MiCOAS

SYSTEMATIC LITERATURE REVIEW OF OUTCOMES AND ENDPOINTS USED IN PREVENTIVE MIGRAINE CLINICAL TRIALS

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EXECUTIVE SUMMARY

This document provides a summary of the systematic literature review of preventive clinical trials for migraine completed by the Migraine Clinical Outcome Assessment System (MiCOAS) team in partial fulfillment of the objectives of the grant provided by the US Food and Drug Administration (FDA; 1 UG3 FD006795-01) to develop a standardized set of patient-centered outcomes and endpoints with a goal of using these endpoints in migraine clinical trial research. This report focuses on the preventive migraine treatment outcomes and endpoints found in the peer-reviewed literature summarizing clinical trials. A second report focuses on outcomes and endpoints for acute migraine treatments.

We conducted a systematic literature review of migraine preventive therapies in adults using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist. We engaged in a two phase process: an initial review of every manuscript identified by key words and other criteria to be a candidate for inclusion yielding 1,506 articles, followed by a review in which 757 of the publications were determined to be eligible and appropriate for the data extraction process. For the data extraction process, we preidentified five broad categories of outcome variable types and three potential endpoint timing possibilities. This report includes the results of the complete publication list and a more in-depth analysis of the 268 studies (35.4%) published in 1988 and later (when the International Classification of Headache Disorders [ICHD] was first published setting clinical criteria for migraine), which were randomized and blinded, and focused on pharmacological or medical device interventions.

For the subset of 268 publications, 68.7% of the publications examined at least one migraine-specific outcome, 39.6% examined at least one headache-specific outcome, 50.8% examined at least one acute/rescue medication use outcome, 40.3% examined at least one migraine or headache-related patient reported outcome (PRO), and 22.0% examined at least one non-headache specific patient reported outcome measure (PROM). The most common study design used only migraine-focused outcomes (17.5%), although the study could include multiple migraine-related outcomes. Of the 184 publications evaluating at least one migraine-focused outcome, 69.0% examined migraine attacks, 51.1% evaluated migraine days, and 48.4% evaluated migraine pain which was most often assessed as “pain severity” or “pain intensity” on a variety of metrics. A “headache index” was used in 9.2% of studies, primarily older studies, but the definition varied among publications.

As demonstrated in the analysis of data extracted from the articles summarizing preventive clinical trials, the outcomes used to define endpoints vary substantially across trials, ranging from migraine or headache frequency (days, attacks, total hours, index/composite measures), use of acute/rescue medication frequency (days, doses), and various headache-related and non-headache specific PROMs, such as those related to the impact migraine has on the patient’s life or more general health-related quality of life (HRQoL). The definition of the endpoints used (e.g., change from baseline, fixed-time point comparisons, categorization of “responders” to treatment based on wide variety of “responder definitions”) also differs substantially across publications. While some of this inconsistency is attributable to the wide publication dates and changes in criteria, the treatment landscape, and the fields’ understanding of migraine, even within our focused subset of more recent publications, a large amount of variability exists in the outcomes and endpoints used and how those outcomes were operationalized. The results from the full set of selected articles demonstrated even more variability and lack of standardization across trials.

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INTRODUCTION

Migraine is a chronic neurological disease (Headache Classification Committee of the International Headache Society [IHS], 2018) that is highly prevalent, severely disabling, and broadly impactful for individuals with the disease, their families, and society as a whole. The 2016 Global Burden of Disease (GBD) analysis (GBD 2016 Headache Collaborators, 2018) reported that migraine is one of the leadings causes of disability in the world. It is estimated that worldwide 1.04 billion people have migraine, corresponding to a prevalence of 14.4% overall, 18.9% in women, and 9.8% in men (GBD 2016 Headache Collaborators, 2018). Analyses from the US, population-based American Migraine Prevalence and Prevention Study (e.g., Buse et al., 2012; Buse et al., 2013; Lipton et al., 2007) found that approximately 12% of respondents, including 17.4% of females and 5.7% of males, met criteria for migraine in the prior year and 0.91% met criteria for chronic migraine (1.29% of females; 0.48% of males). A migraine attack is frequently characterized by intense, debilitating headaches but can also include associated symptoms in various combinations such as nausea, vomiting, sensitivity to light and sound during the headache phase as well as prodrome, aura and postdrome phases (IHS, 2018). Despite the substantial burden and impact of migraine, research is needed to identify and test products that may improve outcomes for migraine patients.

Therapeutic approaches for migraine fall under 2 broad categories: acute and preventive treatments (American Headache Society, 2019). Acute migraine treatments aim to resolve migraine pain and symptoms when an attack occurs and return individuals to a "normal" level of functioning as quickly as possible (Marmura, Silberstein, & Schwedt, 2015). Preventive treatments, which include both pharmacological and non-pharmacological approaches, aim to reduce frequency, severity, and duration of attacks, improve responsiveness to treatment of acute attacks, and reduce level of disability (American Headache Society, 2019; Tassorelli et al., 2018).

The global standard for migraine classification is the International Classification of Headache Disorders (ICHD). With editions in 1988 (ICHD-1; IHS, 1988), 2004 (ICHD-2; IHS, 2004), 2013 (ICHD-3 beta; IHS, 2013) and 2018 (ICHD-3; IHS, 2018), criteria are provided for the types of migraine assessed in clinical trials. Some important types of migraine often studied in clinical trials and defined by the ICHD system include migraine with aura, migraine without aura, chronic migraine (CM), and medication overuse. Though criteria for migraine with and without aura have been relatively stable, criteria for chronic migraine emerged in ICHD-2 and evolved substantially in the ICHD-3 (beta) and were carried into ICHD-3. The term transformed migraine (TM) was first introduced in 1987 (Mathew, Reuveni, & Perez, 1987) and operational diagnostic criteria were provided by Silberstein, Lipton, Solomon, & Mathew (1994) and revised in 1996 (Silberstein, Lipton, & Sliwinksi, 1996). In 2004, the term *chronic migraine* was added to the ICHD-2 as a complication of migraine. The term episodic migraine (EM) refers to persons with migraine and fewer than 15 headache days per month and has only recently been added to the ICHD system (Goadsby & Evers, 2020) but is widely used in clinical trials, research, and clinical care. CM refers to people with migraine and 15 or more headache days per month for at least 3 months of which at least eight days are linked to migraine. In ICHD-3 beta and ICHD-3, forms of CM with and without medication overuse are recognized.

The goal of this work is to provide an overview of the preventive migraine literature to aid in future endpoint, outcome assessment, and treatment developments. The purpose of this document is to summarize the findings

from a systematic literature review that provides a comprehensive picture of concepts, endpoints, and associated outcomes used in clinical trials of preventive treatments for adults (defined as 18 years or older) with migraine published in peer-reviewed scientific journals.

METHODS

A systematic literature review was conducted to understand the frequency of utilization for specific concepts, endpoints, and associated outcome measures used in clinical trials assessing preventive treatments in adults with migraine. PRISMA provides a checklist related to consensus recommendations for the development and execution of high-quality systematic literature reviews (Moher et al., 2009). This checklist includes recommendations for the conduct of the literature search and review, including: pre-specification of eligibility criteria for located publications, the database to be used for the search as well as draft search terms, the standardized process used to review located publications including record tracking/data management systems to be used, the data planned to be extracted from each publication meeting inclusion criteria, and the plan for summarizing the extracted information. The protocol developed for this literature review adhered to PRISMA recommendations.

IDENTIFICATION OF REFERENCES

PubMed, a search engine maintained by the National Center for Biotechnology Information at the U.S. National Library of Medicine, located at the National Institutes of Health was used as the primary database queried to identify initial articles for review. PubMed filters were used to limit results to human clinical trials and to articles published in English. No time frame restrictions were imposed on the results and the date of the final search was 10/28/2019. However, stand-alone abstracts, letters to the editors describing trials, and conference proceedings were not considered, given the limited information and difficulty in obtaining full documents for such references. Case studies were also excluded.

The PubMed search term used to identify the initial articles was:

(((((((preventive) OR prophylaxis) OR prophylactic) AND migraine [Mesh]) AND Clinical Trial[ptyp]) AND Humans[Mesh]) AND English[lang])

The title and abstract of each article were screened by two Vector Psychometric Group, LLC (VPG) methodologists, using the Covidence online systematic review tool, for relevance to the stated goals. Specifically, the inclusion criteria from the protocol were:

- The screening reviews were based on the inclusion of an interventional, adult preventive migraine trial description in the title, abstract, or keywords
- Interventions could be pharmacological (e.g., daily pills, monthly injections), physical (regular acupuncture, massage, exercise regimes, etc.), dietary, or other novel Tx intended to prevent/reduce migraine
- Open-label studies and Phase 4 trials were to be included. This included Post-Marketing Phase IV studies
- Subtypes of migraine (e.g., menstrual migraine; medication overuse headache if sample is specified as migraine patients) were to be included
- Pilot studies with migraine patients were to be included
- Mixed adult and adolescent trials were included. Pediatric/adolescent only trials were excluded

Exclusion criteria were as follows:

- Acute migraine trials were excluded (mixed trials with preventive and acute outcomes included)
- Observational studies, surveys (exception: Post-Marketing Phase IV), epidemiological studies, etc. were excluded
- Trials with ONLY healthy volunteers given a preventive intervention were excluded (mixed healthy/migraine samples were included)
- Given the limited information and difficulty in obtaining full documents for such references, excluded:
    - Peer-reviewed, stand-alone abstracts
    - Letters to the editor describing trials
    - Abstracts/papers from conference proceedings
    - Case studies
    - Trials using only pediatric patients (mixed adult and adolescent trials included)

Once the initial list of screen-pass references was compiled, a review of the reference section in each located publication was undertaken to locate any potentially relevant publications that were previously undiscovered. Newly located articles were added to the "initial" list and title and abstract submitted to the screening review (as detailed above) for inclusion/exclusion in the final version of the initial list.

With the candidate reference list finalized, a brief review of each full publication was undertaken by two VPG doctoral level methodologists to confirm the relevance of the article to the current goals. With an agreed-upon positive assessment from the brief review, the publication was included in the final references list. All agreed upon negative reviews resulted in the exclusion of the publication from this list. Disagreements on the status of an article were reviewed by a third doctoral-level study team member and a discussion among all three reviewers determined the final status of an article regarding inclusion/exclusion in the final list of publications slated for extraction.

All articles in the final list of publications were fully reviewed by a VPG doctoral-level study team member and, if information relevant to the goal of the review was found in the publication during data extraction, it was included in the literature synthesis section of this literature review report.

DATA EXTRACTION

For all located publications included in the final list of publications, salient key features of each preventive migraine trial were extracted. This included extracting all available information related to year of publication, journal name, ClinicalTrials.gov identifier(s), trial name, phase of trial (I - IV), general description of the trial design, sample size, patient descriptives (age, gender, race), salient migraine characteristics (patients with migraine with aura only, menstrually-related migraine [MRM] subjects only, EM vs. CM, etc.), and type of treatment investigated (pharmacologic, neurostimulation, behavioral, complimentary and integrative treatments, etc.). Additionally, data extraction from the articles included the concepts examined, the endpoints used, and any specific outcome measures used.

Data related to the descriptive trial information was extracted by trained research assistants. A second research assistant independently extracted the same data for approximately 5% of candidate publications and

rater/extractor agreement kappas were calculated. Data related to the concepts, outcomes, and endpoints examined were extracted by one of four VPG PhD-level methodologists into a standardized, structured Excel worksheet.

SYNTHESIS OF EXTRACTED INFORMATION

To synthesize the sizeable amount of information collected during the data extraction from the large number of articles on migraine preventive treatment, numerous tables and figures were planned to present summary information in a digestible fashion. These included summary tables focused on the study design characteristics, demographics for the samples used in preventive migraine trials, and outcomes (migraine/headache days, attacks, hours, migraine-related PROs) and endpoints (change from baseline, fixed timepoint comparisons, responder definitions – also called within-person meaningful change thresholds) used.

Outcomes are presented within five broad categories:

1. Migraine-Focused Outcomes – Days, Attacks, Total Hours, Index (composite of days, attacks, or hours), Pain/Intensity/Severity, and Duration (per attack)
2. Headache-Focused Outcomes – Days, Attacks, Total Hours, Index (composite of days, attacks, or hours), Pain/Intensity/Severity, and Duration (per attack)
3. Acute/Rescue Medication Outcomes – Days of use, Doses/Uses of medication
4. Headache/Migraine-related PROs – such as the Migraine Disability Assessment Test (MIDAS; Stewart, Lipton, Dowson, & Sawyer, 2001), the 6-item Headache Impact Test short form (HIT-6; Kosinski et al., 2003), Migraine-specific Quality of Life (MSQ) Questionnaire (e.g., Jhingran, Osterhaus, Miller, Lee, & Kirchdoerfer, 1998; Martin et al., 2000), and other measures of migraine specific quality of life, cognitive constructs, disability and impairment due to migraine and/or headache
    a. Disability/Impairment is a general category (not a single item/scale) that consists of a range of disability, impact, and impairment outcomes. They are placed in the Headache/Migraine-related PROs category for this report.
5. Non-headache related PROs – includes such measures as the Short Form Health Survey (SF-36; e.g., Ware et al., 2007), various depression and anxiety measures, patient global impression of change (PGIC), patient global impression of severity (PGIS), and treatment efficacy/satisfaction/preference items
    a. Measurement of patient global impression, treatment efficacy, satisfaction, and preference varied across manuscripts (e.g., different response scales, varied verbal labels) but were grouped into general categorizes for tabled results.

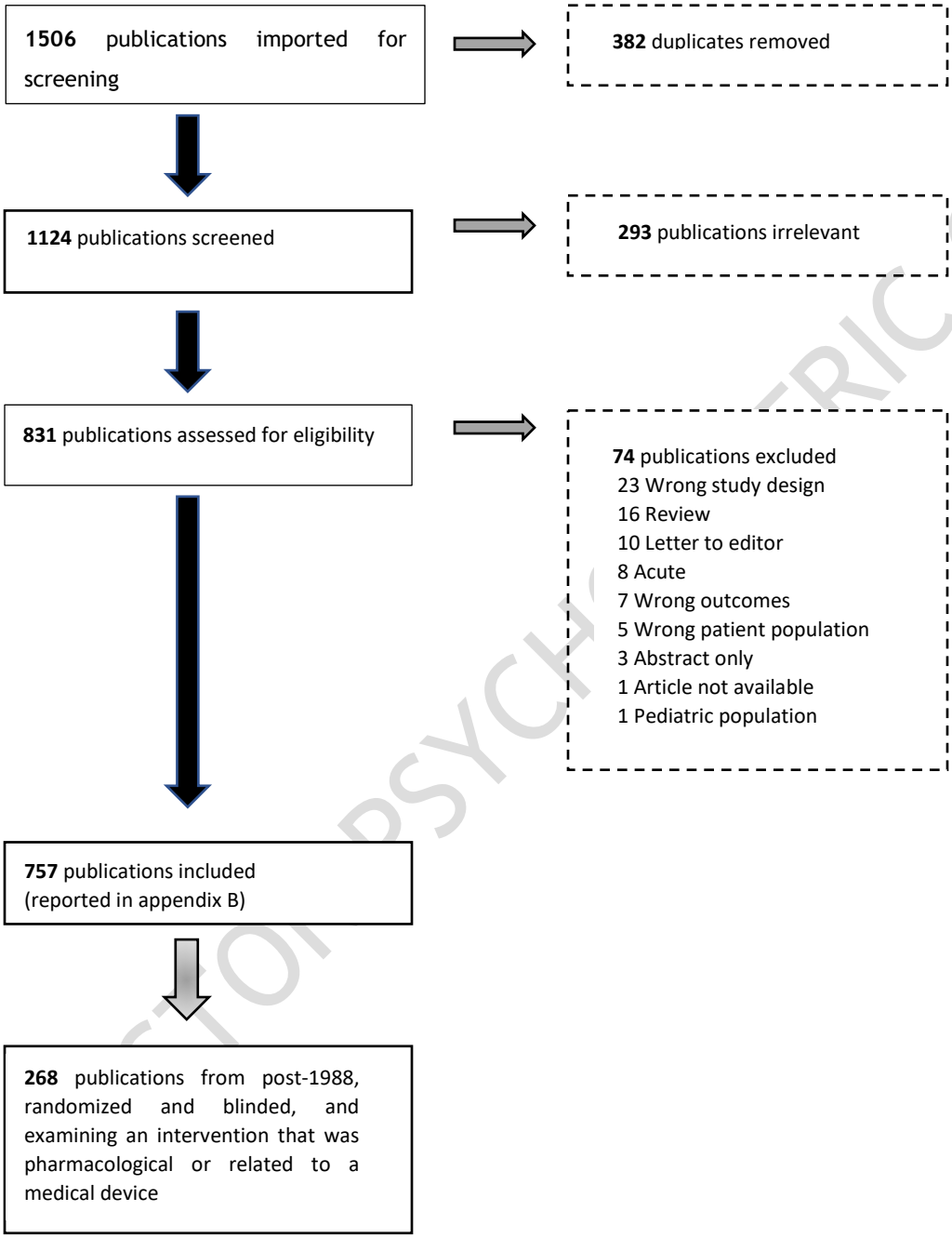
Endpoint timing was categorized within 3 broad categories:

1. Change from baseline
2. Fixed timepoint
3. Responder definitions (50% reduction, 75% reduction, 100% reduction, Other definitions)

RESULTS

Of the 1506 publications found through the initial search and reference section reviews, 757 publications were included for data extraction. Figure 1 provides a more detailed break-down of the review and selection process outcomes. Appendix A provides a complete list of all publications located from the PubMed search and their ultimate status regarding inclusion/exclusion in the final selection of articles.

Figure 1. PRISMA diagram of article flow through the systematic literature review of preventive migraine trials.



With respect to data extraction from the 757 publications, inter-rater agreement kappas for the descriptive variables extracted (age, sex, study design characteristics, etc.) had an average kappa estimate of .87. Given the somewhat inconsistent nature of reporting in the examined articles and the varied age and quality of

reporting in the publications, the observed level of inter-rater agreement was considered acceptable (and was above the recommended lower bound of .6 (McHugh, 2012).

General Study Characteristics

Of the 757 publications included for review, just over half reported on studies that were placebo/sham controlled (58.3%), almost two-thirds were blinded and randomized (62.9%), and about two-thirds of publications used one of the iterations of the ICHD criteria for migraine (65.7%). Many publications published prior to 1988 used the 1962 Ad Hoc Committee criteria for migraine (Ad Hoc Committee on Classification of Headache, 1962) which used similar criteria to the subsequent ICHD criteria for migraine.

Table 1. General Study Characteristics (n=757 publications)

Study Characteristic	Percent	N
Study Purpose(s)		
Efficacy Assessed	98.68	747
Safety Assessed	83.36	631
Pharmacokinetic Study	1.19	9
Study/Design Features		
Study 1988 or Later	77.15	584
Randomized	74.24	562
Blinded	65.79	498
Randomized and Blinded	62.88	476
ICHD Migraine Criteria Used	65.65	497
Placebo/Sham Controlled	58.26	441
Crossover Design	19.02	144
Open-Label Study	22.46	170

Of the 757 publications, most publications examined at least one efficacy outcome (98.7%) or a safety outcome (83.4%). While planned for extraction, phase of study was not reliably reported – over 90% of publications were not clearly marked as Phase I through IV (data not shown).

With respect to the interventions investigated in the 757 reviewed publications, nearly three-quarters of publications investigated pharmacological/medication treatments (pills, injections, etc.), 11.0% examined alternative treatments (acupuncture, herbal remedies, osteopathic manipulation, etc.), 4.0% examined medical devices (e.g., neurostimulation devices, dental devices), and 2.8% examined behavioral interventions. Table 2 provides a detailed break-down of the interventions examined.

Table 2. Preventive Migraine Treatments Investigated (n=757 publications)

Treatment Investigated	Percent	N
Pharmacological/Medication	73.32	555
Complimentary and Integrative (acupuncture, osteopathic manipulation, herbal treatment, etc.)	10.96	83
Other/Multiple Categories	5.02	38
Medical Device (electrical stimulation, dental plate)	3.96	30
Biobehavioral/Psychological (e.g., biofeedback, cognitive behavioral therapy)	2.77	21
Lifestyle (e.g., diet or exercise)	2.25	17
Surgical e.g., (patent foramen ovale closure, other)	1.72	13

Given the presumed interest in outcomes and endpoints used in the publications that employed ICHD criteria to identify participants with migraine, from this point on we focus on the 268 publications that were published in 1988 or later (following the ICHD-1 publication), that were also randomized and blinded, and included interventions that were pharmacological or related to a medical device (35.4% of articles). Results from the full sample of 757 articles are provided in Appendix B.

Demographic and Descriptive Variables of Patients

Available demographic characteristics for the subjects from the selected publications (pooled over all treatment groups) are summarized in Table 3. The median total sample size was n=92.5 (25th percentile: 52; 75th percentile: 355). Of publications that reported age, gender, and/or race descriptives, the average age was found to be 39.4 (SD = 4.1), with 82.2% of patients identifying as female, and 86.9% of patients reported as White/Caucasian.

Table 3. Demographic Characteristics of the Samples in Select Recent Publications (n=268 publications)

Variable	Number of Publications Reporting	Mean	Std Dev	Min	25th Percentile	Median	75th Percentile	Max
Total N	268	314.98	520.52	11	52	92.50	355	4520
Mean Age	239	39.37	4.09	24.13	37.00	39.8	42.00	51.00
% Female	253	82.15	10.82	41.00	78.57	83.99	87.50	100.00
% White	86	86.87	11.60	0.00	83.27	89.74	92.30	100.00

Of note in these demographic summary values is that publications conducted exclusively outside of the United States (e.g., Chinese, Indian, or Iranian studies) often did not report the breakdown of patients into

race/ethnicity categories and, therefore, did not contribute data to the summary value; the "typical" patient in an acute migraine is a middle-aged white female, but there is slightly more racial/ethnic diversity in the overall trial population than indicated by the reported values.

Tables 4 and 5 summarize migraine and aura group characteristics of the publications that reported such features. Almost 76% of the publications looked at general migraine (unspecified/multiple types) and 17.2% of publications looked at chronic/transformed migraine exclusively.

Table 4. Migraine and other Primary Headache Diagnoses (n=268 publications)

Migraine Group Definitions and Criteria	Percent	N
General Migraine (with or without aura, "classical/common" migraine, EM, multiple other subtypes, unspecified)	75.74	203
CM/TM	17.16	46
MRM (also called menstrual migraine or menstrually associated migraine)	5.97	16
Medication Overuse Headache only	1.12	3

Note. CM = Chronic migraine. TM = Transformed migraine. EM = Episodic migraine. MRM = Menstrually-related migraine.

More than half the publications examined migraine with or without aura together (61.6%). In 28.7% of publications, migraine with or without aura diagnoses were not specified, 9.3% enrolled only patients without aura, and only 1 study (0.4%) included only subjects with aura.

Table 5. Migraine and Aura Status Diagnoses (n=268 publications)

Aura Diagnosis Groupings	Percent	N
Migraine with and without aura	61.57	165
Not specified	28.73	77
Without aura only	9.33	25
With aura only	0.37	1

Outcomes and Endpoints used in selected subset of more recent publications (n=268)

As noted earlier, the primary outcome and endpoint results of this review will focus on the subset of the examined publications that were published in 1988 or later, were randomized and blinded, and included interventions that were pharmacological or related to a medical device. To classify the outcomes used across the various publications, broad groups were created. Migraine-focused outcomes is used as a collective term to describe migraine days, migraine attacks, total hours of migraine, migraine index (which was defined in multiple ways and is detailed below), migraine pain/severity/intensity, and migraine duration (per attack).

Similar to the migraine-focused outcomes, the overarching headache-focused outcomes category includes headache days, headache attacks, total hours of headache, headache index, headache pain/severity/intensity, and headache duration (per attack). Categories were also created for acute/rescue medication use outcomes, migraine/headache-related PROMs, and non-headache specific PROMs, such as broader HRQoL measures and depression and anxiety scales.

As can be seen in Table 6, over two-thirds of the publications examined one or more migraine-specific outcomes, 39.6% examined one or more headache-specific outcomes, 50.8% examined one or more acute/rescue medication use outcomes (acute and/or rescue medication use was not reliably differentiated in publications and are amalgamated here as well), 40.3% examined one or more headache-related PROs, and 22% examined one or more non-headache specific PROs.

Table 6. Outcome Types Assessed Across Publications (n=268 publications)

Outcome type (n=268)	Percent	N
Migraine-focused outcome	68.66	184
Headache-focused outcome	39.55	106
Acute/rescue medication use	50.75	136
Migraine/Headache-specific PROs	40.30	108
Non-migraine/headache specific PROs	22.01	59

Additionally, as trials often assessed multiple outcome types, we also provide Table 7, which details the most commonly used combinations of outcomes types seen in the 268 publication subset.

Table 7. Combinations of Outcome Types Used (n=268 publications)

Migraine-focused outcomes	Headache-focused outcomes	Acute/rescue medication use	PROMs (both headache-related and non-headache specific)	Percent	N
Yes	*No*	*No*	*No*	17.54	47
Yes	*No*	**Yes**	*No*	14.93	40
Yes	*No*	**Yes**	**Yes**	13.81	37
No	**Yes**	*No*	**Yes**	8.21	22
Yes	**Yes**	**Yes**	**Yes**	8.21	22
Yes	*No*	*No*	**Yes**	7.46	20

No	**Yes**	*No*	*No*	6.72	18
No	**Yes**	**Yes**	*No*	4.85	13
No	**Yes**	**Yes**	**Yes**	4.85	13
Yes	**Yes**	**Yes**	*No*	3.36	9
No	*No*	*No*	*No*	2.99	8
No	*No*	*No*	**Yes**	2.99	8
Yes	**Yes**	*No*	**Yes**	1.87	5
		Other		2.2	6

As can be seen, the most common study design used only migraine-focused outcomes (17.5%), although the study could include multiple migraine-related outcomes. The next most-common combination was migraine-focused outcomes paired with one or more acute/rescue medication use outcomes (14.9%), followed by migraine-focused outcomes with acute/rescue medication outcomes and one or more PROs (13.8%).

MIGRAINE-FOCUSED OUTCOMES

Of the 184 publications evaluating one or more migraine-focused outcomes, 69.0% examined migraine attacks, 51.1% evaluated migraine days, and 48.4% evaluated migraine pain (top section of Table 8). Migraine pain was most often assessed as "pain severity" or "pain intensity" on a variety of metrics, including via a visual analog scale (VAS) of varied length or through ordinal categories – often with 4 response categories, but sometimes with as few as 3 or as many as 11 response options. There is also considerable variability in how researchers refer to certain response scales, with a 0-10 numerical rating scale often (incorrectly) labeled as a VAS. An author-named "headache index" was used in 9.2% of the publications, but within this grouping the actual calculation of the index value varied among publications. Most often, publications used index = pain intensity*frequency (with varied response scales used to assess pain as just noted), but other headache index definitions also included duration in the index calculation (e.g., index = pain intensity*frequency*duration or index = frequency + (duration*pain intensity)).

With respect to timing of endpoints, the majority of the publications (87%) evaluated change from baseline and a somewhat limited number of publications (n=55, 29.9%) examined between-group differences within a pre-specified, fixed timepoint (e.g., 'Week 12'; Middle section of Table 8). The timepoint used to define endpoints varied across publications and the exact operationalization of the value (e.g., a Week 12 value could be a weekly mean, a 28-day mean, a mean over Baseline to Week 12, etc.) also varied across publications; it was originally planned to extract and synthesize differences in these operationalizations but extraction of these details was intractable (not clearly reported, highly variable across studies). For this reason, the planned extraction was abandoned.

About 55% of publications using migraine-focused outcomes examined differences between groups created by one or more within-person meaningful change threshold values (also known as responder definitions) applied

to the target variable (e.g., a 50% reduction in migraine days, a 75% reduction in migraine attacks). Of the 102 publications that used responder definitions, the vast majority examined the 50% thresholds (94.1%).

Table 8. Migraine-focused Outcomes, Endpoints, and Responder Definitions (n=184 publications)

Variables	Percent	N
Migraine-focused Outcomes		
Attacks	69.02	127
Days	51.09	94
Pain intensity	48.37	89
Duration (e.g., average length of attack)	32.61	60
Hours (e.g., total headache hours per 4-weeks)	10.87	20
Index	9.24	17
Endpoint Timing		
Change from baseline	86.96	160
Fixed timepoints	29.89	55
Responder definition	55.43	102
Responder Definition		
50% reduction	94.12	96
75% reduction	18.63	19
100% reduction	17.65	18
Other responder definition	10.78	11

HEADACHE-FOCUSED OUTCOMES

As seen in the top section of Table 9, almost 75% of the 106 publications that utilized one or more headache-focused outcomes examined headache days, 28.3% examined headache attacks, and 38.7% evaluated headache pain. Almost 90% of the 106 publications looked at change from baseline in one or more headache-focused outcomes while 28.3% looked at group differences at fixed times. Just under 41% compared treatments by the proportion of patients achieving a set responder definition. Of the 43 publications that used responder definitions, the vast majority (90.7%) examined the 50% threshold.

Table 9. Headache-focused Outcomes, Endpoints, and Responder Definitions (n=106 publications)

Variable Used	Percent	N
Headache-focused Outcomes		
Attacks	28.30	30
Days	74.53	79
Pain intensity	38.68	41
Duration (e.g., average length of attack)	15.09	16
Hours (e.g., total headache hours per 4-weeks)	17.92	19
Index	18.87	20
Endpoint Definition		
Change from baseline	87.74	93
Fixed timepoints	28.30	30
Responder definition	40.57	43
Responder Definition		
50% reduction	90.70	39
75% reduction	6.98	3
100% reduction	6.98	3
Other definition	18.60	8

ACUTE/RESCUE MEDICATION USE OUTCOMES

Of the 136 publications that utilized acute or rescue medication outcomes, just over 35% of the publications examined days of medication use and 66.9% examined number of doses used (Top of Table 10). With respect to the timing of acute/rescue medication use endpoints, 82.4% of the 136 publications looked at change from baseline and 25.7% compared treatment groups at fixed times without computing change scores. Very few publications systematically examined responder definitions for acute/rescue medication use in preventive trials (n=8, 5.9%). For example, it was uncommon for publications to evaluate endpoints such as the proportion of subjects showing a 50% reduction in rescue medication doses from baseline.

Table 10. Acute/Rescue Medication Use Variables (n=136 publications)

Variables	Percent	N
Acute/Rescue Medication		
Days	36.03	49

Doses	66.91	91
Endpoint Definition		
Change from baseline	82.35	112
Fixed timepoints	25.74	35
Responder definition	5.88	8

HEADACHE/MIGRAINE-RELATED PROS

Of the 108 publications within the selected subset that used headache or migraine-related PROs, the MIDAS (Stewart, Lipton, Dowson, & Sawyer, 2001; 49.1%), MSQ (e.g., Jhingran, Osterhaus, Miller, Lee & Kirchdoerfer, 1998; Martin, et al., 2000; 31.5%), and the HIT-6 (Kosinski et al 2003; 30.6%) were the most frequently encountered measures used as outcomes (Table 11). There were several other headache/migraine-related PROs less frequently used that are not included in Table 11. The full list of these PROs is available in Appendix B. More than 90% of the 108 publications that included one or more headache/migraine-related PROs looked at change from baseline and 23.2% utilized a fixed time comparison, typically comparing groups cross-sectionally at several different timepoints, including the end of the blinded trial phase. Few publications examined headache/migraine-related PROs in conjunction with one or more responder definitions (n=13, 12.0%).

Table 11. Headache-related PRO Outcomes and Endpoints (n = 108 publications)

Variables Used	Percent	N
Headache/Migraine-related PROs Used		
MIDAS	49.07	53
MSQ (all versions)	31.48	34
HIT-6	30.56	33
Disability/impairment	22.22	24
Endpoint Definitions		
Change from baseline	91.67	99
Fixed timepoints	23.15	25
Responder definition	12.04	13

Note. Only PROs seen in 5 or more publications are broken out. MIDAS = Migraine Disability Assessment. MSQ = Migraine-specific Quality of Life Questionnaire. HIT-6 = 6-item Headache Impact Test short form.

Non-headache Specific PROs

Of the 59 publications in the selected 268 publication subset that used at least one non-headache specific PRO measure, a Patient Global Impression of Change item (PGIC; 25.4%), the SF-36 (23.7%), Beck Depression Inventory (BDI; 17.0%), and a treatment satisfaction item (13.6%) were the most frequently used "standardized" outcomes (top section of Table 12). However, the PGIC and treatment satisfaction items were varied with respect to wording (if given), as well as the number of response options, and the verbal labels applied to those response options.

Many publications evaluating a non-headache specific PRO used a measure that was not frequently used in other trials or did not fall within the displayed non-headache specific PRO summary categories. The full list of these PROs is available in Appendix B. These infrequently encountered PROs included established measures, such as the Hospital Anxiety and Depression Scale (HADS; Zigmund & Snaith, 1983) or the Patient Health Questionnaire (PHQ-9; Kroenke, Spitzer, & Williams, 2001), but also items or scales that were often idiosyncratic to specific authors or author-groups; this diversity highlights how the field could benefit from a standardized set of outcomes.

Almost three-quarters of the 59 publications that used at least one non-headache specific PROM looked at change from baseline while 49.2% looked at differences between groups at fixed timepoints. Only 3.4% of the examined 59 publications using a non-headache specific PRO investigated groups created by applying a responder definition to the PRO scores (Bottom section of Table 12).

Table 12. Non-headache Specific PROs (n=59 publications)

Measure	Percent	N
Non-headache Specific PROs Used		
PGIC (item)	25.42	15
SF-36	23.73	14
BDI	16.95	10
Treatment Satisfaction (item)	13.56	8
Treatment Efficacy (item)	10.17	6
Endpoint Definition		
Change from baseline	71.19	42
Fixed timepoints	49.15	29
Responder definition	3.39	2

Note. Only PROs seen in 5 or more publications are broken out. PRO = Patient reported outcome. PGIC = Patient global impression of change. SF-36 = Short Form Health Questionnaire (36 items). BDI = Beck Depression Inventory.

DISCUSSION

We conducted a systematic literature review of clinical trials for migraine preventive therapies in adults published in peer-reviewed outlets. Of the complete set of 757 publications, approximately three quarters were published in 1988 or later, three quarters utilized randomization, 65.8% utilized a blinded approach and 65.7% used ICHD criteria to identify migraine or other headache diagnosis. More than half of the publications were placebo/sham controlled (58.3%) and more than three-quarters assessed a pharmacological or medical device treatment (77.3%). Nearly all (98.7%) assessed efficacy and 83.4% assessed safety.

Within a subset of 268 articles published from 1988 on and employing designs that met certain criteria (randomized, blinded, etc.), on average, participants were around 39 years old, 82.2% female and 86.8% white. A little over 75% of publications looked at general migraine, 17.2% of publications included patients with CM/TM only, and 6.0% included participants with some form of MRM. These were primarily studies of short term prevention paradigms. With respect to the outcomes used in this subset, 68.7% of the publications examined at least one migraine-specific outcome, 39.6% examined at least one headache-specific outcome, 50.8% examined at least one acute/rescue medication use outcome, 40.3% examined at least one migraine or headache-related PRO, and 22% examined at least one non-headache specific PRO. The most common study design used only migraine-focused outcomes (17.5%), although the study could include multiple migraine-related outcomes; around 8% of publications included at least one of each type of outcomes. Of the 184 publications evaluating at least one migraine-focused outcome, 69% examined migraine attacks, 51.1% evaluated migraine days, and 48.4% evaluated migraine pain which was most often assessed as “pain severity” or “pain intensity” on a variety of metrics. An “index” was used in 9.2% of the studies, primarily older studies, but its definition varied from study to study.

The majority of the publications (87%) in our subset evaluated change from baseline while about a quarter (29.9%) examined group differences at fixed time points. About 55% of publications using migraine-focused outcomes examined differences between groups created by one or more within-person meaningful change threshold values (also known as responder definitions) applied to the target variable (e.g., a 50% reduction in migraine days, a 75% reduction in migraine attacks). Of the 102 publications that used responder definitions, the vast majority (94.1%) examined a 50% reduction threshold.

Almost 75% of the 106 publications that utilized one or more headache-focused outcomes examined headache days, 28.3% examined headache attacks, and 38.7% evaluated headache pain. Of the 136 publications that reported acute or rescue medication outcomes, 36% reported days of medication use while 66.9% reported number of doses used. Of the 108 publications within the noted subset that used migraine or headache/migraine-related PROs, the MIDAS (49.1%), MSQ (31.5%) and the HIT-6 (30.6%) were most commonly selected for use by researchers designing the trials.

As can be seen in this report, there was wide variety in study design, endpoints included, and how endpoints were measured across studies. The endpoints and outcomes used in preventive migraine treatment trials, even when “common” outcomes are used, had inconsistent operationalizations across publications. We use the term publication because, in some cases, several or many publications came from a single study. As demonstrated in summaries of data extracted from the articles reporting on preventive clinical trials, the outcomes used to define endpoints in such trials vary substantially, ranging from migraine or headache

frequency (days, attacks, total hours, index/composite measures), use of acute/rescue medication frequency (days, doses), and various headache-related and non-headache specific PRO measures, such as those related to the impact migraine has on the patient's life or more general HRQoL. The definition of the endpoints used (e.g., change from baseline, fixed-time point comparisons, categorization of "responders" to treatment based on wide variety of "responder definitions") also differs substantially across publications.

We narrowed our focus to a subset of publications from 1988 or later that reported on randomized and blinded trials of pharmacologic and medical device interventions to attempt to summarize the field as it currently stands and to focus on clinical trials likely to be similar to future trials designed to obtain FDA approval for new preventive therapies. Even within this subset, a large amount of variability exists in the outcomes and endpoints used and how those outcomes were operationalized. The results from examining the full set of 757 articles (see Appendix B), with an even wider range of publications and including changes in diagnostic criteria, the treatment landscape, and the fields understanding of migraine, demonstrated even more variability and lack of standardization across trials.

This report has limitations. We did not group publications by the parent study, so there may be unequal weighting for some studies or data sets which have several publications and we did not capture the exact timing of many endpoints (e.g., change in migraine days from baseline to Week 12, where Week 12 could be defined as the average from Weeks 9-12 versus the average from Weeks 1-12) because there was significant inter-study variability in timing, study design, and level of detail in reporting.

Our goal was to provide a comprehensive review of the existing preventive migraine literature to understand the commonly used endpoints and outcomes currently, assess the extent to which a "standardized" set of endpoints and outcomes has developed in the research without formal structure/guidelines, and identify possible areas where new assessments may serve to better understand the patient experience of preventive migraine treatments. Based upon the findings of this review, a wide range of inconsistencies within this literature reporting clinical trials of preventive migraine therapies exists. The development of a uniform set of primary and PRO-based endpoints to be included in future preventive migraine trials would facilitate comparability across study reports and meta-analysis. This set of measures should be fully informed by the patient voice with robust qualitative research. Any measures included in a standardized set of outcomes and endpoints should be reliable, valid, and sensitive to group level and within person change. Ideally, measures would have similar characteristics for EM and CM, migraine with and without aura and other subtypes, but the ability of these scales to be used in the populations mentioned would have to be adequately tested.

Many of the existing measures fulfill some of these criteria. Future work should evaluate existing scales and subscales against a prespecified set of criteria. There are currently migraine-related instruments that measure physical function and impact. However, measures of other domains such as cognitive functioning in migraine do not currently exist and may also be needed to fully capture the impact of migraine on patients' lives. Additionally, future work should both capture and distinguish between the ictal and interictal burden of migraine.

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APPENDIX A: PUBLICATION TRACKING MATRIX OF IDENTIFIED CANDIDATE PUBLICATIONS

Appendix Preventive Literature Review Arti

Appendix B: Results from all 757 examined publications

Demographic and Descriptive Variables of Patients

Available demographic characteristics for the patients from the included publications (pooled over all treatment groups) are summarized in Table A-1. The median total sample size was n=60 (25th percentile: 32, 75th percentile: 147). Of publications that reported age, gender, and/or race descriptives, the average age was found to be 39.4 (SD = 5.2), with 80.9% of patients being female, and 86.0% of patients reported as White/Caucasian.

Table A-1. Demographic Characteristics (n=757 publications)

Variable	Number of publications	Mean	SD	Min	25th Percentile	Median	75th Percentile	Max
Total n*	753	176.63	357.44	3	32	60	147	4520
Mean Age	612	39.35	5.16	23.00	36.25	39.37	42.12	64.70
Percent Female	686	80.90%	11.42	36.09%	75.00%	82.35%	87.50%	100.00%
Percent White	116	86.00%	15.40	0.00%	83.00%	89.90%	93.17%	100.00%

Note. *4 publications were protocols only so total sample was not applicable.

Tables A-2 and A-3 summarize migraine and aura group characteristics of the publications that reported such features. Over 80% of the publications looked at general migraine (unspecified/mixed types) and 11.0% of publications looked at chronic/transformed migraine exclusively. More than half the publications examined mixed aura types (58.0%), 28.4% were not specified, 10.8% were without aura, and 2.8% were with aura only.

Table A-2. Migraine Group Characteristics (n=757 publications)

Patient group characteristics	Percent	N
General migraine (classical migraine/common migraine, EM, multiple types, unspecified)	83.49	632
CM/TM	11.00	83
MRM	5.02	38
Medication overuse headache only	0.53	4

Note. CM = chronic migraine. TM = transformed migraine. MRM = menstrually-related migraine.

Table A-3. Aura Group Characteristics (n=757 publications)

Aura Characteristics	Percent	N
Migraine with and without aura	57.99	439
Not specified	28.40	215
Without aura only	10.83	82
With aura only	2.77	21

Outcomes and Endpoints Used

As seen in Table A-4, two-thirds of the publications looked at one or more migraine-specific outcomes while 38.3% examined one or more headache-specific outcomes. A little over 40% of publications looked at medication use-related outcomes, while only about one-quarter of publications looked at one or more headache-related or non-headache specific PROs.

Table A-4. Outcomes Assessed Across Publications (n=757 publications)

Outcome grouping	Percent	N
Migraine-focused Outcome	66.31	502
Headache-focused Outcome	38.31	290
Medication Use Days/Doses	40.55	307
Headache-Related PRO	28.40	215
Non-headache specific PRO	25.63	194

In examining the various combinations of outcomes used (Table A-5), almost one-quarter of publications looked only at one or more migraine-specific outcomes. About 10% of publications looked at one or more headache-specific outcomes (12.2%), one or more migraine-specific and one or more medication use outcomes (11.5%), one or more migraine-specific, medication use, and PROs (11.5%), and one or more migraine specific outcomes and one or more PROs (9.6%).

Table A-5. Combinations Assessed Across Publications (n=757 publications)

Migraine-specific outcomes	Headache-specific outcomes	Acute/rescue medication Use	PROMs (both headache-related and non-headache specific)	Percent	N
Yes	*No*	*No*	*No*	23.65	179

No	**Yes**	*No*	*No*	12.15	92
Yes	*No*	**Yes**	*No*	11.49	87
Yes	*No*	**Yes**	**Yes**	11.49	87
Yes	*No*	*No*	**Yes**	9.64	73
No	**Yes**	*No*	**Yes**	6.21	47
No	**Yes**	**Yes**	**Yes**	5.68	43
Yes	**Yes**	**Yes**	**Yes**	4.89	37
No	**Yes**	**Yes**	*No*	4.23	32
No	*No*	*No*	*No*	2.77	21
Yes	**Yes**	**Yes**	*No*	2.11	16
No	*No*	*No*	**Yes**	1.98	15
Yes	**Yes**	*No*	**Yes**	1.85	14
Yes	**Yes**	*No*	*No*	1.19	9
Other Combinations				0.66	5

MIGRAINE-FOCUSED OUTCOMES

Of the 502 publications examining one or more migraine-specific outcomes, almost three-quarters of publications looked at migraine attack frequency, nearly half looked at pain/intensity/severity, and 39.0% looked at migraine day frequency (Table A-6).

Table A-6. Frequency of Migraine-focused Outcomes Evaluated (n=502 publications)

Migraine-focused Outcome	Percent	N
Attacks	74.10	372
Days	39.04	196
Pain Intensity	48.41	243
Duration (e.g., average length of attack)	29.88	150
Hours (e.g., total hours per 4-weeks)	8.17	41
Index	15.74	79

Of the 502 migraine-related outcome publications, about one-quarter evaluated the migraine-specific outcome at a fixed timepoint, over 82% evaluated one or more migraine-specific outcome change from baseline, and 47.8% evaluated a responder definition (Table A-7).

Table A-7. Frequency of Migraine-focused Endpoints Evaluated (n=502 publications)

Endpoint Used	Percent	N
Change from baseline	82.47	414

Fixed timepoints	27.29	137
Responder definition	47.81	240

Table A-8. Frequency of Responder Definitions Evaluated (n=240 publications)

Responder Definition Used	Percent	N
50% Reduction	88.33	212
75% Reduction	12.08	29
100% Reduction	17.50	42
Other Responder Definition	17.08	41

Of the 240 migraine-related outcomes that evaluated a responder definition, the majority (88.3%) used a 50% reduction from baseline as the responder definition (Table A-8).

HEADACHE-FOCUSED OUTCOMES

Of the 290 publications examining one or more Headache-specific outcomes, 59% of publications looked at headache day frequency, 33.8% headache attacks, 41% examined headache pain, and 19.7% look at a headache index (Table A-9).

Table A-9. Frequency of Headache-focused Outcomes Evaluated (n=290 publications)

Headache-focused Outcome	Percent	N
Attacks	33.79	98
Days	58.97	171
Pain Intensity	41.03	119
Duration (e.g., average length of attack)	13.45	39
Hours (e.g., total hours per 4-weeks)	10.00	29
Index	19.66	57

Of the 290 Headache-related outcome publications, about one-quarter evaluated the Headache-specific outcome at a fixed timepoint, over 85% evaluated one or more Headache-specific outcome change from baseline, and 40.0% evaluated a responder definition (Table A-10).

Table A-10. Frequency of Endpoints Evaluated (n=290 publications)

Endpoint Used	Percent	N
Change from baseline	86.21	250
Fixed timepoints	23.45	68
Responder definition	40.00	116

Of the 116 headache-related outcomes that evaluated a responder definition, the majority evaluated 50% responder definition (90.5%) (Table A-11).

Table A-11. Frequency of Responder Definitions Evaluated (n=116 publications)

Responder Definition Used	Percent	N
50% Reduction	90.52	105
75% Reduction	8.62	10
100% Reduction	8.62	10
Other Responder Definition	15.52	18

ACUTE/RESCUE MEDICATION USE OUTCOMES

As shown in Table A-12, almost 75% of all publications that examined Acute/Rescue Medication Use looked only at doses and about 25% examined days only.

Table A-12. Acute/Rescue Medication Use Outcomes (n=307 publications)

Days	Doses	Percent	N
No	Yes	72.96	224
Yes	No	24.43	75
Yes	Yes	2.61	8

When examining acute/rescue medication use, more than 80% of publications examined only change over time and just one-quarter of publications looked at fixed timepoint comparisons (Table A-13). Responder definitions for acute/rescue medication use variables were rarely used (~5%).

Table A-13. Acute/Rescue Medication Use Endpoint Timing (n=307 publications)

Acute/Rescue Medication Use Endpoint	Percent	N
Change from baseline	81.76	251

Fixed timepoints	26.71	82
Responder definition	5.21	16

In the full sample of examined articles, a little over a quarter of publications (28.4%) used a headache-or migraine-specific PRO and a quarter (25.6%) used one or more non-headache specific PRO, which in the constructed category includes such things as scales to assess HRQoL, depression, and anxiety, and many single item measures, such as patient satisfaction or patient-rated treatment efficacy (Table A-14).

Table A-14. PRO Type Assessed (n=757 publications)

PRO Type	Percent	N
Headache-related (including migraine specific)	28.40	215
Non-headache specific	25.63	194

Headache/Migraine-related PROs

Of the 215 publications that assessed one or more headache or migraine-related PROs, almost half (48.4%) used MIDAS, 30.2% used HIT-6, 24.7% examined disability/impairment (included both multiple item/composite scores as well as single item assessments), and 21.4% used MSQ (Table A-15).

Table A-15. Headache/Migraine-related PROs Assessed (n=215 publications)

Headache-related PROM Used	Percent	N
MIDAS	48.37	104
HIT-6	30.23	65
Disability/impairment	24.65	53
MSQ	21.40	46
Headache Self-Efficacy Scale (Martin, Holroyd, & Rokicki, 1993)	5.12	11
Migraine-specific Quality of Life Measure (MSQoL; Wagner, Patrick, Galer, & Berzon, 1996)	4.19	9
Headache-specific Locus of Control Scale (Martin, Holroyd, & Penzien, 1990)	4.19	9

Note. Only PROs seen in 5 or more publications are broken out. PRO = patient reported outcome. MIDAS = Migraine Disability Assessment Scale. HIT-6= 6-item Headache Impact Test short form. MSQ = Migraine specific quality of life questionnaire.

For the interested reader, other headache-related “named” scales that were encountered, but less frequently (in fewer than 5 publications), are provided in Table A-16.

Table A-16. Breakdown of "Other headache-related PROMs in Table A-15: Frequency of use for "named" scales.

PRO	Percent	N
Migraine Physical Function Impact Diary (Kawata et al., 2017)	1.86	4
24hr Migraine-specific Quality of Life (Hartmaier et al., (1995)	0.93	2
Headache Disability Inventory (Jacobson et al., 1994)	0.93	2
Headache-specific Pain Quality of Life (e.g., Elkind et al., 2006)	0.93	2
Allodynia Symptom Checklist (Lipton et al., 2008)	0.47	1
Interview of Coping Efforts – Migraine (Hill, 2003)	0.47	1

Almost 90% of the publications assessing one or more headache/migraine-related PROs examined change from baseline, about one-quarter of publications examined fixed timepoint (24.2%), and only 7.4% looked at a responder definition (Table A-17).

Table A-17. Headache/Migraine-related PROs Endpoint Timing (n=215 publications)

Headache/Migraine-related PROs Endpoint	Percent	N
Change from baseline	89.77	193
Fixed timepoints	24.19	52
Responder definition	7.44	16

Non-headache Specific PROs

Of the 194 publications that included an non-headache specific PRO, the most commonly used measure was the SF-36 (18.6%), 17% of publications used the BDI, 14.4% used the PGIC, and around 8-13% looked at either treatment preference, satisfaction, or efficacy (typically as individual items; Table A-17). Several publications evaluated a non-headache specific PRO that was not commonly used or did not fall within our constructed broad categories. This diversity of outcomes used in headache and migraine trials, combined with the observation that many PROs were items or scales idiosyncratic to specific authors or author-groups, highlights one of the potential benefits that could be derived from a standardized set of outcomes.

Table A-18. Non-headache Specific PROs Assessed (n=194 publications)

Non-headache specific PROMs Used	Percent	N
SF-36	18.56	36
BDI	17.01	33
PGIC (item)	14.43	28
Treatment Efficacy (item)	12.89	25
Treatment Satisfaction (item)	9.28	18
Treatment Preference (item)	7.73	15
Zung Depression (Zung, 1965)	6.70	13
Hamilton Rating Scale for Depression (Hamilton, 1960)	5.67	11
HADS	5.15	10
Pain Disability Index (Tait et al., 1987)	4.12	8
State-Trait Anxiety Inventory (Spielberger, 1989)	3.61	7
Short Form Health Questionnaire (12 items) (Ware, Kosinksi, & Keller, 1996)	3.09	6
PGIS (item)	3.09	6
Hamilton Rating Scale for Anxiety (Hamilton, 1959)	2.58	5
Center for Epidemiologic Studies-Depression (Radloff, 1977)	2.58	5
Zung Anxiety (Zung, 1971)	2.58	5

Note. Only PROs seen in 5 or more publications are broken out. PRO = patient reported outcome, SF-36 = Short Form Health Questionnaire (36 items). BDI = Beck Depression Inventory. PGIC = Patient global impression of change. HADS = Hospital Depression and Anxiety Scale. SF-12 = Short Form Health Questionnaire (12 items)

Other “named” non-headache specific PROMs that occurred less frequently (fewer than 5 publications) are provided in Table A-19.

Table A-19: Breakdown of “named” non-headache specific PROMs encountered in preventive publications (N = 194)

Non-headache specific PROM	Percent	N
Beck Anxiety Inventory (Osman et al., 1997; Steer & Beck, 1997)	2.06	4
Pain Catastrophizing Scale (Sullivan et al., 1995)	1.55	3
Pittsburgh Sleep Quality index (Buysse et al., 1989)	1.55	3
Schmerzempfindungsskala (SES) [German] (Geissner, 1996)	1.55	3
McGill Pain (Melzack, 1987)	1.03	2
Menstrual Distress Questionnaire (Moos, 1968)	1.03	2
Perceived Stress Scale (Cohen & Williamson, 1988)	1.03	2
PROMIS pain interference (Amtmann et al., 2010)	1.03	2

Brief Pain Inventory (Cleeland & Ryan, 1994)	0.52	1
Chronic Pain Acceptance Questionnaire (McCracken et al., 2004)	0.52	1
Chronic Pain Coping Inventory-42 (Jensen et al., 1995)	0.52	1
Coping Efficacy Measure (Lawler, 1999)	0.52	1
Depression Anxiety Stress Scales (Lovibond & Lovibond, 1995)	0.52	1
Dizziness Handicap Inventory (Jacobson & Newman, 1990)	0.52	1
Epworth Sleepiness Scale (Johns, 1991)	0.52	1
Event-specific Coping List (Sorbi & Tellegen, 1988)	0.52	1
Eysenck Personality Inventory (Eysenck & Eysenck, 1964)	0.52	1
Fatigue Index Scale (Fisk et al., 1994)	0.52	1
Fear-Avoidance Beliefs Questionnaire (Waddell et al., 1993)	0.52	1
Fragebogen zur Erfassung des motorischen Funktionsstatus [German] (Boes et al., 2002)	0.52	1
Freiburger Personlichkeits-inventar (Diehl & Paul, 1985)	0.52	1
Generalized Anxiety Disorder -7 (Spitzer et al., 2006)	0.52	1
German Pain Questionnaire [German] (Lowedorf, n.d.)	0.52	1
International Physical Activity Questionnaire (Ekelund et al., 2006)	0.52	1
Leeds Dependence Questionnaire (Raistrick et al., 1994)	0.52	1
Multidimensional Pain Inventory (Kerns et al., 1985)	0.52	1
Neck Disability Index (Vernon & Mior, 1991)	0.52	1
Pain Anxiety Symptom Scale (McCracken et al., 1992)	0.52	1
Pain Behavior Scale (Philips & Hunter, 1981)	0.52	1
Pain-related Self-Statements scale [German] (Fritsche et al., 2010)	0.52	1
Profile of Moods States (McNair et al., 1981)	0.52	1
Psychosocial Adjustment to Illness Scale (Derogatis, 1986)	0.52	1
Questionnaire for assessment of control beliefs about illness and health [German] (Lohaus & Schmitt, 1989)	0.52	1
Sleep Problem Index (Hays & Stewart, 1992)	0.52	1
Social Behavior Scale (Arrindell et al., 1984)	0.52	1
Stress Management Questionnaire [German] (e.g., Starke, 2000)	0.52	1
Utrecht Coping List [Dutch] (Schreurs et al., 1984)	0.52	1
Wechsler memory scale (Wechsler, 1945)	0.52	1
Weekly illness impact recordings (Holroyd et al., 1993)	0.52	1
Work Ability Index (Tuomi et al., 1998)	0.52	1
Work Productivity and Activity Impairment (Reilly et al., 1993)	0.52	1
Yale-Brown Obsessive-Compulsive Scale (Kim et al., 1990)	0.52	1
Zung Pain and Distress scale (Zung, 1983)	0.52	1

For the publications examining one or more non-headache specific PROs, about two-thirds (66%) examined change from baseline, while 51% looked at differences between fixed timepoints (Table A-20). Only 3.6% of the examined 194 publications using a non-headache specific PRO investigated groups created by applying a responder definition to the PRO scores.

Table A-20. Non-headache Specific PROs Endpoint Timing (n=194 publications)

Non-headache specific PROs endpoint	Percent	N
Change from baseline	65.98	128
Fixed timepoints	51.03	99
Responder definition	3.60	7

APPENDIX REFERENCES

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