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**Migraine-Related Disability According to Headache Frequency Subclassifications: A Systematic Review and Meta-Analysis**

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**ADMINISTRATIVE INFORMATION**

**Support -** Salvia Bioelectronics BV.

**Review Stage at time of this submission -** Completed but not published.

**Conflicts of interest -** boards for AbbVie/Eli Lilly/Lundbeck/Pfizer/Salvia/TEVA; has received payment for educational presentations from AbbVie/Eli Lilly/Lundbeck/Organon/Pfizer/TEVA; has received grants from Abbott/Medtronic/Ehlers Danlos Society; and has a patent on system and method for diagnosing and treating headaches (WO2018051103A1, issued). Within the past 24 months, HY has received funding from AHS Early-Stage Investigator Research Award; institutional support for serving as an investigator from Teva/Abbvie/Ipsen/Parema; consultant fees from Salvia/Abbvie/Pfizer/Cerenovus; and royalties from Cambridge University Press/MedLink. DE & RC received consulting fees from Salvia BioElectronics. TS, within the prior 24 months, has received consulting fees from AbbVie/Amgen/Eli Lilly/Linpharma/Lundbeck/Salvia BioElectronics/Scilex/Theranica and royalties from UpToDate. He holds/held stock options in Aural Analytics/Nocira. He has received research funding from the American Heart Association/Henry Jackson Foundation/National Headache Foundation/National Institutes of Health/Patient Centered Outcomes Research Institute/Pfizer/Spark Neuro/United States Department of Defense. MLM reports personal fee for advisory boards, speaker panels or investigation studies from Allergan/Amgen/Astellas/ATI/BMS/Boehringer/Boston Scientific/CoLucid/Convergence/Eli Lilly/GlaxoSmithKline/Grunenthal/Eli Lilly/IPSEN Lundbeck/Medtronic/MSD/Novartis/Perfood/Pfizer/Reckitt Benckiser/Saint-Jude/Salvia BioElectronics/Sanofi-Aventis/Teva/UCB/UPSA/Zambon. MO received scientific support, travel support and/or consulting fees from Biogen Idec/Novartis/Sanofi/Genzyme/Pfizer/Teva/Ely Lilly/Noema Pharma/Salvia BioElectronics. He received research grants from Allergan/Electrocore/Heel/German Ministry for Education and Research (BMBF).

**INPLASY registration number:** INPLASY2024120039

**Amendments -** This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 10 December 2024 and was last updated on 10 December 2024.

**INTRODUCTION**

**Review question / Objective** To systematically review and synthesize the burden of headache-related disability in migraine according to headache frequency

subclassifications, including low-frequency episodic migraine (LFEM), high-frequency episodic migraine (HFEM), and chronic migraine (CM).

**Rationale** Although several studies have recently published data on migraine-related disability in

episodic migraine subclassifications, to the best of our knowledge, a comprehensive review synthesizing these findings is lacking. To address this evidence gap, we conducted a systematic review and meta-analysis of disability outcomes in headache frequency subclassifications of migraine, with a focus on characterizing disability in the subset of migraineurs with HFEM.

**Condition being studied** We are studying migraine, a complex neurological disorder characterized by recurrent, disabling headache attacks, associated with a combination of nausea, vomiting, photophobia, and phonophobia]. Individuals may also experience cognitive impairment, dizziness, and fatigue, among other symptoms.

## METHODS

**Search strategy** PubMed search strategy:

- #1. "low frequency" OR "high frequency" OR LFEM OR HFEM
- #2. "8-14" OR "9-14" OR "10-14"
- #3. #1 OR #2
- #4. disab\* OR burden OR resourc\* OR work OR econom\*
- #5. migraine[MeSH Terms] OR migrain\*
- #6. #4 AND #5
- #7. #3 AND #6
- #8. subgroup\* OR subdivid\* OR divid\* OR stratif\*
- #9. frequency OR "headache days" OR "migraine days"
- #10. #8 AND #9
- #11. #10 AND #6
- #12. #7 OR #11

Cochrane Library search strategy:

- #1. low frequency OR "high frequency" OR LFEM OR HFEM
- #2. 8-14 OR "9-14" OR "10-14"
- #3. #1 OR #2
- #4. disab\* OR burden OR resourc\* OR work OR econom\*
- #5. MeSH descriptor: [Migraine Disorders] this term only
- #6. migrain\*
- #7. #5 OR #6
- #8. #4 AND #7
- #9. #3 AND #8
- #10.† ("low frequency" OR "high frequency" OR LFEM OR HFEM OR "8-14" OR "9-14" OR "10-14") AND (disab\* OR burden OR resourc\* OR work OR econom\*) AND migrain\*
- #11. subgroup\* OR subdivid\* OR divid\* OR stratif\*
- #12. frequency OR "headache days" OR "migraine days"
- #13. #11 AND #12

#14. #13 AND #8

#15.† (subgroup\* OR subdivid\* OR divid\* OR stratif\*) AND (frequency OR "headache days" OR "migraine days") AND (disab\* OR burden OR resourc\* OR work OR econom\*) AND migrain\*

#16. #9 OR #15

#17.† ("low frequency" OR "high frequency" OR LFEM OR HFEM OR "8-14" OR "9-14" OR "10-14") AND (disab\* OR burden OR resourc\* OR work OR econom\*) AND migrain\*) OR ((subgroup\* OR subdivid\* OR divid\* OR stratif\*) AND (frequency OR "headache days" OR "migraine days") AND (disab\* OR burden OR resourc\* OR work OR econom\*) AND migrain\*)

†Included as checksums only, not required.

**Participant or population** Patients with migraine.

**Intervention** Not applicable.

**Comparator** Not applicable.

**Study designs to be included** Noninterventional.

**Eligibility criteria** Articles were eligible for inclusion if they reported headache-related disability outcomes from a noninterventional study that included individuals with chronic migraine and subclassifications of episodic (eg, low-frequency episodic migraine [LFEM] and high-frequency episodic migraine [HFEM]). Publications were excluded if they were not peer-reviewed or had no full-text manuscript available (eg, conference proceedings); no original data were presented (eg, data duplication, protocol and technical descriptions, commentaries, and review articles); or relevant data could not be extracted for the population(s) of interest.

**Information sources** We searched the PubMed and CENTRAL electronic databases. Other sources included Google Scholar and reference lists of retrieved publications.

**Main outcome(s)** The following data were extracted from eligible publications: study design variables, demographics, sample size, MHD or monthly migraine days (MMD) subgroup definitions, and headache-related disability data.

**Quality assessment / Risk of bias analysis** The risk of bias was assessed for each included study using the Joanna Briggs Institute (JBI) critical appraisal tools, considering the following items:

1. Was the sample frame appropriate to address the target population?
2. Were study participants sampled in an appropriate way?

3. Was the sample size adequate?
  4. Were the study subjects and the setting described in detail?
  5. Was the data analysis conducted with sufficient coverage of the identified sample?
  6. Were valid methods used for the identification of the condition?
  7. Was the condition measured in a standard, reliable way for all participants?
  8. Was there appropriate statistical analysis?
  9. Was the response rate adequate, and if not, was the low response rate managed appropriately?
- The reviewers classified the studies according to the number of “yes” answers as high risk ( $\leq 5$ ), moderate risk (6-7), or low risk ( $\geq 8$ ). Disagreements were resolved by consensus.

**Strategy of data synthesis** Studies were considered for meta-analysis if they (1) reported the mean value or proportion of a headache-related disability measure for each specified headache frequency subgroup, and (2) defined HFEM as 8-14, 9-14, or 10-14 MHD or MMD. The studies were grouped according to headache frequency measure (MHD or MMD), HFEM frequency subgroup (8-14, 9-14, or 10-14), and disability parameter. A meta-analysis was conducted on disability parameter groups containing at least 3 studies to ensure the validity of the analysis in the presence of heterogeneity. For continuous disability variables, we conducted a random-effects meta-analysis of single means to calculate the overall mean. For categorical disability variables, we conducted a random-effects meta-analysis for single proportions. All data pooling was performed using inverse variance weighting. We used the I-squared test ( $I^2$ ) to assess heterogeneity between studies.

**Subgroup analysis** Not applicable.

**Sensitivity analysis** A sensitivity analysis was performed by evaluating and comparing the pooled estimates from a fixed-effect and random-effects meta-analysis.

**Country(ies) involved** UK, USA, Belgium, France, Germany.

**Keywords** Migraine, high-frequency episodic migraine, chronic migraine, disability, diagnostic criteria, headache, classification.

#### **Contributions of each author**

Author 1 - Manjit Matharu - Author 1 contributed to study conceptualization, methodology, review, and editing. The author approved the final manuscript. Email: m.matharu@uclmail.net

Author 2 - Stephen Silberstein - Author 2 contributed to review and editing. The author approved the final manuscript.

Author 3 - Hsiangkuo Yuan - Author 3 contributed to review and editing. The author approved the final manuscript.

Author 4 - Deborah Edgar - Author 4 contributed to study conceptualization, methodology, review, and editing. The author wrote the original manuscript draft and approved the final manuscript.

Author 5 - Roos Colman - Author 5 contributed to study conceptualization, methodology, review, and editing. The author conducted the statistical analyses and approved the final manuscript.

Author 6 - Todd Schwedt - Author 6 contributed to review and editing. The author approved the final manuscript.

Author 7 - Michel Lanteri-Minet - Author 7 contributed to review and editing. The author approved the final manuscript.

Author 8 - Mark Obermann - Author 8 - contributed to review and editing. The author approved the final manuscript.