=40 interview transcripts.

5.3.1 Associated Symptoms

Participants described associated symptoms that would begin to present during pre-headache and ramp up in intensity during the headache phase of their attack. One participant described the increasing intensity of symptoms from pre-headache to headache in the following terms:

> *00-14: 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.*

Additional examples of this pattern are provided in the interview quotes below where three participants describe relative experiences with progressively more intense sensory sensitivities and nausea throughout the course of their migraine attack (Box 17).

<table>
<tr><th colspan="2">Box 17: Some Associated Symptoms Progress in Intensity from Pre-headache to Headache</th></tr>
<tr><th>Pre-headache</th><th>Headache</th></tr>
<tr><td>00-01: Light and 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.</td><td>00-01: Light and sound sensitivity
It [sensitivity to light and sound] just becomes even more intense.</td></tr>
<tr><td>00-38: 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.</td><td>00-38: Light sensitivity
I want to be in a dark room....Very clearly, if I look at light there are stabbing pains in my eyes,</td></tr>
<tr><td>00-07: Nausea
Sometimes I get chills. Nauseated.</td><td>00-07: Nausea
As soon as I get a migraine, I'm bound to end up in the bathroom at some point. And my eyes close. I just basically will sometimes pass out, like fainting.</td></tr>
</table>

While increased intensity from pre-headache to headache phases of the migraine attack was commonly cited for symptoms like nausea and sensory sensitivities, other associated symptoms did not hold universally to this pattern. In many participants, associated symptoms like numbness, pins and needles, and clumsiness (to cite a few) would either improve (Box 18a) or become less noticeable in the context of increasingly debilitating head pain (Box 18b-d). In the latter, participants described an attentional shift of focus to their head pain and thus, less ability to attend to other symptoms.

Box 18: Some Associated Symptoms Improve or Become Less Noticeable in Context of Increasing Head Pain

18a 00-03: 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. [headache]

18b 00-04: My focus is – like I said, it gets down to survival, so it's only on my pain and not really on anything else. [headache]

18c 00-21: I think I'm just too consumed with the headaches that I don't – I can't focus on anything else. You know what I mean? I'm so the headache is over – is just consuming my whole being, so that's all I'm focused on. [headache]

18d 00-44: Well, the hot flashes seem to dissipate. The aura, if I did have an aura, that takes its 20 or 30 minutes, and that dissipates. If I have nausea, it's usually not too bad. Like I don't vomit or anything. So I guess I would say they kind of dissipate once the pain takes hold. [headache]

5.3.2 Head Pain as a Universal Symptom

Head pain during headache phase of the migraine attack was the only universally experienced symptom among participants in our interview sample. Interview participants used visceral descriptions and analogies to describe their experiences with pain during the headache phase of their migraine attacks. Participants commonly described head pain as completely debilitating and compared it to other intensely painful sensations (Box 19a-b). Participants were also in tune with other points of body and face pain and generally able to identify areas where head pain originated from and/or spread to (Box 19b-d).

Box 19: Head Pain as a Universal Symptom

19a 00-14: Where you can't even get up off the floor, that's where I was at with that kind of pain. [headache]

19b 00-08: Well, the thing that I usually say to my partner is that it feels like almost a piece of rebar is going in one temple and out the other, like listing or something. It's just like this really severe pounding in my temples and inside my brain and then my – the base of my neck, at the back of my skull, is really tender and sore-feeling and my shoulders just are extremely tight, and then sometimes it'll feel like there's ice picks or something going into my eyeballs. Sometimes my jaw feels really tight and hurts and then I just feel sick to my stomach and dizzy, extremely tired, like hot all over. [headache]

19c 00-20: Sure. So I wouldn't say it takes a single form, but it – usually I can feel it – my neck muscles are so tight at that point that they really hurt quite a lot, and right at the base of the skull where they connect – that has a lot of pain, and then probably the frontal lobe area has a lot of pain. But it's basically like a headache squared. [headache]

19d 00-44: Well, it's throbbing pain. For most migrainers, they have pain on one side of the head or the other. I don't. My pain in a full-blown attack is at the top middle of my skull. And it can be frontal pain across my forehead and temples, too. [headache]

5.3.3 Pain Presentation During Pre-headache and Post-headache

Pain was also commonly experienced in the pre-headache and post-headache phases preceding and following a migraine headache. Pain descriptions during pre-headache/post-headache often differed from the visceral accounts of headache phase-related head pain. During pre-headache it was not uncommon for pain to originate in other parts of the body, including neck and shoulders, before traveling to the front, back, and temples of the head (Box 20a-c). Head, neck, and shoulder discomfort during pre-headache were also commonly described in terms of tension rather than pain, with a progressive build towards a more intense pain sensation (Box 20d-e). For some, pain resolved in full at the onset of post-headache. For those who continue to experience lingering pain during the post-headache period, it was often described as having a dull, manageable quality (Box 20f-g).

Box 20: Pain Presentation During Pre-headache/Post-headache	
20a	00-38: Migraines may start as pain anywhere in the body, back pain, hip pain, shoulder pain, anywhere in part of my body that is a little bit s – inflamed. That might – the first symptom is sometimes every part of my body that has – can have an ache or pain. They'll all be aching all at once and I'll realize it's a migraine. [pre-headache]
20b	00-25: But usually if I notice them – it can start with neck pain. Not always, but the neck pain definitely tells me that it's happening. [pre-headache]
20c	00-34: Well, sometimes I will get like – my neck will get stiff, like in the back of my neck and it will be very like tender, in a sense. And then that's how I kind of like know. Sometimes (inaudible) I'm going to get ready like because migraine is going to come. [pre-headache]
20d	00-36: But then, from there, it'll be like my neck and my shoulders will start to get really tense, to where I have to roll my neck around or squeeze my shoulders. And even then, I'm like – you would think I would learn by now, but – I guess I have now, since I can recall it, but I'll be like that's weird. Maybe I just sat wrong or I slept weird or whatever. [pre-headache]
20e	00-10: It's a pressure. It's a – I notice my eyes become very – kind of like a dry, gritty feeling, a pressure behind the eyes, a pressure right at the back of my neck. Shoulders get really tight. [pre-headache]
20f	00-08: Sometimes my head's – my head or neck will still hurt, but it'll be like a different kind of pain, like just like a soreness or a dull pain. [post-headache]
20g	00-17: 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. [post-headache]

5.3.4 Symptom Presentation During Post-headache

During post-headache, participants generally experienced fewer symptoms compared to those present during pre-headache and headache phases. However, fatigue and exhaustion were commonly cited during the post-headache period and seemed to play an even greater role in limiting participants' daily function during post-headache than in other stages of their attack (Box 21a-c).

Experiences with symptoms during post-headache could be highly variable across participants and even within the same individual across attacks (Box 21d-e). Unlike pre-headache and headache phases, which seemed to carry a certain consistency in presentation, experiences with symptoms during post-headache ranged the gamut from speedy and nearly symptom free recovery (Box 21f) to long-lingering residual symptoms that take between hours and days to resolve (Box 21g-i).

Box 21: Symptom Presentation During Post-headache

21a 00-10: It can last all day, up until the next day or so, even two days after. It takes me a couple hours to finally get back into a position where I feel normal again. It’s exhausting for sure. It’s very tired – very tired, where a nap comes into play big time. Sometimes, I can bounce back within two hours. Sometimes, it takes a couple days. But it’s very – it’s a slow process. Very slow process. [post-headache]

21b 00-11: After it reduces from its worst to a medium level or a low level, generally there's a certain amount of fatigue – exhaustion – and, once again, speaking to the doctor about it and other doctors, they seem to feel that the body's just so exhausted from compensating, because what does your body do when you have motion issues? It goes into kind of overdrive to compensate. So now, from all this work it had to do, it's saying, well, I'm kind of tired now. I'm going to rest. [post-headache]

21c 00-17: 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. [post-headache]

21d 00-04: Oh, it can last from – it can last minutes to hours, so sometimes I don’t really feel good even until I go to sleep the next day or I don’t – I won’t feel 100% for days. And so it can be hours. It can be days, I guess. [post-headache]

21e 00-42: At least a day, sometimes two days, sometimes longer. I’ve had this experience several times where I’ll have a migraine, it will switch sides, I’ll feel a little bit better, but I just keep getting headaches every day for like the next week – or, in a really bad year, it was like the next two months. So it’s like the migraine broke something. And I couldn’t return to normal. [post-headache]

21f 00-18: I'm so relieved that I'm wired and I can dance a jig. And sometimes I'm wa – I will mop my whole apartment and go for a walk, because woo-hoo and hooray. But it’s definitely relief. [post-headache]

21g 00-09: I still have some of the residual effects. That usually takes like a day for everything to settle down. So that’s probably why I’m not really noticing that the head pain isn’t there anymore, because I still have the other symptoms, like the half a vision, the stumbling, the loss of words. [post-headache]

21h 00-03: 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. [post-headache]

21i 00-36: It can be – I’d say the least amount of time is probably about – oh, man – three, four, five days is the shortest. But it can – to me, being chronic, it’s like I’m in any of the three phases at all times, so I’m either getting ready for one, I’m going through one, or I’m recovering. So it’s just like it feels like a never-ending cycle. But it can take days to weeks, or until I just have another attack. [post-headache]

5.3.5 Symptom Presentation During Inter-Ictal Period

Over half the interview sample described themselves as completely "symptom free" during the periods in between their migraine attacks (Box 22a). Among those that did report experiencing lingering symptoms between attacks, there does not seem to be one universally held inter-ictal symptom profile. For a few participants, inter-ictal symptoms included low-levels of head/body pain or tension (Box 22b). More commonly, vertigo, sensory sensitivities, or nausea experienced during migraine attacks lingered to a lesser extent during inter-ictal periods (Box 22c). Fatigue/exhaustion and related insomnia was also reported by some as a key aspect of their inter-ictal symptom burden (Box 22d) (Table 7).

Most individuals who experienced symptoms between migraine attacks had learned to cope with them as an irritating, but manageable, consequence of their migraine disease. Both those with and without symptoms during the inter-ictal 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 (Box 22e-f). It is important to note that even if symptoms are not present between attacks, surveillance anxiety (Box 22f) and other emotional impacts like guilt/shame, depression, and frustration do play a bigger role in inter-ictal burden. This is discussed in greater detail in section 5.4.2 below.

Box 22: Symptom Presentation During Inter-Ictal Period	
22a	00-05: So between the attacks I'm usually really good. I don't notice that I'm just super sensitive to things at that point. I'm usually able to function at my normal self between those attacks. But it depen – I guess it also depends on if it's – I guess, then it wouldn't be between. But yeah. Yeah, I think I'm functioning at 100% during that time. [inter-ictal]
22b	00-06: 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. [inter-ictal]
22c	00-18: 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. [inter-ictal]
22d	00-02: I'm exhausted. I'm very exhausted a lot. I'm fatigued. [inter-ictal]
22e	00-44: 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 don't know what the next day's going to bring. So I do as much as I can. [inter-ictal]
22f	00-41: I am completely, 100% my normal self – no symptoms whatsoever, no brain fog, no left-sided weakness or pain, hardly any muscle pain at all…I'm just 100% on top of things. I can multitask. I can make plans. And I will show up. I'm just basically my normal self, before migraine really became chronic for me. So I'm pretty on top of things. I get a lot of things done. I do things. It almost feels like, oh, I'm back to my old self for a couple days. And really, that's all it is is a couple of days. Sometimes I'll get lucky and have a full week like that. Those are the best weeks ever. They're like the best things ever, so – but it's always in the back of my mind – when's the next attack? So how long is this going to last? I hope this lasts a long time. Those are always my thoughts.[inter-ictal]

5.3.6 Challenges Differentiating Phases of the Migraine Attack

The majority of participants in our sample were able to clearly differentiate between phases of their migraine attack (pre-headache, headache, post-headache, and inter-ictal periods). The headache phase was most easily identified by participants, due largely to dramatic expressions of head pain. However, for some participants, particularly those with chronic migraine and/or consistent/daily low-level migraine symptoms such as dull pain, sensitivities, and nausea, identifying the beginning and end of a migraine attack can be difficult (Box 23a-c). For some of these participants, migraine attacks were described as going from a baseline-level of dull pain and associated symptoms to a higher degree of intensity, and then back to a noticeable but functional symptom baseline, without a period of relief (Box 23d).

Box 23: Challenges Differentiating Phases of the Migraine Attack

23a 00-11: We've talked about it, and – because I've asked him [my doctor], how do you differentiate between the phases? And his answer to me was, since I have chronic migraine, it's kind of difficult, because you really – it's difficult to ferret out what's the beginning and the end if it's ongoing….does the balance go off first and cause the migraine, the headache, or does the headache start first, then cause the balance? You know, I haven't been able to ferret out exactly the relationship between them.

23b 00-25: Lately – yeah, a lot lately, being like the least year, it's [photo- and phonophobia] kind of manifested at different phases. And, again, these phases aren't discreet. It's not like I'm like oop, I'm in this. Oop, I'm in that. It's just a way to explain it. But I can be experiencing all of it. Like I don't know. It's hard to say.

23c 00-42: I don't really get a lot of pre-headache symptoms. In fact, one of the problems I have with migraine is that I never know what's an attack and what's not, because I get regular headaches frequently, so if I look back, it's very rare, but once or twice a year, I'll have an attack that starts out with me yawning a lot. And I don't notice it at the time – or once in my life, I got really, really thirsty before an attack. But those kinds of experiences are incredibly rare for me. Usually, everything starts with just a regular headache. It's a solid pain. It doesn't throb. I can move. I can bend up and down. And that's OK. And I don't know – is this going to turn into a migraine or is this just a regular crappy headache?

23d 00-06: I know it as pre-headache, but it's really hard for me to always define specific things to go with it, just because 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.

5.4 Migraine-Related Changes in Mood/Emotions

Table 8 summarizes the frequency with which participants reported migraine attack-related changes in emotion and mood. The table compares frequencies of endorsed emotion/mood changes across phases of the attack and in the inter-ictal period according to interview participants' descriptions of typical migraine experiences. The figures presented in each table cell represent the number of interview cases that reported experiencing that emotion/mood change within the 40 conducted and coded interviews for this study.

The participants included in this analysis often used terms like irritation and impatience, elation and happiness, and guilt and shame interchangeably and did not ascribe to distinctions that we, as researchers, may have originally assumed to be meaningful. Thus, the research team was mindful to avoid semantic distinctions that were not clearly supported in the data and thus, may not hold significance to the participants themselves. However, when to split and when to group concepts is a difficult balance that we will continue to assess as we move into a more targeted, second phase of qualitative interviews.

Table 8. Frequency of migraine related emotion/mood changes reported by interview participants (N=40) across pre-headache, headache, post-headache, and inter-ictal phases of their typical migraine attacks.

Emotions	Pre-Headache	Headache	Post-Headache	Inter-Ictal
Anger	5	3	1	1
Anxiety	12	8	7	11
Apprehension	3	0	2	0
Depression	8	10	9	6
Euphoria (elation/happiness)	1	1	11	2
Fear	3	4	4	3
Flat affect	2	5	1	0
Frustration	5	4	2	5
Helplessness/hopelessness	3	1	1	0
Guilt	0	5	3	2
Irritability/Impatience	24	26	10	0
Negative thoughts/patterns of thinking	5	7	1	0
Relief	0	0	24	0
Sadness	3	3	2	1
Suicidal ideation	0	2	0	0

A high-level overview of Table 8 frequencies suggest that migraine related emotion/mood changes are varied and can be observed across all phases of the migraine attack and in the inter-ictal period in between attacks. Irritability/impatience was the most frequently cited attack-related negative emotion/mood change within our sample, followed by anxiety and depression, which were also experienced by individuals in our sample between attacks .

Frequencies and case counts of emotion/mood endorsements alone do not provide a full picture of the emotional burden of migraine as was reflected through the insights and observations of interview participants. For example, while irritability/impatience represents the most common migraine-related emotion within our sample, anxiety and depression, although reported less often, may hold greater implications for the participants that experience them. Thus, below we outline additional observations on emotional burden among people living with migraine based on our analysis of coded content for N=40 interview transcripts.

5.4.1 Irritability/Impatience

Feeling irritable or impatient during a migraine attack was a particularly common experience among interviewed participants. A total of 33 out of 40 (82.5%) of participants reported feeling irritable/impatient at some point during their migraine attack. Many individuals described this mood change during pre-headache as an early sign of their impending migraine headache (Box 24a-c) only to increase in intensity at headache onset (Box 24d-f) and either resolve or linger to a less significant extent in the post-headache period (Box 24g-h), and disappearing in the inter-ictal period between attacks. Participants discussed being “set off” at first by minor annoyances and eventually, as head pain intensifies, being unable to cope with any form of disruption, impacting both professional and personal relationships (Box 24i-k).

Box 24: Irritability/Impatience

24a 00-02: Even mood-wise, I get a little bit more on edge, because I can feel it coming. [pre-headache]

24b 00-12: But before that, like when the – when it’s at the silent part, I guess, of the headache, that’s when I'm more aware. And sometimes I've been able to be like well, wait a minute. I'm getting irritated because I'm hearing the dehumidifier going. I need to shut it down and maybe that’ll calm me down and I've done that lots of times and I do it frequently actually. [pre-headache]

24c 00-32: 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. [pre-headache]

24d 00-20: It's – yeah, I'd say probably – I just don't want to be near anybody, and I will probably lash out at anybody that tries to get near me, because it's like, dude, get the f*** away from me. I can't pay attention to anything you're doing right now. [headache]

24e 00-09: No, it’s at the point like where everything enrages me. So it could be the littlest thing, and I’m like 2,000 – not even 100 – 2,000. Especially when I haven’t paid attention, and now the symptoms are starting to get progressively worse or more extreme, and I didn’t take the abortive on time. Then like everything irritates me. I could drop a piece of paper and it’s like, God, you stupid piece of paper. [headache]

24f 00-35: 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? [headache]

24g 00-16: I just am almost like coming back to myself. Like I’ll be very tired – still kind of cranky, but not bad. [post-headache]

24h 00-41: Normally, afterwards, I’m just exhausted, so I’m – I – I mean my – that’s my mood is pretty much just leave me alone. I’m tired. Let me recuperate. And I promise I’ll be shiny and new. Maybe a little irritated, coming out of depression. Because I’m finally feeling better, my depression’s lifting. But I’m also tired and a little irritated. [post-headache]

24i 00-18: It – like last week, my dog wanted to go out, which is a perfectly normal canine thing to do, and I – it was like he had demanded the most ridiculous thing of me, like how dare a dog that I love so much want to go out at this time? Oh my God. Anything will set me off, because it feels like not one more thing – I can't handle one more thing. Yeah. And it’s like things that I have no contro – so it’s the dog going out, or there was somebody make – I think XXXX or somebody was making noise outside. That was just like the universe had come and done this on purpose to me. Everything feels very personal. [headache]

24j 00-17: Could get more irritable because, like I said, we’ve got six kids. It gets loud in the house, so – as you can imagine. So them being really loud or playing really loudly or screaming or hollering at each other, something that. I know that it makes it worse, so I could tell I get a little bit more irritable. I’m like, stop. I have to pretty much yell back at them to get them to even listen to me. You got to stop, you got to calm down. Mommy’s got a very, very – they don’t know what a migraine is, I hope they never experience it, but I’ve got a very, very bad headache. You have to be quiet. And it’s hard for some of them to understand that, like I said, because my youngest is three. [headache]

Box 24: Irritability/Impatience	
24k	00-12: Yeah. I'm sure people think badly of me, because they think I'm just all about myself, and I don't want to talk to them. It's just I'm irritated. They're not – they want – I was coming back actually from my parents' and it was just – this was just two days ago – and a bunch of them were standing and they're just saying hello. I know these people. They say hello to me all the time. I didn't even walk close to them…I just don't feel like engaging with anybody. My neighbor dropped off – she had made pizza and I didn't even talk to her again. I think – I mean, I did write her a note and thank you card and all that, but she's attempting to engage me, to be friendly with me and I just don't like it. [post-headache]

5.4.2 Depression and Anxiety

Feelings of depression and/or anxiety manifest for a subset of participants in our sample throughout all phases of the migraine attack and in the inter-ictal period. For those who experience depression and/or anxiety, these feelings can carry a significant emotional burden.

A total of 19 out of 40 (47.5%) participants reported feeling depressed at some point during their migraine attack or in-between attacks. Participants often related their feelings of depression to the overwhelming nature of living with migraine and the way migraine has dominated all aspects of their day-to-day life (Box 25a-d). Thus, depression was not notably associated with any one phase of the migraine attack but rather presented as a global/chronic and serious implication of living with migraine disease within our interview sample. For a small minority of individuals in our sample (n=2; 5%), feelings of depression were severe enough to lead to suicidal ideation (Box 25a-c).

Box 25: Depression	
25a	00-07: To be totally honest, I will sometimes get suicidal. I just – because it is just so bad that I'm just like, I just want this pain to stop. I want to stop getting them. I'm tired of this. They've interfered with every day of my life. I hate planning around them… So it just depresses me. It's just like I just feel so disappointed if I have to leave somewhere – just angry because I can't go to certain things or I can't stay at certain things.
25b	00-02: Feeling of why me, worthlessness, like my body that's – I feel worthless as a person, as a mom. The migraines also have caused PTSD. And so the migraines have affected so much that I get like suicidal ideation.
25c	00-43: And that's when I explain to people that's why I would be one of those people who jump off the cliff. I would be the one back then – I don't know – I'd be scared to have a hole in my head, but I understand why people did it, because the – if you don't have any relief, you have no life. And if you have it every day without a break, you have no life. Why am I here going through this? Eventually, you start – I don't want to be here anymore. I can't deal with it.
25d	00-13: It just makes your life a living heck. But I'm depressed all the time with them. All the time…I'm very agitated. I'm very depressed all the time. Because I just can't get my life together.

Similarly, anxious feelings were expressed across all phases of the migraine attack and anxiety was documented as the most commonly experienced emotion/mood change among participants in our sample during inter-ictal periods. A total of 21 out of 40 (52.5%) participants reported experiencing anxiety at some point during their migraine attack or in-between attacks. The cause, characteristics, and implications of anxiety varied somewhat across phases. For example, surveillance anxiety in the post-headache and inter-ictal period were often related to a nagging concern about one's next attack, including when it will arise, how long it will last, and how severe it will be (Box 26a-b). While participants described experiencing similar anxious feelings during pre-headache and headache, anxiety took on a somewhat different quality during these phases when compared to post-headache and inter-ictal periods. Post-headache and inter-ictal surveillance anxiety seemed to be triggered by a certain level of *uncertainty* (e.g., when will I experience my next attack?) (Box 26c-d). In contrast, anxiety during pre-headache and headache seemed to be driven by the *certainty* of knowing a migraine headache was occurring or near (i.e., I know I'm in for a challenging few hours or days) (Box 26e) and the *uncertainty* of its progression (e.g., how long will it last? how bad will it get?) (Box 26f-g).

Box 26: Anxiety	
26a	00-18: Either I'm waiting for the next one and that's ugh, there are going to be storms next week, it's going to be a bad week. Or I've had headaches for three days in a row. I wonder if that's going to turn into a migraine. And I know it's just low-grade either anxiety or anticipation, so if I'm smart, I'll try to get as much done as I can before a migraine hits, so I don't have to do it then. And if not, I'll totally give in to the emotional aspect of just like waiting for it, like oh no, when's it going to come? [inter-ictal]
26b	00-14: That the fear and the anxiety, that goes down, but it's always in the back of your mind. OK, when's the next one? I just had this one, got through this one. But you can't help but have that thought in the back of your mind. I don't want to say it controls you. To a certain degree it does. [post-headache]
26c	00-04: I worry it's going to come back and, if it comes back, how it's going to come back and what – now I've taken all I can – taken all the medication I can take for the day, so I'm left with either go to the ER to get Toradol or to suffer. So that's anxiety-provoking for me, because I'm now done with medicine for the day. And I'm in that after phase. And yes, they do come back and, no, they don't come back….And so there's more anxiety in that phase than the pre phase because, in the pre phase, I know what's going to happen. I know I'm going to have a migraine. In the post phase, I don't know what's going to happen. I have fear kicking in because I don't know if I'm going to get another one. I don't know if I can get to the ER. I don't know if I can finish driving. I don't know if I can finish this meeting or this conference or what have you that I may have started to take – partake in after the fact that my migraine went away. I don't know when – I don't know if and when I have to escape again. So yeah, there's anxiety there. [post-headache]
26d	00-29: Simply put, frustrating, in all honesty. Like I am terrified of overdoing it or not doing enough and it triggering a migraine. I live in this constant fear, constant anxiety that I can get one at any time and there's no rhyme or reason half the time. It just happens. [inter-ictal]
26e	00-14: I know I can't – something that I can't control and that's going to be very painful and not being able to stop it, have no way of controlling it. And it's just going to happen anyway. I sense something coming on that I have no – absolutely control over. I know it's going to be

Box 26: Anxiety	
	very, very painful… There's no switch you can turn on or off to make it not happen. It's just – it's the inevitability of it. Very stressful. [pre-headache]
26f	00-10: I think the anxiety, because you're like, crap, I'm in the middle of who knows what. I don't have time for this. What is this going to pre – what is this going to cause me to do? Is it going to be one that's going to react towards my preventatives – I mean, to my – or to my rescues, or is it going to be one that's going to be very stubborn and not? And do I need to go home? Do I need to stay? Do I need to just give it 15 minutes? I think the anxiety end of that point, because you really don't know what's going to happen on this episode. [pre-headache]
26g	00-04: 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. [pre-headache]

5.4.3 Complex Constellation of Negative and Positive Emotions During Post-headache

Characterizations of emotional burden during post-headache demonstrated a layered and complex constellation of both negative and positive feelings and mood changes as individuals recover from the intense pain and symptoms experienced during their migraine attack. Emotion/mood changes at post-headache were commonly and spontaneously characterized by interview participants using the term "relief". Participants viewed relief not just as an expression of symptom reduction but as a characterization of positive emotional change and decreases in emotional burden during post-headache (a-c). However, relief or elation and negative emotions or thoughts/patterns of thinking like anxiety, depression, fear, anger, frustration, guilt, and sadness were not mutually exclusive experiences in the post-headache period. Many participants described feeling simultaneously grateful/relieved/happy for their reprieve from migraine pain and symptoms, fearful/anxious/apprehensive for their next migraine attack (d), angry/frustrated/saddened/ depressed (e-f) by their circumstance, and guilty/ashamed of their previous disengagement from household and/or work responsibilities (f-h).

Box 27: Negative and Positive Emotions During Post-headache	
27a	00-18: Either – it's always relief and either I'm so relieved that I am like Jell-O floppy, exhausted in a totally different way, like my – I have just completed a triathlon of migraine pain and my body is done for the day. Or – and this one is bizarre – I'm so relieved that I'm wired and I can dance a jig. And sometimes I'm wa – I will mop my whole apartment and go for a walk, because woo-hoo and hooray. But it's definitely relief. [post-headache]
27b	00-39: 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. [post-headache]
27c	00-43: All you can do is go – all I do is go to myself, thank God, oh my God, I can't take this anymore. And that's all. You keep repeating it over and over and over again, because it's like you're running from some – 20 people looking to shoot you with guns. And it's like you're finally – they're not chasing you anymore. It's not attacking you anymore. And that's all you

Box 27: Negative and Positive Emotions During Post-headache	
	can do is thank God it's all – oh, it's over. I could – oh, I could breathe. I could be – it's like the world is lifted up off your shoulders. [post-headache]
27d	00-08: Just kind of a sense of relief and a little bit of apprehension that it might not actually be over or that I might – it might just be one of the periods during it when it gets a little less, but definitely a sense of relief and almost elation, like now it's finally time I can do stuff and get out of the house. [post-headache]
27e	00-25: There will be, I think, a bit of a euphoria when the pain stops. Not euphoria, but it's like, oh my God, it stopped. And then I'll just pass out usually, and then when I wake up, that's when I feel the depression and everything else. [post-headache]
27f	00-10: At times, sadness, because you just lost a certain amount of time with the day, whether it be with your family or work. But mostly family gets me sad, because it's like, crap, we're in the middle of this game, and, well, Mom's got a migraine, so we got to go – I got to go inside. I think it's just realizing of the time, that precious time, that life's too short, and you're losing out because of this stupid situation you're having to deal with. [post-headache]
27g	00-08: Well, those are the main things, but I guess I also feel frustration and guilt sometimes, like if I shirked my duties for days or I haven't gotten anything accomplished at work, then I feel overwhelmed and anxious about trying to make amends or finish stuff. [post-headache]
27h	00-02: After you wake up, you start to think about the things you didn't do that you should've done and how it affected you pre-headache, pre-migraine or migraine, I should say, and you – so you have to toy with that. When I first wake up, I think gee, I didn't do this. I didn't do that. And you s – there's the guilt definitely. The emotional part is definitely there, but I'm more pleasant for sure when I'm starting to go down that hill, as you can imagine. If you're riding a bike, you're not wanting to go up it, but you like to come down the hill. So I definitely – I smile a lot more. [post-headache]

5.5 Impact on Daily Living

Significant disruptions to daily function during migraine attacks were commonly reported in our interview sample.

5.5.1 Daily Function During Headache

For 75% (n=30) of the interview sample, the headache phase of the migraine attack was equated with essentially zero function defined by the complete absence of activities, both physical or cognitive in nature, as the individual's full attention is diverted to coping with migraine pain and symptoms (Box 28a-c). In this context, discussions about engagement in home, work, family, and social life during headache were not particularly relevant. This finding may be a consequence of sampling from a population with more severe migraine (i.e., connected to CHAMP and its advocacy coalition). Thus, the spectrum of daily function during headache may be broader in the general migraine population than our qualitative findings suggest.

Box 28: Daily Function During Headache	
28a	00-04: It has to stop. I guess my life has to stop. And that's the most unfortunately part – like I have to stop like if – or I have to exit or I have to – whatever I'm doing has to change dramatically because I can't function. I don't know how else to put it. I can't function. I guess that's the only thing I can say is I really can't function. [headache]

28b	00-02: I would call it function. It's the I can't function time. I simply cannot function. I have to be alone and in darkness, no lights. I'm just – I don't know how else to describe it. [headache]
28c	00-43: Yeah. It's total. You can't – you're overwhelmed with pain, so it's not like I have to think about the pain. It's like somebody with their hands on your throat or somebody twisting your arm. You focus on it because there's no way to un-focus. It's just overwhelming pain. So th – it's just you can't do anything. You can't think. You can't function. [headache]

5.5.2 Daily Function During Pre-headache

Participants descriptions of daily function during the pre-headache period were more varied. Some preferred to continue home, work, and social activities at limited capacity until otherwise unable (Box 29a-b). Others did their best to disengage from daily living during pre-headache in an attempt to rest and mitigate the severity of their attack (Box 29c-d). Still others, felt they would benefit from a reduction in activity during the pre-headache period but were unable to focus on rest due to existing responsibilities at home or work (Box 29e-f).

Box 29: Daily Function During Pre-headache	
29a	00-26: I try to continue on because I have to make myself know this is how I've got to live and this is what it's going to be. [pre-headache]
29b	00-41: But so when it comes to the tolerable stuff, I can push through. I don't like to say that too much, but it is – it's the truth, like we have to push through the pain sometimes to do what we need to do. And I'm able to, like I can do that today – but not too hard, because then I could make it worse. So it's always a balance. It's always – I'm always having to self-evaluate. That's very exhausting. [pre-headache]
29c	00-02: I need to rest. As soon as I feel it coming on, I almost find myself dropping what I'm doing to be able to lay down to get to my m – I have my medication with me, but if I feel like I'm getting stick, oftentimes it means coming home to be able to rest so that I can avoid it becoming a really bad h – migraine versus a moderate one. [pre-headache]
29d	00-25: So if I know it's coming or suspect it might come or it's going to be worse, I pretty much immediately institute getting in bed, being in the dark…I – sometimes I get my icepack. Sometimes I don't. I'll put topical analgesics on my head and – or around my scalp. So I just kind of try to do – eat very light, mildly. So I just kind of institute that immediately because it seems like, the faster I do it, the better. [pre-headache]
29e	00-30: The – well, the changes that I have to make – I have to – well, I can't miss work, so I have to be really careful about what I'm doing, because it seems like my thinking is not clear. It's kind of – I'm kind of fuzzy. So – and I'm a lot slower at doing something than I would normally be. If I know that it – I'm going to get one, really, I just – it just like slows down life, I guess. [pre-headache]
29f	00-28: But as a mom, a lot of times I haven't been able to cancel events, so the only way I avoid a event – if it's not with my daughter, because even at a 10, I will take a ibuprofen – I will drink two cans of Mountain Dew if I have to when it comes to my daughter, because she doesn't understand, oh, Mom head's hurt, we can't go today. If that was fact, we would never go anywhere. [pre-headache]

5.5.3 Daily Function During Post-headache

For most participants, the post-headache period was marked by a gradual return to normal daily living. Many in the interview sample described lingering symptoms or cognitive effects that necessitate an ease back into full daily function (Box 30a-b). Some interview participants additionally described feeling apprehensive of their recovery and thus, were careful to pace and avoid activities they felt may trigger a relapse (Box 30c-d).

Box 30: Daily Function During Post-headache	
30a	00-44: Well, it's usually at least a day I call myself in recovery. I don't have the – I don't have the throbbing pain anymore, but my body is kind of coming back to my normal. So it's a slow day. It might not have me going out at all. Might just be – I may not even get dressed. I may stay in my robe. It's just a very slow day. [post-headache]
30b	00-24: I have said that – like sometimes I would tell people that what also makes migraine very hard is that it's almost like you feel like you still have it afterwards for a number of hours and even a day, sometimes two days, where it's like you have this recovery, so you don't have the head pain but your body feels completely like – I often will compare it to the flu. It feels like the flu is gone, but now you're exhausted and trying to recover from – recover back to your regular self. [post-headache]
30c	00-25: I have to be careful. If I try to just get right back up, I'll trigger another migraine, I've found, so I really try to pace myself. I usually want to get up and do things, because I'm glad the pain's over, and whatever I had to put off, but yeah, it's a tricky one. Like for my health management, I shouldn't do anything at that point still, but I sometimes do, because – like yeah, I'm still really low-energy, so I'm not doing much physically or making plans or anything like that, but yeah, I might start to do like housework. [post-headache]
30d	00-39: I try to slowly get back into it, just because I don't want to – if this makes sense – it's like – how can I explain it – you don't want to do anything to retrigger it. So I try to not just jump right back – oh, let me go clean the house, let me go get on my knees and scrub the bathroom. It's not getting right back into stuff. It's just, OK, I'm up, I'm walking around. Let me fix something to eat…It's almost like you don't want to reinjure what just healed. [post-headache]

5.5.4 Daily Function During Inter-Ictal Period

During the inter-ictal period, some interview participants identified trigger activity avoidance and challenges with long-term planning as major disruptions to their daily life. Individuals described missing out on simple pursuits they used to enjoy over concerns about triggering a migraine attack (Box 31a). Some also were burdened by the overwhelming sense of caution they exercised between migraine attacks and felt that this excessive need for vigilance reduced their overall quality of life (Box 31b). Some participants were also bothered by the impact migraine has had on future planning. Several cited migraine-related disruptions to previously planned travel, social/family engagements, and professional and academic work. These personal experiences led some in our sample to limit long-term planning in family, social and professional circles (Box 31c-e).

Box 31: Daily Function During Inter-Ictal Period	
31a	00-14: It's kind of like a hidden handicap. There's things I used to do as far as yard work, cutting the lawn, those kind of things, exercising. It's kind of taken those kind of things away

Box 31: Daily Function During Inter-Ictal Period	
	from me. Being outside, where I used to go out and do it all the time no matter what the weather conditions were like. It never bothered me. Now it's, like, I really have to pay attention and work what I want to do around the environment versus the other way around…I should be able to go do whatever I want to do. It's kind of limited that. I feel like I'm missing a limb or something sometimes. [inter-ictal]
31b	00-08: Kind of like walking on eggshells, in a way, because I will try to just not do anything that I think could trigger one, whether it was from the – a small amount of information I gained from keeping that journal, like I'll try to not eat sugary things, especially in the morning, and then I'll try to not stay out in the heat or humidity for too long and I'll just try to de-stress as much as possible. So I kind of feel like I'm always just trying to keep it from happening again. [inter-ictal]
31c	00-25: I can't travel. Like I used to travel a lot. Like I was really social. And I used to work. I can't work anymore, because too much screen time on the computer will trigger a migraine. Also, like I don't – I used to dance, take dance classes. I can't do that anymore. What else?...I'm limited by my disability income, but that's another story – I guess not for this. Like I can't make a new website, because they'll be worried that means I can work, which is ridiculous. So I feel like I have to live this really weird life. [inter-ictal]
31d	00-02: I work with an organization, Italian organization, in the neighborhood and they cater to – they're sort of an Italian welfare agency, if you will, and so I go and I volunteer there and I committed to going this morning and I was just too sick, so I had to cancel and I'm still feeling guilty about it. I'm still feeling very affected by how I affected everyone else. So it's rare that I make commitments, because of this reason. I really don't make a lot of commitments. I'm too afraid to. [inter-ictal]
31e	00-09: I don't make long-distance plans. I don't make any plans past a week, so – yeah, because I never know. Because I used to plan out – like I was like, OK, so three weeks from today, we're going to go do so-and-so and so-and-so. And then the morning of, it's a bad day, and then I can't do it, and everybody's disappointed, or they think I'm just using the migraine as an excuse to – not to do something. [inter-ictal]

5.5.5 Impact on Driving

Interview participants had varied views on driving both in the general context of their migraine disease and during specific phases of their migraine attacks.

A few individuals in the interview sample have stopped driving altogether as they consider the activity too dangerous to undertake given the unpredictable nature of their migraine disease and quick onset of their migraine attacks (Box 32a).

Among the majority of individuals in the interview sample that still consistently drive, many view driving during the pre-headache period as dangerous given the constellation of symptoms and cognitive impacts that affect them in this phase, including sensory sensitivities, trouble with focus/concentration, visual changes, and tension/pain in various parts of their head and body (Box 32b-d). Given this, most individuals try to avoid driving during pre-headache but described many circumstances when driving at the onset of a migraine attack was unavoidable (Box 32e).

During the headache phase of an attack, when pain and associated symptoms are generally at their peak and physical and cognitive function at its worst, driving was described by most as an impossible and exceedingly dangerous activity that they avoided at all costs (Box 32f). Most individuals in the sample, aside from those that avoid driving in general, felt capable of driving once their migraine progressed into the post-headache period. Some individuals, however, still avoid driving in post-headache due to lingering issues with concentration/focus and/or other bothersome symptoms, like light sensitivity (Box 32g-h).

Box 32: Driving

32a 00-09: I'm no longer allowed to drive, because they hit fast and furious. So I can be talking to you now and be fine, and three minutes later, the attack has happened, and that's a whole big other scenario. [inter-ictal]

32b 00-35: And if I'm moving fast, I see streaks in my vision. So it's hard to – when I'm driving, it's hard to see where I'm going. [pre-headache]

32c 00-26: I guess it's because of the neck thing, I guess, and then trying to hold the steering wheel and then focus on other people. You've got to watch what's going on around you. Watch what you're doing, looking out for other people. So I just don't like to drive at night, no way. [pre-headache]

32d 00-03: I get that fogginess first. Before the visual stuff gets really bad, I usually have a few-minute warning, anyway, bef – it's kind of a – I feel it come on suddenly, but then it gets gradually worse over a period of time. And if I feel it coming, I usually am able to get somewhere I need to be, or I'll have my wife drive if we're together, which is usually what I end up doing – just saying that I can't drive right now…I just know well enough that my vision – there are times where it's not as bad and maybe the sunglasses might be enough to help me. But generally speaking, I don't – I really prefer not to drive, if I can avoid it, during that stretch. [pre-headache]

32e 00-30: Oh, I drive a lot for my job. It is challenging, because like I said, the lights and the sounds and – they really bother me when I'm in that state. So basically I slow down when I'm driving. I try to take a break or two during that time so that I can just kind of regroup if I'm able to. [pre-headache]

32f 00-16: Oh, I'll refuse. It's almost like drunk driving. [headache]

32g 00-03: That's – I don't feel bad about driving the next day at all. Nothing is ever so severe – unless, again, I get another headache that day – that I wouldn't drive. [post-headache]

32h 00-04: I really don't want to drive. Driving is not only I got to deal with the light but I have to deal with – I have to – it's more of a processing, like my processing ability is – it's like I was running a Intel i9, generally, is how I classify myself – I'm like an i9 processor. And when I have – post-migraine, I would say like I'm an i3 processor, like I just don't have enough. It takes a lot more effort. So the higher processing things like driving – or if I'm on vacation, I don't want to be flying – or things that I have to do a lot of processing, I guess, so to speak. [post-headache]

5.6 Physical Limitations

5.6.1 Pain with Movement

Most migraine-related physical limitations reported in our interview sample were attributed by participants to experiences with worsening pain due to movement. Participants generally avoided physical actions like bending over, climbing stairs, moving or exerting head/neck/shoulder muscles, and even walking because of the impact of these movements on pain severity (Box 33a-b). Often, these physical limitations presented at pre-headache and worsened at headache onset (Box 33c-d).

Participants struggled to detail their physical limitations during headache. Most individuals described experiencing a global physical impact that required them to lay or sit perfectly still and avoid all movements or exertions. These participants described headache as a period of zero physical function and immobility and thus, had few recent experiences with physical movement during headache to inform a more detailed description of movement thresholds or distinctions between different types of motion (Box 33e-g).

Basic physical limitations (e.g., walking, bending, climbing) related to pain with movement did not seem to play a notable role in post-headache or inter-ictal burden for most participants. Some participants described avoidance of strenuous physical activity like exercise and yard work but otherwise viewed the period between attacks as a return to “normal” physical function (Box 33h).

Box 33: Physical Limitations: Pain with Movement

33a	00-25: I don't bend over. Like I wouldn't vacuum. I wouldn't broom. Anything that requires me to bend my neck down, I don't do, because that will trigger a migraine or make it worse. [pre-headache]
33b	00-29: Definitely the moving my head. I feel like if I move my head back and forth, it just makes it worse or like speeds up the process. [pre-headache]
33c	00-03: But yeah, movement is – like any sort of head movement or – side to side or that sort of thing, and the pain is worse. Bending down, the pain is worse. Moving too fast, the pain is worse. That sort of thing. So yeah, I would say I feel – when the pain comes on, I feel more limited physically, just because anything I do could kind of have a jolt of extra pain then. [headache]
33d	00-14: But to me it’s almost like a hidden handicap when you get them really bad because it even hurts to move. Sometimes the throbbing will get so bad, there were times where I couldn’t even get up off the bathroom floor because it hurt too much to stand, the actual movement, physically moving. [headache]
33e	Physically, don't do a lot of physical stuff because it'll all – if I do, I'll throw up. So even if I'm still at work, I'll just stay put in my chair. I don't go anywhere. [headache]
33f	00-43: But it hurts to walk. It hurts to move your arms around. It hurts to do anything. When you have a migraine, even when you want to go to the bathroom, you don’t want to get up. You don’t want to leave the ice bag. You don’t want to go to the bathroom. It’ll wait. It’s just everything is on hold at that point, because basically you’re dehabilitated. You’re almost like you’re alive, breathing in the bed, curled up in like a ball. You don’t know what position you could get to. [headache]
33g	00-01: If, for some reason, I’m alone, I have that Lifeline button thing. But if, for some reason, I’m alone and my husband’s traveling or visiting his family or whatever, then I’m screwed. I have to call 911, because I won’t be able – if I fall or – you know, I can’t get up, literally. [headache]
33h	I'm usually very busy in between, because I know I get them so frequent. We're usually always running around and getting stuff for our home or playing with our dog. We're pretty active people. Me and my daughter are very active. So my time in between is just being very active. [inter-ictal]

5.7 Migraine Tracking

The majority of interview participants reported currently and/or previously tracking their migraine attacks and symptoms. Participants reported using a variety of mediums to track their migraine attacks including mobile apps or internet sites, journals, and calendars. A mobile app called

"Migraine Buddy" was frequently cited by participants and was often recommended by a participant's headache specialist or neurologist.

Commonly cited benefits to migraine tracking included identifying triggers (such as food, sleep, sensitivities, weather, etc.), identifying symptoms as well as their presentations and variations in severity, tracking the effectiveness of treatment regimens, and tracking effects of migraines on quality of life (e.g., school, work, family, etc.) (Box 34a-b). When the tracking was reviewed with their healthcare provider, participants cited that dates, severity, length, and frequency of migraines were often the only items given consideration, specifically in a provider's decision to regulate or adjust medications (Box 34c-d).

Participants also expressed a variety of challenges associated with migraine tracking that led some to inconsistently track or not track at all. Participants cited the added burden of tracking a complex constellation of frequently experienced symptoms, the difficulty of logging effects during migraine attacks, and challenges in pinpointing symptom patterns or triggers as major barriers to continued participation in migraine tracking (Box 34e-h). Participants also expressed that their tracking was seldom reviewed by their physician and thus, seemed to make relatively no impact on migraine treatment experience (Box 34i). Some participants also felt that migraine tracking increased their focus on migraine in an unhealthy way and as a result, "fed" their migraine symptoms and pain, resulting in a perceived increase in migraine severity and negative feelings/patterns of thinking (Box 34j-k).

Box 34: **Migraine Tracking**

34a 00-41: I did finally settle on Migraine Buddy, mainly because of the charting that it gives you and the result that it can give you for the doctor's office. They really like that, so – but yeah, because my symptoms are kind of – so I've been told, even by headache specialists, that my symptoms are just not clear cut. I'm like a round peg trying to fit in a square hole or whatever – however that saying goes. And so I have symptoms that just don't make sense. And so trying to track some of the symptoms that I was experiencing – they just weren't on there. So of course, I had to create my own little symptom list. Thankfully, they allowed that on those trackers – but yeah, it was just things like that.

34b 00-18: I think the benefits are that I realized that this hair bruisey thing was actually connected to migraine attacks, so I was able to say to my doctor, hey, this weird thing is happening and you're not going to believe it, and then she did, and it felt validating and also a reason to do something about it, which was great. And if I hadn't been consciously inserting symptoms into this tracker, I think I just would've brushed it off.

34c 00-10: Yes. She does recommend – or she did recommend a paper log. It's not easy for me to maintain a paper log with everything. So with this app, I'm actually able to email her the log, and it will give the dates as well as the severity as well as side effects, medications used, how long the duration of the symptoms, etc.

34d 00-34: She – they use it to see if I need to – you got to add more (inaudible) in there – to see if I need – it's like if I need a medication adjustment. To see, you know, just basically to see if the medication is actually working for me. They use it to count how many migraines I've had – stuff like that.

34e 00-07: I've had problems being consistent with that because they happen so frequently, I'm just like – I just can't track them. They're just – you know, they're so arbitrary, I can't figure out what – I know some of my triggers. But other times, it's just – like I said, I could sneeze and get a migraine. I bend over, get a migraine. I laugh, I get a migraine. I smile – you know – yeah.

Box 34: **Migraine Tracking**

34f 00-12: That’s a very good question, because my neurologist had asked me to keep the apps for this. You know what? It was too complicated for me to follow. I forget – a couple of them I downloaded, but you know what? I don’t feel good. So I just write it down. This is why it was like headache, no headache. Headache, no headache. I had to end up doing it like that, because it – there are too many things for me to follow and track and because I'm already blurry and in pain, and just for me to look at a screen with like five things on it is too much.

34g 00-26: No, because I really couldn't find anything. I didn't know what was – when I first started to go a neurologist, it was like, could I find something that would trigger it as far as foods. But I never really found foods that would trigger a migraine because I was eating everything. And I really couldn't figure – distinguish what was causing them.

34h 00-27: I really don't. I've downloaded apps and stuff like that, but I find the time I'm least likely to keep reasonable records or be objective is when I have a migraine. When they start, even if they're minor, my head is going to explode and the world is ending. Yeah. And I don't feel like tapping on anything, or anything like that. So no, I don't keep track

34i 00-06: Sometimes they reviewed it. Sometimes it was for – it was meant to be for my own purposes. Sometimes we went over it in appointments. And sometimes the idea of like we’re going to go over the headache diary in appointments is more like a – quote-unquote – I’m just going to write down all the numbers. And it’s like data tracking of how many days were you at this level per month, and then just writing it down and never talking about it. But that’s m – it’s mostly that last one, where it’s just like, OK, we’ll just take down the data but not do anything with it, and it doesn’t mean anything.

34j 00-06: So I did that for a while. But I found that, by – especially whereas mine are more constant – that keeping a diary like that isn’t helpful for me in the long term, just because it’s – it causes me to focus too much on the pain levels, which then makes them worse.

34k 00-36: So I used to do it really heavily. I had papers – paper calendars and a color-coding system, this whole thing, when I was doing not great at all, because obviously just trying to track triggers or whatever it may be. But I found that to be – it was like I was feeding it too much, where I was thinking about it too much. And then every single day, having to recall when in the day I felt the worst or whatever it may be just kind of sent me into some spirals. So I kind of have branched away from that.

5.8 COVID-19 Impacts

Overall, the majority of participants did not cite fundamental changes to their symptom profile, disease impacts, or treatment priorities due to the COVID-19 pandemic. However, we did observe some variation in participants’ migraine experiences over the last several months. Impacts due to COVID-19 included changes to treatments and care access, changes in migraine severity and frequency, and improvement in daily living.

With the COVID-19 pandemic and related stay-at-home orders, participants expressed both disruptions and easier access to care and treatments. Common disruptions to care included cancelations of in-person appointments and treatments (e.g., Botox, infusions), the switch to telehealth appointments, delayed/backordered prescriptions, and avoidance of urgent care and emergency rooms (Box 35a-d). A few participants also cited difficulty in obtaining a new healthcare provider as former providers either retired or left their practice during the pandemic (Box 32e). Conversely, some participants expressed easier access to care due to the pandemic. Common care and treatment benefits included lower burden of telehealth appointments (e.g., reduced travel, exposure to triggers, more efficient), coordination of at-home treatments leading to quicker pain and symptom relief, and better communication with providers (Box 35f-g).

Increases in migraine severity and frequency as a result of the COVID-19 pandemic were often attributed to increased stress and anxiety over potential lockdowns and stricter guidelines as well as less opportunity to engage in preventive behaviors and therapies. Notably, participants cited potential mask-wearing in public spaces, closures of school dorms, and competition for employment as factors affecting stress levels and increased frequency and severity of migraine attacks (Box 35h-j). In addition, disrupted access to preventive treatments (e.g., Botox) and therapies (e.g., physical therapy) sometimes contributed to increased attack frequency (Box 35b, Box 35k).

Many participants also reported improvement in their migraine experience due to the pandemic including fewer concerns about the need to engage in activities outside the home (e.g., remote work and school, errands, appointments), reduced guilt over canceling social events with friends or family, and more access to online services (e.g., delivery services, telehealth). As a result, participants felt they had more control over their daily environment (Box 35l-m).

Box 35: COVID-19 Impacts

35a 00-02: The Botox treatment, is that counted? Because I did have a little difficulty with that in the beginning, because my doctor didn't want to – we didn't want to go – to do any clinic visits. So we had to decide whether I wanted to go with her assistant – the other doctor in her practice – who was giving it or if I should hold off and we agreed that I should continue with treatment, because we were concerned about rebound headaches. So that was a – a change, but I did continue with it, with her other doctor.

35b 00-42: Yeah. It definitely has. So I rely on massages a lot to help control the migraines, because a lot of the migraines come from the muscle knots in my neck. And during the beginning of the pandemic, physical therapy and massage therapy was out of the question. And I tried to see my neurologist via telemedicine, but the connection from his office wasn't very strong. And it didn't really work out, so I was forced to go back in…So yeah, it was really disruptive. But as time has gone on and we have learned more about the virus, I feel more confident attending my appointments with an N95 mask.

35c 00-23: But during the heat of the pandemic, my medications were delayed. Sometimes the pharmacy couldn't get their shipments in or whatever else, and so I would be delayed getting my preventative or any of my migraine-related prescriptions, which was not the best thing.

35d 00-29: I am not going to the hospital as much, because it's riskier than normal. So that's some of the only like big changes is that I refuse the majority – unless it's like super, super-bad, I'm not going to the hospital. I'll just tough it out and be with it or something.

35e 00-06: I'm between three clinicians, actually, because of COVID-19. So I was – my first clinician left the practice. And I was between providers, trying to see a new one. And that was scheduled to be in March, and then got transitioned to telehealth, and then that provider left the practice. So I'm now between the provider that I saw for telehealth in March and seeing the next provider, which I actually see this week.

35f 00-04: Now, benefits of COVID is (a) I don't have to get in my car in the sun and drive to my doctor and deal with an idiot secretary that doesn't know what she's doing and all the other things that gets me anxious… and then having a doctor that may or may not prescribe the medicine that I'm seeking, having that stress – that anxiety. One of the things about COVID is I can click a button and hang up on people pretty quickly – we're done. And so that's a positive.

Box 35: COVID-19 Impacts

35g 00-06: Coronavirus is probably the one thing that actually helped my access to treatments…I want to say three – years, to get the Toradol, Compazine, and Cogentin combination that I was just talking about – the only way that I could get that was by going to an emergency room, so that was for two months at a time in different cycles throughout the year, I would be in an emergency room once a week just for that. And even though my headache specialist knew about it, my primary care knew about it, they didn't ever think to come up with another solution that wasn't having me in emergency room every week, especially because the cost difference for those is significant but – and it's the same exact treatment. So now – so coronavirus actually helped me be able to get the treatment to be – to do it at home, because my doctors didn't want me to be going to emergency rooms.

35h 00-02: I have the mask on, it has affected me, because generally, I'm getting headaches more often, so – whereas before, I'd be like – say, for example, at the grocery store and I'd be doing my usual thing for her – I wouldn't be – it's always on my mind now because of the mask, so I wouldn't – I think it's affected me in terms of my forward thinking. Whenever I'm outside, I'm not feeling as well, just because I'm wearing a mask right away. So my symptoms are definitely intensified and magnified because of COVID.

35i 00-06: I know that sometimes high stress situations – in the same way that high brain power can bother me, high stress can. So before everything shut down, there was a lot of debate – like I don't know what's happening, the news is saying terrible things every day… it was very concerning to me, because I was still in school at the time, that school wasn't shutting down. What if school shut downs? What are they going to do? Are they going to kick me out of my dorm or where am I going to live? All of that was all happening at the same time. And at the same time, that was when I was supposed to be finally getting back to having headache management care, and that all went out the window a little bit.

35j 00-13: During this whole pandemic situation, I've had more headaches this year than I've experienced in a long time…I have it at work and then Coronavirus – then that made it even worse because in my state alone there were so many of us unemployed that it was ridiculous. And it's more or less we fighting for employment. And when you be fighting for employment, it makes things more stressful and you're holding your head. I know I've been holding mine. And I'm in and out the doctor's office, I'm in and out the emergency room. My life has been miserable. Just totally miserable.

35k 00-17: When it first started, we had went down to XXXX to visit – XXXX and XXXX, our family, and then it had broke out, and we were stuck there for a little bit because they were not allowing people through certain places. And I missed my Botox by about – I think it was three weeks late, time I was able to come back and get in and get it done. And it, of course, was worse. I was getting them every – back to every other day again, the way I was before.

35l 00-36: And so it's like it's so wild, because it's like all of these things that could absolutely just set me off and that entire period – in this entire period of time could also be accompanied by awful debilitating migraine symptoms, as well. But it just hasn't. And it's just the wildest thing. It's not so disabling, because I just – now, you can say, look, I don't feel comfortable being at work for this amount of time, like I'm going to work from home, which is what I did. I – we went back fulltime for a month or two. And now I'm like, eh, it's getting bad again, and so I want to work from home three days a week and come in two days. And they were like, yup, sure. So it's like you have power to kind of take control of that stuff, so that also helps – just kind of being my own advocate for that sort of thing.

35m 00-25: Just that the world kind of has to live the way I have now. Has to stay inside, and things are more accessible to me. There's a lot more online that I couldn't access and I'm afraid will be gone again. But actually, the world's like a better place for me, in a f**ked up – I mean, not really.

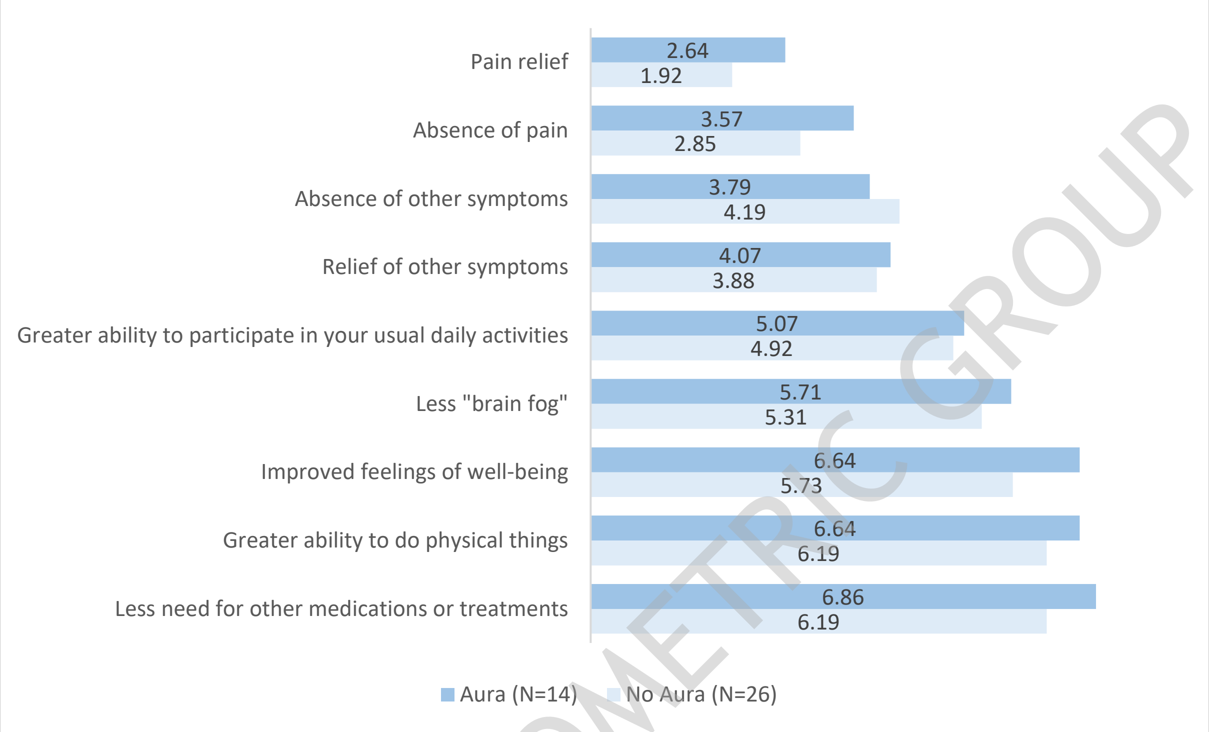
5.9 Persons with Aura: Priorities for Treatment

A total of 14 participants (35%) within our interview sample reported experiencing aura during their migraine attacks. We examined this sub-population of participants for any notable variation in reported experience with migraine compared to the key findings observed in the total 40-person interview sample. Across most concepts/domains including overall symptom burden, emotion/mood changes, cognitive interference, daily function, and physical limitations, migraine experience among interview participants reporting aura did not appear to differ in a substantial way from non-aura interview participants. However, in terms of treatment priorities, some participants with aura did express an increased focus on associated symptom relief (i.e., reduction in symptoms other than pain) relative to others. According to interview participants, aura related symptoms that create full or partial vision loss, greying, and/or obstruction led to significantly reduced functioning (even in the absence of pain) and thus, may be prioritized for treatment to a greater degree than other associated symptoms experienced by those living with migraine (Box 36a-b).

Box 36: Persons with Aura: Priorities for Treatment	
36a	00-03: Yeah, I think it's just because I hate the visual disruptions and the mental fog so much that in a weird way, as I said, there are times, particularly when the headache itself isn't as severe, where those symptoms have been more disruptive to me in recent years – not every time, but there are times – they are consistently disruptive. Let me put it that way. The other symptoms are always disruptive for me, whereas sometimes the pain I can kind of work through. So if I had something that could magically clear up my visual disruptions and stuff, that would be lovely.
36b	00-36: Next would be – the second most important is relief of other symptoms, just because the head pain is obviously just one thing, right? It can be all over your head or it can be different things. But when you take just that one thing is head pain versus the plethora of other symptoms that I feel, the majority is going to be those other symptoms. So once I can get a handle on those, then the head pain usually follows. So I would say that.

Figure 3 provides a comparison of average treatment priority rankings across aura and no aura interview sub-samples (rank of 1 reflects highest priority/most desired outcome.) This exercise, in combination with a comparative examination of coded content related to acute treatment priorities, suggests that, on average, individuals with aura in our interview sample gave slightly greater priority to absence/relief of other symptoms compared to individuals without aura, whose ranking averages suggest a heavy prioritization of pain relief/absence over all other potential acute treatment benefits. Given the smaller sub-sample of interview data available from individuals with aura, additional targeted qualitative inquiries on the migraine experience of those with aura is needed to further substantiate this observation and identify any other differences between groups.

Figure 3. Comparison of average priority rankings for acute treatment benefits/outcomes reported by interview participants with aura (n=14) and without aura (n=26) during virtual ranking exercise (rank of 1 reflects highest priority/most desired outcome).



5.10 Chronic vs Episodic Migraine Experience

The interview sample for this qualitative study was stratified to include equal numbers of individuals living with both episodic (n=20) and chronic migraine (n=20). We examined/compared data from stratified episodic and chronic migraine participants for any notable variation in reported experience and found a great deal of agreement across groups as well as several small but notable differences.

5.10.1 Symptom Burden in Individuals with Chronic vs. Episodic Migraine

In terms of overall symptom burden, individuals with chronic and episodic migraine in our interview sample reported a similar complex pattern of symptoms across all phases of the migraine attack (Please see Appendix G for full, stratified symptom report frequency figures). However, a close examination of symptom frequencies did identify two notable differences between groups, described in greater detail below.

5.10.1.1 Pain and Vertigo Across Sub-Groups

Variation was seen in the expression of pain and vertigo symptoms among chronic and episodic migraine participants in the pre-headache and headache phases of their migraine attacks. Some form of head or body pain during the pre-headache period was reported nearly twice as often in our chronic migraine sub-sample when compared to individuals with episodic migraine, suggesting that early onset of pain during attacks may be more characteristic in those with chronic migraine

(Table 9). One individual with chronic migraine described their experience with pain at pre-headache as follows:

> *00-06: 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.*

Experiences with vertigo during pre-headache and headache were reported three times more often by chronic migraine participants when compared to those with episodic migraine disease, suggesting that vertigo at onset and during migraine headache may be a more prevalent experience in individuals with chronic migraine. However, overall numbers for vertigo symptom frequency were small and thus, may not be sufficient to identify conclusive patterns across chronic and episodic migraine sub-groups (Table 9).

Table 9. Frequency comparison of migraine-related pain and vertigo reported by interview participants with episodic (n=20) and chronic (n=20) migraine across pre-headache and headache phases of their typical migraine attacks.

	Pre-Headache		Headache	
	Episodic	Chronic	Episodic	Chronic
Pain	8	15	20	20
Vertigo	2	6	3	9

5.10.1.2 Inter-Ictal Symptom Burden Across Sub-Groups

Symptom experience during inter-ictal periods also seemed to vary substantially across chronic and episodic sub-groups. Among those with episodic migraine, 80% (16/20) reported experiencing no symptoms in the inter-ictal period. In comparison, only 30% (6/20) of individuals with chronic migraine reported being symptom-free in-between attacks. This suggests that individuals with chronic migraine may carry an overall greater inter-ictal symptom burden despite less time spent in the inter-ictal state relative to those with episodic migrain.

5.10.2 Emotional Burden in Individuals with Chronic vs. Episodic Migraine

Much like symptom burden, emotion/mood changes across phases of the migraine attack were similarly reported across chronic and episodic interview sub-samples and it was difficult to distinguish notable differences in emotional burden across groups (Please see Appendix G for full, stratified emotion/mood report frequency figures), especially in reference to more commonly experienced feelings of irritability/impatience and burdensome experiences with anxiety and depression (Table 10). These emotion and mood changes seemed to bear a similar impact across individuals with chronic and episodic migraine. We also observed similarity in the co-occurence of anxiety and depression across episodic and chronic sub-samples. Among participants with chronic migraine, 14 reported anxiety and/or depression in one or more phases of their migraine. Of these 14, 6 (43%) reported experiences with both. Among participants with episodic migraine, 15 reported experiencing both anxiety and/or depression in one or more phases of their migraine. Of those 15, 5 (33%) reported experiences with both.

Shared experiences with depression, anxiety, and co-occuring emotion/mood changes across classifications of migraine disease is an especially interesting observation considering perhaps flawed assumptions that individuals with more frequent migraine attacks and thus, less reprieve from migraine symptoms, may be more susceptible to negative thoughts or feelings. It is important to note that among the small number (n=2) of individuals who reported experiencing suicidal ideation, both were categorized as having chronic migraine.

Table 10. Frequency comparison of migraine-related anxiety, depression, and irritability/impatience reported by interview participants with episodic (n=20) and chronic (n=20) migraine across pre-headache, headache, post-headache, and inter-ictal phases

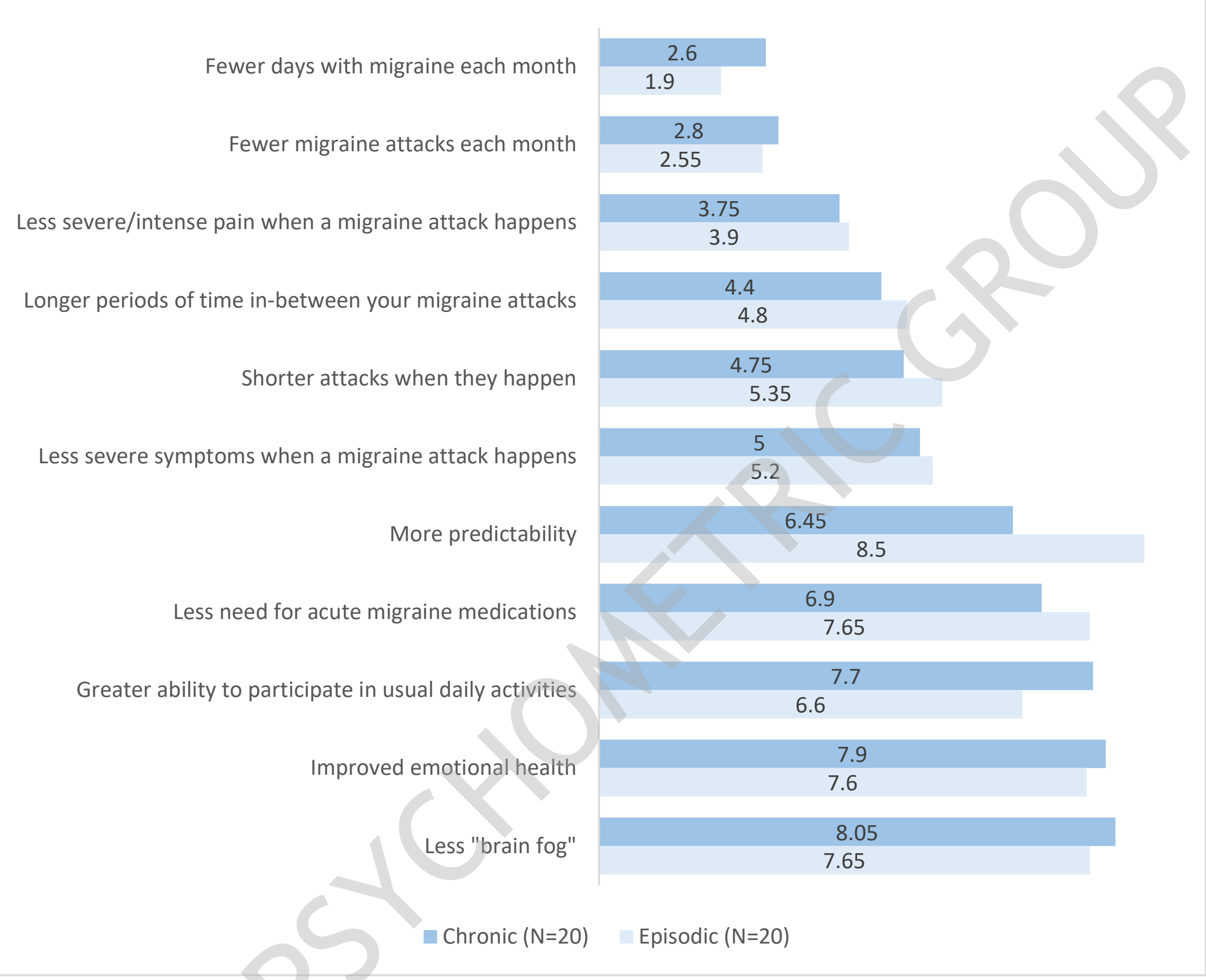
Emotions	Pre-Headache		Headache		Post-Headache		Inter-Ictal	
	Episodic	Chronic	Episodic	Chronic	Episodic	Chronic	Episodic	Chronic
Anxiety	5	7	4	4	4	3	5	6
Depression	6	2	4	6	5	4	3	3
Irritability/Impatience	14	10	15	11	4	6	0	0
Suicidal ideation	0	0	0	2	0	0	0	0

5.10.3 Treatment Priorities in Individuals with Chronic vs. Episodic Migraine

No major differences were noted across chronic and episodic sub-samples in terms of their priorities for acute migraine treatment. For acute therapies, both groups seemed to prioritize quickly achieved pain relief and a return to function.

In terms of priorities for preventive therapy, some notable differences were observed between chronic and episodic classifications. Figure 4 provides a comparison of average treatment priority rankings across episodic and chronic interview sub-samples (rank of 1 reflects highest priority/most desired outcome). This exercise, in combination with a comparative examination of coded content related to preventive treatment priorities, suggests that, on average, individuals with episodic migraine in our interview sample heavily prioritized reduction in the number of migraine days and migraine attacks per month, downweighting all other additional potential benefits of prophylactic treatment including reductions in pain and/or symptom severity during breakthrough attacks. Individuals with chronic migraine in our interview sample similarly prioritized a primary preventive treatment objective of fewer days with migraine and fewer migraine attacks each month but also placed more value on secondary objectives like less severe pain/symptom severity during attacks when compared to the priorities expressed by participants with episodic migraine (Box 37a-d). Differences in prioritization of secondary pain and symptom related benefits from preventive treatment may be due to an underlying assumption among individuals with chronic migraine that even with a significant reduction in frequency, they could still expect to experience several migraine attacks per month and thus, value prophylactic therapy that also minimizes pain and symptom burden when migraine attacks happen.

Figure 4. Comparison of average priority rankings for preventive treatment benefits/outcomes reported by interview participants with episodic (n=20) and chronic (n=20) migraine during virtual ranking exercise (rank of 1 reflects highest priority/most desired outcome)



Box 37: Reducing Symptom Severity Through Preventives- Chronic Migraine	
37a	00-39: So being able to have less severity of pain is also an improvement. It's not ideal. But it's an improvement. And when you are in the throes of it, you will take whatever relief you can get. So if that means the intensity is down, then I'll take that. [chronic]
37b	00-06: For a preventative, I'd really want it to address frequency first – reducing the number of bad days, but also would be really great to reduce the severity of the bad days…But really controlling how much – how many high pain days there are and how high the pain is is really important. [chronic]
37c	00-42: The most severe attacks make you completely nonfunctional. So if you could have the same number – like if I had the same exact number of attacks that I do now but I could function through them, that would be a huge improvement. [chronic]

Box 37: Reducing Symptom Severity Through Preventives- Chronic Migraine	
37d	00-29: The main thing would probably 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. [chronic]

5.10.4 Cognitive Interference in Individuals with Chronic vs. Episodic Migraine

Cognitive interference across pre-headache, headache, and inter-ictal phases were similarly reported across chronic and episodic interview sub-samples. Thus, it was difficult to distinguish any notable differences in cognitive burden across groups during these stages of migraine (Please see Appendix G for full stratified cognitive interference report frequency figures). Some variation was noted between chronic and episodic subgroups in terms of the reporting of cognitive impacts during post-headache. Individuals in our interview sample with chronic migraine reported fogginess, losing words/speech, and difficulty processing information in the post-headache period more than twice as often as participants with episodic migraine (Table 11). This suggests that individuals with chronic migraine may be comparatively more prone to persistent and prolonged cognitive interference that lingers beyond onset of pain relief (Box 38a-c).

Table 11. Frequency comparison of migraine-related cognitive interference reported by interview participants with episodic (n=20) and chronic (n=20) migraine during post-headache.

Cognitive Interference	Post-Headache	
	Episodic	Chronic
Trouble with concentration/focus	5	6
Confusion/disorientation	1	1
Avoid making decisions	3	3
Fogginess	5	12
Losing words/speech	3	6
Memory	5	6
General	3	4
Learning	1	4
Retrieval/recall	1	3
Slurred words/speech	0	0
Difficulty processing information	2	5

Box 38: Cognitive Interference in Post-headache: Chronic vs. Episodic Migraine

38a	00-41: I'll still have brain fog. I actually will still have brain fog for days. And I won't realize it until later. I could be completely fine, have ba – brain fog and work on my report, like my budget or whatever, and come back a couple days later without brain fog and be like, OK, that makes no sense. I don't know why I did that. I must have had brain fog. And I'll have to fix it. [post-headache; chronic]
38b	00-06: Sometimes brain fog will continue, but it's a different brain fog. So the pain brain fog is more like wading through water trying to get there, versus the after-pain brain fog is less like fog and more like brain jumble. So if you're looking at a subway map and there's all the lines crossing over each other and you're trying to go on the blue line, and the blue line, at one station, intersects with yellow and green, it may be like you're going down the blue line and you're trying to get to the end of the blue line, but you end up getting to the end of the green line instead. So things get more jumbled rather than they do lost and harder to find. They're there. They're just in the wrong order. [post-headache; chronic]
38c	00-14: It's gotten more back – it was I would say more back to normal because I didn't have that pain that would distract my focus, take away from my focus. From my memory – like my memory, I don't remember anything about my memory being off or anything like that. But definitely my focus came back together because I didn't have that intense pain. It's kind of hard. When you have that type of pain, you can't really think about anything. [post-headache; episodic]

6 Conclusions and Future Research

This phase 1 exploratory qualitative study collected and analyzed in-depth interview data from 40 individuals living with episodic or chronic migraine to explore a wide range of issues related to migraine experience including symptom burden, cognitive impacts, emotion/mood changes, impacts on daily living, physical limitations, and acute and preventive treatment priorities.

This exploratory qualitative inquiry established a complex set of migraine symptoms and impacts that, together, motivate patient priorities for treatment. Analysis of interview data across concepts/domains of interest consistently suggests that return to function is a primary priority for preventive and acute treatment among individuals with migraine. The desire to function/maintain productivity at home, school, work, and social settings seemed to drive other commonly expressed priorities including rapid pain/symptom relief, substantial reduction in migraine frequency, improved cognition, management of taxing emotions/mood changes, and reductions in inter-ictal burden (i.e., symptoms and emotions).

A comparative examination of the qualitative data across sub-groups of interest (i.e., chronic v. episodic; aura v. non-aura) was undertaken to identify differences and similarities in reported experiences and prioritized treatment benefits. This comparative, stratified analysis found, in large part, more commonalities than differences between groups. That being said, the comparative analysis of stratified interview data did identify some distinctions among individuals with chronic migraine for future consideration. This includes individuals with chronic migraine reporting a relatively higher inter-ictal symptom burden, more frequently reporting pain during pre-headache, and more experiences with lingering cognitive deficits during post-headache. Participant expressed treatment priorities seemed to stay relatively consistent across sub-groups with the exception of two variations: 1) greater focus on treating visually disruptive associated symptoms among individuals with aura, and 2) greater value placed on preventive treatment reductions in pain/symptom severity during attacks among individuals with chronic migraine.

6.1 Future Research

Findings from this exploratory qualitative study will be examined alongside results from an exhaustive literature review of existing migraine-related clinical outcome assessments, and endpoints, input from the study's external technical advisory committee, and additional discussions among the MiCOAS project team and stakeholders to identify targeted areas of focus for the next phase of qualitative work. This will include a list of potential/preliminary concepts of interest based on qualitatively-captured patient input and research priorities. This list of preliminary concepts of interest will drive the construction of the phase 2 interview guide and protocol, which will be designed to inform the construction of new outcome items/instruments (as needed) to accurately assess the identified concepts important to both people with migraine and other stakeholders, and/or serve as evidence of content validation of existing measures. Given the general alignment of the current results with existing endpoints (e.g., 2-hour pain freedom; reduction in monthly migraine days) commonly used in migraine trials, the goal of this future work will be to fill gaps in existing outcomes/endpoints available for use. Results of the current study and input from stakeholders suggest that a focus on function/disability (especially cognition which is currently not well measured) and the impacts of migraine-related function/disability would be well advised.

6.2 Study Limitations

The following study limitations should be considered in the interpretation of qualitative findings outlined in this report:

- This phase of qualitative data collection and analysis was exploratory and thus, covered a very wide range of concepts/domains related to migraine experience and treatment priorities. Due to the expansive nature of this inquiry, additional evidence may be needed to further develop certain qualitative findings in support of core outcome set identification and/or specific item/instrument construction and content validation. This was an anticipated phase one limitation of a two-phase qualitative approach. The next phase of qualitative data collection and analysis is explicitly designed to address the need for additional, more COA-focused qualitative evidence generation.
- The stratified qualitative analysis for chronic, episodic, and aura sub-groups undertaken in this study are constrained by small sample sizes. Additional qualitative data collection targeting these sub-groups may be required in future research to confirm/further explore distinctions between groups that might influence the perceived appropriateness of specific COA tools. In addition, future analyses may want to examine differences within each of these groups (from low frequency to high frequency EM and low frequency to high frequency CM).
- Recruitment for qualitative interviews targeted CHAMP's network through their established online communication channels (i.e., social media, email lists). Despite successful efforts to diversify the study population through iterative, purposeful sampling, we were unable to target individuals who do not engage, on some level, with CHAMP or its advocacy coalition through these online resources. This may lead to a sample who are in some ways different from the population (.e.g., disease severeity, treatment history, and health literacy). It is possible that

the experiences of individuals outside CHAMP's online network differ from the available participant pool and were not captured by our analysis. It was also not possible to find participants with 1 or fewer average monthly migraine days through this recruitment strategy.

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8 Appendices

1. **Appendix A: Online Screening, Informed Consent, and Data Collection platform**
2. **Appendix B: Interview Guide**
3. **Appendix C: Acute Treatment Ranking Exercise Screenshot**
4. **Appendix D: Preventive Treatment Ranking Exercise Screenshot**
5. **Appendix E: Full Sample Saturation Grid**
6. **Appendix F: Full and Stratified Sample Concept Frequency Tables**
7. **Appendix G: Full and Stratified Sample Concept Frequency Figures**