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Requires Data Access? Yes

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Requires Data Access? Yes

Are external grants or funds being used to support this research?: No external grants or funds are being used to support this research.
How did you learn about the YODA Project?: Other

Conflict of Interest

https://yoda.yale.edu/wp-content/uploads/2025/12/COI-2.pdf
https://yoda.yale.edu/wp-content/uploads/2025/12/COI-FORM-AH.pdf
https://yoda.yale.edu/wp-content/uploads/2025/12/COI-FORM-JD.pdf

Certification

Certification: All information is complete; I (PI) am responsible for the research; data will not be used to support litigious/commercial aims.
Data Use Agreement Training: As the Principal Investigator of this study, I certify that I have completed the YODA Project Data Use Agreement Training

1. NCT00216619 - TOPMAT-MIG-303 - A Double-Blind, Randomized, Placebo-Controlled, Multicenter Trial to Investigate the Efficacy and Tolerability of Topiramate in Prolonged Migraine Prevention
2. NCT00216606 - TOPMAT-MIG-201 - A Randomized Double-Blind Placebo Controlled Trial to Investigate the Efficacy and Tolerability of Topiramate in the Prophylaxis of Chronic Migraine

3. NCT00210860 - CAPSS-296 - An Open-label Study of the Safety and Efficacy of Topiramate for Migraine Prophylaxis: Extension Study to CAPSS-277
4. NCT00237302 - CAPSS-122 - A Comparison of the Efficacy and Safety of Topiramate Versus Placebo for the Prophylaxis of Migraine in Pediatric Subjects
5. NCT00210535 - TOPMATMIG3006 - A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Topiramate for the Prophylaxis of Migraine in Pediatric Subjects 12 to 17 Years of Age
6. NCT00210821 - CAPSS-277 - A Comparison of Topiramate Versus Amitriptyline in Migraine Prophylaxis
7. NCT00210912 - CAPSS-276 - A Comparison of the Efficacy and Safety of Topiramate Versus Placebo for the Prophylaxis of Chronic Migraine
8. NCT00212810 - CAPSS-381 (INTREPID) - TOPAMAX (Topiramate) Intervention to Prevent Transformation of Episodic Migraine: The Topiramate INTREPID Study
9. NCT00236561 - TOPMAT-MIGR-003 - A Randomized, Double-Blind, Parallel-Group, Dose-Response Study to Evaluate the Efficacy and Safety of Two Doses of Topiramate Compared to Placebo and Propranolol in the Prophylaxis of Migraine
10. NCT00231595 - TOPMAT-MIGR-002 - A Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Dose-Response Study to Evaluate the Efficacy and Safety of Topiramate in the Prophylaxis of Migraine
11. NCT00236509 - TOPMAT-MIGR-001 - A Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Dose-Response Study to Evaluate the Efficacy and Safety of Topiramate in the Prophylaxis of Migraine

What type of data are you looking for?: Individual Participant-Level Data, which includes Full CSR and all supporting documentation

Research Proposal

Project Title

Association Between Monthly Migraine Days and Disability Outcomes

Narrative Summary:

Migraine prevention trials usually measure success by counting how many migraine days a person has each month. However, this number alone does not fully reflect the extent to which migraines disrupt daily life, work, and overall well-being.

This study will reanalyze data from several completed clinical trials to better understand how the number of monthly migraine days relates to patient-reported disability and quality of life.

By examining these relationships over time within the same individuals, the study aims to identify migraine frequency levels that are associated with significant functional impairment.

The results will help clinicians, researchers, and decision-makers better interpret trial outcomes and understand the implications of reductions in migraine days for patients' everyday lives and public health.

Scientific Abstract:

Background: Monthly migraine days (MMDs) are the primary efficacy endpoint in preventive migraine trials, yet frequency alone does not directly capture functional impairment or quality of life. Patient-reported outcome measures such as HIT-6 and MIDAS more directly quantify disability but are less commonly used as primary endpoints.

Objective: To quantify cross-sectional and longitudinal relationships between MMDs and disability and quality-of-life outcomes, and to identify MMD thresholds associated with clinically meaningful disability.

Study Design: Secondary analysis of individual participant data from randomized, double-blind migraine prevention trials, using concurrent MMD and outcome measurements.

Participants: Adults enrolled in three trials with baseline MMD data.

Outcomes: HIT-6 score and very severe impact (HIT-6 >=60), MIDAS score and severe disability (MIDAS >=21), SF-12 physical and mental component scores, MSQ domains, and other trial-collected quality-of-life measures.

Statistical Analysis: Longitudinal mixed-effects models will be used to estimate within-person associations between concurrent MMD and outcomes, adjusting for trial, treatment assignment, time, and baseline covariates, with the inclusion of restricted cubic splines to assess nonlinearity. Mixed-effects logistic models and ROC analyses will identify clinically interpretable MMD thresholds predicting severe disability, with internal validation across trials.

Brief Project Background and Statement of Project Significance:

Monthly migraine days (MMDs) are the dominant efficacy endpoint in preventive migraine clinical trials and are central to regulatory approval, clinical decision-making, and payer coverage determinations. While migraine frequency is clinically intuitive and operationally simple, it is an incomplete proxy for the real-world burden of disease. Patients and clinicians are primarily concerned with functional impairment, reduced quality of life, and the ability to work and participate in daily activities--domains that are more directly measured by patient-reported disability instruments such as the Headache Impact Test (HIT-6) and the Migraine Disability Assessment (MIDAS).

Despite widespread use of both MMDs and disability measures in trials, the quantitative relationship between migraine frequency and disability has not been well characterized, particularly using within-person longitudinal data aligned to trial visit schedules. As a result, it remains unclear how specific MMD levels translate into clinically meaningful disability, whether important disability occurs below traditional chronic migraine thresholds, and how reductions in MMDs should be interpreted in terms of patient benefit.

This project addresses these gaps by conducting a secondary analysis of individual participant data from multiple randomized trials of migraine prevention. By leveraging repeated, concurrent measurements of MMDs and validated disability and quality-of-life outcomes, the study will estimate both cross-sectional and longitudinal dose--response relationships between migraine frequency and functional impact. The analysis will also identify clinically interpretable MMD thresholds associated with severe disability and examine whether these relationships vary by baseline disease severity or patient characteristics.

The information generated will materially enhance the interpretability of migraine trial results, providing a clearer linkage between commonly reported frequency outcomes and patient-centered measures of disability. These findings will inform clinical practice, trial design, and health policy by clarifying the implications of changes in MMDs for patients' daily functioning and the overall public health burden.

Specific Aims of the Project:

Specific aims and hypotheses
Aim 1. Dose--response relationship (cross-sectional and longitudinal)
Within-person, concurrent association between MMD and disability outcome, adjusted for time, treatment assignment, trial, and baseline covariates.

- H1a: Disability increases monotonically with increasing MMDs, with nonlinear escalation at mid-to-high frequencies.
- H1b: Clinically meaningful disability occurs at MMD levels below chronic migraine thresholds.

Aim 2. Clinically meaningful MMD thresholds

Probability of severe disability as a function of concurrent MMD.
- H2: Distinct MMD cut points predict very severe impact (HIT-6 >= 60) and severe disability (MIDAS >= 21).

Aim 3. Robustness, modifiers, and generalizability

Shift in the MMD--disability curve associated with prespecified modifiers.
- H3: Depression/anxiety measures, baseline disability, and baseline MMD shift the disability curve upward at any given MMD.

Study Design:

Methodological research

What is the purpose of the analysis being proposed? Please select all that apply.

New research question to examine treatment effectiveness on secondary endpoints and/or within subgroup populations

Research Methods

Data Source and Inclusion/Exclusion Criteria to be used to define the patient sample for your study:

Study population
Inclusion criteria
- Participants enrolled in included trials
- Baseline MMD and >=1 post-baseline trial visit with both MMD and disability outcome available

Exclusion criteria
- None beyond parent-trial definitions
- Secondary headache disorder requires alternative evaluation.
- Another primary headache disorder is the dominant diagnosis (e.g., cluster headache).

Primary and Secondary Outcome Measure(s) and how they will be categorized/defined for your study:

Outcomes
Primary outcome
- HIT-6 (continuous)
- Very severe impact (HIT-6 >= 60)

Secondary outcomes (as available)
- MIDAS (continuous) and severe disability (MIDAS >= 21)
- SF-12 physical and mental component scores
- MSQ domain scores
- Other trial-collected outcomes (e.g., Quality of Life Enjoyment and Satisfaction Questionnaire, Weight Satisfaction Scale)

Main Predictor/Independent Variable and how it will be categorized/defined for your study:

The primary independent variable is the number of monthly migraine days (MMDs). MMDs are defined according to each parent trial's protocol as the number of days within the prespecified reporting window (typically 28 days) on which a participant experienced a migraine headache

meeting trial-defined criteria.

For all analyses, MMDs will be treated as a time-varying exposure and paired concurrently with disability and quality-of-life outcomes measured at the same trial visit. All available MMD observations from baseline and post-baseline visits (e.g., weeks 4, 8, 12, and the end of the double-blind period) will be included.

In primary analyses, MMDs will be modeled as a continuous variable to preserve information and allow estimation of dose--response relationships. Nonlinear associations will be evaluated using restricted cubic spline functions. For threshold and interpretability analyses, MMDs will also be categorized into clinically meaningful cut points (e.g., 0--3, 4--7, 8--9, 10--14, and >=15 days per month), consistent with commonly used migraine frequency groupings in clinical practice and trials. These categories will be used to estimate the probability of severe disability and to identify MMD levels associated with clinically meaningful impairment.

Other Variables of Interest that will be used in your analysis and how they will be categorized/defined for your study:

Key covariates and variables of interest will be harmonized across trials using parent-trial definitions where possible.

Design/structure variables

Trial indicator: categorical variable for each parent study.

Treatment assignment: randomized arm (active vs placebo; or specific dose groups if applicable).

Time/visit: categorical visit indicator aligned to trial schedules (baseline; post-baseline visits such as weeks 4/8/12; end of double-blind), and/or continuous time in weeks as appropriate.

Baseline MMD: continuous baseline value (and categorized for descriptive tables using the same cut points as MMD when needed).

Demographics

Age: continuous in years (and summarized in categories for descriptives, e.g., <40, 40--49, 50--59, >=60 if needed).

Sex: categorical (female/male as recorded).

Race/ethnicity: categorical as recorded in the parent trials; may be collapsed to maintain cell sizes.

Clinical characteristics

Baseline disability/quality-of-life: baseline HIT-6, MIDAS, SF-12, MSQ (continuous; also binary severity indicators where defined).

Depression/anxiety measures: trial-collected scale scores (continuous) and/or clinically relevant cut points if established in the parent trials; used for adjustment and effect modification.

Migraine history variables: duration of migraine, baseline headache frequency/chronicity classification, and/or medication use variables if available consistently across trials (coded per trial definitions; included if harmonizable).

Effect modifiers (prespecified)

Depression/anxiety measures, baseline disability, sex, and baseline MMD will be evaluated via interaction terms with concurrent MMD and presented as stratified predicted curves/probabilities.

Missingness patterns will be described for all covariates. Models will utilize available concurrent MMD--outcome pairs with covariate adjustment based on harmonized variables available across trials.

Statistical Analysis Plan:

Statistical analysis plan
Descriptive analyses
- Baseline characteristics by trial and pooled.
- distributions of MMD and disability outcomes by trial
Aim 1: Cross-sectional models
- Baseline outcome ~ baseline MMD
- Regression models adjusted for trial indicator, treatment assignment, and baseline covariates.
- Restricted cubic splines for MMD to assess nonlinearity.
Aim 1: Longitudinal models (primary)
- Linear mixed-effects models for continuous outcomes (e.g., HIT-6):
o Random intercepts for participants
o Fixed effects: concurrent MMD, treatment assignment, trial indicator, baseline MMD
o Restricted cubic splines for MMD
- Binary outcomes (e.g., HIT-6 >= 60): mixed-effects logistic regression; GEE as sensitivity.
All models use MMD and outcome pairs only.
Effect modification
- Prespecified modifiers: depression/anxiety measures, baseline disability, sex, baseline MMD.
- Interaction terms with MMD; present stratified predicted curves
Aim 2: Threshold identification
- ROC analyses predicting severe disability using concurrent MMD.
- Report AUC, sensitivity, and specificity for clinically interpretable cut points (e.g., 4, 8, 10, 15 MMDs).
- Threshold selection emphasizes clinical interpretability over purely data-driven cut points.
Aim 3: Validation
- Internal validation using trial-level cross-validation (train on two trials, test on the third).
- Assess calibration and discrimination across trials.
Missing data
- Mixed-effects models assume MAR.
- Describe missingness patterns and sensitivity analyses if substantial.
Multiplicity
- Emphasis on effect sizes and uncertainty intervals; secondary outcomes interpreted descriptively.

Software Used:

R, RStudio

Project Timeline:

Deliverables and timeline (24 months)
- Months 0--3: Data access, harmonization,
- Months 4--9: Descriptive analyses; primary longitudinal models
- Months 10--15: Threshold analyses; effect modification; validation
- Months 16--20: Manuscript drafting; figures and tables
- Months 21--24: Revisions, submission, and dissemination of materials

Dissemination Plan:

The primary product of this project will be a peer-reviewed manuscript that quantifies the cross-sectional and longitudinal relationships between monthly migraine days and patient-reported disability and quality-of-life outcomes. The manuscript will emphasize clinically interpretable dose--response curves and migraine frequency thresholds associated with meaningful functional

impairment.

The target audience includes clinicians treating migraine, clinical trialists, outcomes researchers, regulators, and health policy and payer stakeholders who rely on migraine trial results to inform decisions. Secondary products may include figures and summary tables that map migraine frequency to expected disability, suitable for clinician-facing or methodological presentations.

The completed manuscript will be submitted to a high-impact, peer-reviewed neurology or headache-focused journal that is appropriate for clinical outcomes research, such as those specializing in neurology, headache medicine, or clinical epidemiology. Study results will also be reported back to the YODA Project in accordance with data use requirements and may be presented at relevant scientific meetings to maximize dissemination to the migraine research and clinical communities.

Supplementary Material:

https://yoda.yale.edu/wp-content/uploads/2025/12/Association-Between-Monthly-Migraine-Days-and-Disability-Outcomes-Research-Proposal.docx