Review

Cephalalgia Reports

Cephalalgia Reports
Volume 5: 1–8

DOI: 10.1177/25158163221096867
journals.sagepub.com/home/rep
SAGE

The impact of topiramate, botulinum toxin type A, and CGRP-antibodies on medication overuse headache in patients with chronic migraine: A protocol for systematic review and meta-analysis

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Abstract

Medication overuse headache (MOH) is defined as headache occurring ≥15 days/month developing as a consequence of regular overuse of acute or symptomatic headache medication for more than 3 months. MOH is present in more than 50% of patients with chronic migraine (CM). Although, studies have shown a positive impact for MOH patients of early introduction of preventive treatment and withdrawal of overused medication, uncertainties remain. The main purpose of this systematic review and meta-analysis is to assess the relative impact of topiramate, botulinum toxin type A, and human monoclonal antibodies (mAbs) targeting calcitonin gene-related peptide (CGRP) or its receptor (CGRPr) among MOH patients with CM. The PRISMA guideline for conducting systematic review will be followed. CENTRAL, MEDLINE, Embase and Web of Science databases will be searched. RCTs reporting outcomes such as change in migraine/headache frequency, change from MOH to no MOH, and ≥50% response rate will be included. The effect will be measured as mean difference (MD) for continuous data and odds ratio (OR) for dichotomous data. Heterogeneity across studies will be assessed using the Cochrane I^2 statistics. The Cochrane RoB2 tool will be used to assess risk of bias, and the quality of evidence for outcomes will be rated according to five factors defined in Cochrane GRADE approach. The revision of the included articles, data extraction, risk of bias assessment, and quality rating of evidence will be independently done by two reviewers. Any discrepancies will be resolved through consensus with the third reviewer.

Keywords

botulinum toxin type A, CGRP, medication overuse headache, topiramate

Date received: 16 December 2021; Received revised March 21, 2022; accepted: 3 April 2022

Introduction

Background

Migraine is the sixth most common disorder, affecting one billion people worldwide.[1,2] According to the data from the Global Burden of Disease study (GBD) 2019, migraine is ranked as the second most disabling condition for all ages and the most disabling in people under 50 years.[3,4] The third edition of the International Classification of Headache Disorders (ICHD-3) has classified headache disorder as

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primary headache including migraine and tension-type headaches (TTH), and secondary headache including medication-overuse headache (MOH). Chronic migraine (CM) is a transition from episodic migraine to more frequent headache attacks, influenced by lifestyle, comorbidity, genetic factors that often leads to drug overuse.[5] ICHD-3 has classified CM as primary headache, headache for ≥15 days per month for ≥3 months, of which headaches and associated symptoms for at least 8 days a month fulfills the diagnostic criteria for migraine headache.[6] Approximately 2% in the general population suffer from CM.[7,8] In Norway, the prevalence of chronic headache is 2.5% including those with CM (0.5%).[8,9] Each year, almost 2.5% of patients with episodic migraine develop CM.[10] Patients with established primary headache disorders often tend to overuse medications to alleviate the symptoms of their primary headaches. However, an unfortunate cycle of medication overuse results in increased headache intensity and frequency, whereby the medications specified for the headache treatment becomes the cause of MOH.

MOH also known as drug-induced headaches or medication-misuse headaches is a common neurologic disorder commonly affecting those aged 30 to 50 years, and is three to four times more common among women than men.[11,12] The prevalence of MOH ranges from 0.5% to 7.2% in the general population with a mean of 1–2% in the industrialized countries.[13] In Norway, the prevalence of MOH ranges from 0.4 to 1%.[8,9] MOH classified as a secondary headache disorder secondary to a pre-existing primary headache,[6] and is also considered as a complication of CM.[5,14] ICHD-3 has defined MOH as headache occurring ≥15 days per month in individuals with existing primary headache and developing as a consequence of regular overuse (use on 10 or more or 15 or more days/month, depending on the medication) of acute medication for more than 3 months that significantly worsen pre-existing headache disorder.[6] MOH has eight sub-forms; MOH induced by ergotamine, triptans, analgesics including paracetamol, aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs), opioids, combination analgesics, multiple drug classes not individually overused, unspecified or unverified overuse of multiple drug classes and other medication.[6]

The optimal way to treat patients with MOH is still debated. Whether to use preventive treatment during withdrawal therapy, or if needed afterward is probably the most disputed subject.[12]

Description of the intervention

The intervention of interest will be required to have at least one of these three different preventive treatments; topiramate, botulinum toxin type A, and human monoclonal antibodies (mAbs) targeting calcitonin gene-related peptide (CGRP) or its receptor (CGRPr), which include eptinezumab, erenumab, fremanezumab and galcanezumab. We will focus on RCTs comparing the mentioned preventive treatment with placebo. The outcomes of preventive treatments for MOH is a reduction in a monthly migraine frequency and severity of migraine attacks.

Rationale

Suffering from migraine attacks results in substantial disability that may affect employment, school, family and social life, cost of healthcare and medication.[15] MOH is a complication in patients with pre-existing primary headache including chronic migraine who overuse medication to reduce the symptoms of their primary headache.[6] Acute treatments is taken for pain and symptom relief during a migraine attack, whereas preventive pharmacological treatments may be beneficial to reduce the frequency and severity of migraine.[16] The need of preventive therapies depends upon the frequency and severity of migraine attacks, thus is not required for all migraine patients. Previously, there was a general belief that patients with MOH rarely respond to preventative medications while overusing acute medication, which was also stated in the ICHD-2.[17] However, more recently several randomized trials have demonstrated that MOH patients may respond positively to early introduction of preventive treatment.[17,18] In the last two decades, three new types of preventive treatments have demonstrated effect on patients with chronic migraine; namely treatment with topiramate, botulinum toxin type A, and mAbs targeting CGRP(r). In Norway, treatment with botulinum toxin type A, and CGRP-antibodies are restricted to patients with CM. However, uncertainties remain regarding the relative effectiveness between these three established preventive medications for patient with MOH. To our knowledge, no systematic review has previously been published focusing on the impact of topiramate, botulinum toxin type A, and mAbs targeting CGRP(r) on MOH. Thus, this comprehensive systematic review of the clinical evidence of the identified preventive medications on MOH patients will benefit both medical doctors and stakeholders.

Objectives

To compare the relative effects of preventive treatment of topiramate, botulinum toxin type A, and CGRP-antibodies in chronic migraine patients with MOH.

Research question: In migraine patients with MOH, what is the comparative efficacy, safety and effectiveness of topiramate, botulinum toxin type A, and CGRP-antibodies (eptinezumab, erenumab, fremanezumab, and galcanezumab), versus placebo, in terms of migraine-related outcomes.

Table 1. Inclusion criteria by PICOS.

Population	– Adult ≥18 years – Individuals diagnosed with CM following MOH – Diagnostic criteria fulfilled for MOH and CM according to ICHD-2, ICHD-3 beta or ICHD-3
Intervention	– Intervened with topiramate, botulinum toxin type A, and mAbs targeting CGRP(r) (eptinezumab, erenumab, fremanezumab, and galcanezumab) – All available dosing regimens included
Comparator	Placebo
Outcomes	Primary outcomes – Mean reduction of migraine (and headache, if reported) attacks/frequency – Individuals changing status from MOH to episodic migraine without MOH (<15 headache days/month) – ≥50% response rate Secondary outcomes – Reduce acute headache medications from baseline to treatment weeks (analgesics or triptans) per month decreased – Adverse events if reported (intervention vs placebo)
Study design	– Only RCT & placebo-controlled trials included
Others	– No date restriction – Both published and unpublished trials in any languages

Methods

The study will follow the criteria of Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA).[19]

Eligibility criteria

Inclusion criteria. The inclusion criteria are summarized in Table 1 based on Population, Intervention, Comparison, Outcomes and Study (PICOS) that will be used to select the study articles for the review and analysis.

Exclusion criteria

- Studies comparing preventive medications.
- Studies not reporting response rates to the interventions.
- Guidelines, letters, editorials, narrative reviews, case reports, non-randomized comparative studies, and news.
- Trials that include only a primary headache.
- Articles with incomplete information or if study quality is insufficient.

Outcomes and prioritization

Outcomes are self-reported by the patients. For example, headache/migraine frequency will be reported at the baseline and after the intervention.

Primary outcomes

- The main outcome of interest is mean reduction of migraine frequency from baseline (intervention vs placebo). Measured outcomes as mean reduction in;
  - Monthly headache frequency (if reported)
  - Monthly migraine frequency
  - Monthly headache days (if reported)
  - Monthly migraine days
  - Monthly headache hours (if reported)
- Proportion of individuals changing status from MOH to episodic migraine without MOH (less than 15 headache days/month)
- ≥50% response rate (reduction in migraine attack or migraine/headache frequency by at least 50% from baseline) in intervention vs placebo group.

Secondary outcomes

- Frequency of acute medications (analgesics and triptans and other types of pain killers) intake measured by number of tablets per month and number of days used per months, if reported.
- Medications adverse events rate will be reported if available
- Efficacy of preventive medications for ≥30% response rate (intervention vs placebo)
- Levels of disability and quality of life, if reported
- Treatment specific adverse events, if available

Information sources

All search strategies will be based upon PICOS method. For this study, we will search for Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE Embase and Web of Science. The search strategy includes a combination of indexing terms, MeSH terms in Medline and EMTREE terms in EMBASE. The selected databases are important for this systematic review because the majority of studies on clinical/drug-related trials are published in these databases.[20,21] Ongoing trials will be identified through ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP) portal and other sources as appropriate. For further help on ongoing and unpublished studies, we will consult with librarian or information specialist for the help.

Table 2. Keywords for search strategy.

Population (P)	(migraine OR migraine disorders OR chronic migraine OR migraine with aura OR migraine without aura) AND (medication overuse headache OR medicine overuse headache OR withdrawal headache)
	AND
Intervention (I)	(topiramate OR botulinum toxin type A OR onabotulinumtoxin A OR calcitonin gene-related peptide OR CGRP OR eptinezumab OR erenumab OR fremanezumab OR galcanezumab)

Table 3. Data extraction summary.

Study details	ID of the primary reviewer, study ID (a numeric code to identify the study), data extraction date, study title (full title of the stud), author of the study, publication year, journal published
Methodology	Aims of the study (as stated in the report), study design (RCT), setting, country, study duration/follow-up, sample size, withdrawals, data analysis, funding source, ethical approval
Population characteristics	Age, sex, headache diagnosis, duration of MOH, headache frequency, migraine frequency, headache pain intensity, acute medication use, co-existing diseases, psychiatric illness, other confounding factors
Description of the interventions, dosing and comparison	– Preventive drug types, dosage, route of administration, duration, parallel therapy or placebo – Information on use of acute medications among participants (type, frequency)
Outcomes and results	Proportion or numbers, mean difference or RRs or ORs, or HRs – changing status from MOH to episodic migraine – individuals with MOH at inclusion with at least 50% reduction of headache days/month – changes in use of acute medications – Outcome measures collected for intervention vs placebo as: reduction in headache days/month, reduction in mean monthly migraine/headache days/frequency, reduction in mean monthly headache hours – Difference for adverse events (intervention vs placebo)
Others	Quality assessment of individual studies, possible bias (randomization, blinding, publication), authors comments, reviewer's comments/consensus of the included studies.

Summary of search strategy

Search process for this study includes two search concepts (population and intervention). We will use free text term and MeSH terms to identify the relevant studies (Table 2).

Study records

Data management. The reviewer will collect the identified studies in the reference manager EndNote 2.0 and will delete the duplicates. Two independent reviewers will use Endnote software to screen the articles by titles and abstracts based on the predefined inclusion and exclusion criteria.[22]

Selection process. Two independent reviewers will screen the studies (titles and abstracts) based on predetermined inclusion and exclusion criteria. Studies accepted during abstract screening will be retrieved in full text, and the two reviewers will screen these independently. The reviewers will discuss the results of their decisions, and the third reviewer will be consulted if disagreement between the first two reviewers arises. Reasons for exclusion will be reported according to PICO elements. At the abstract screening level, studies will not be excluded due to insufficient information. For example, in cases when outcome of interest is not reported in the abstract, we would rather accept article for full text review. Manual screening of the citations of the relevant studies (primary studies and systematic reviews) will be conducted if required and seek information from the authors/experts in the field. Relevant authors will be consulted for any additional studies (ongoing or completed; published or unpublished) that might be relevant. After a final decision on study inclusion, the reviewers will proceed toward data extraction. PRISMA flow diagram will be used to demonstrate the number of identified studies, screening process, eligibility and included studies in the review.

Data extraction

The first reviewer will develop a checklist of items (Table 3) to be considered in the data collection that will probably outline tables and figures for the review. We will either use Covidence software (www.covidence.org) or a purpose-built electronic form (Microsoft Excel) for data extraction and management. Covidence is a web-based screening and data extraction tool that is recommended by Cochrane Collaboration.[23] Data extraction sheet will be developed based on five main domains (details in Table 3) that includes study details, eligibility, study methods, population characteristics, interventions, outcomes and others. This sheet will include information or comments regarding decision

on inclusion and exclusion criteria, boxes for codes will be used to save time and will have detail instructions about the coding. Two reviewers will independently extract relevant information as mentioned in the PICO table for all available medication dosages. Both individual patient-level data and summary estimates will be extracted where available. One author will extract information from the selected articles, and a second author will validate the extracted data. The extraction sheet will be piloted before the final implementation. The primary authors will be contacted for important missing data or any further information. Disagreement will be resolved through discussion with a third author. The inter-rater reliability of the two reviewers independently extracting data will be evaluated using Cohen's kappa statistics with 95% confidence intervals.

Included studies may have several interesting information, however, this review will extract information related to the research question and the outcome of interest. For studies that include multiple intervention groups, we will then only extract data on the groups eligible for this review. For the primary outcome measurement, we will choose 50% response rates because 50% response (reduction in migraine attack frequency or headache days) to any migraine preventive medications is used to measure the efficacy in clinical practice and required as an outcome by the regulatory agencies.[24] The items included in the data extraction form is shown in Table 3.

Risk of bias of included individual studies

Two review authors will independently assess the risk of bias for each of the included studies using Cochrane RoB2 tool based on both empirical evidence and theoretical consideration in each included study.[25] The authors will assess how the study was conducted and provide risk of bias judgment as, "Low risk" or "High risk" or "some concerns." Five main domains included in RoB2 tool will be used that covers almost all types of bias that might affect the results of randomized trials. Risk of bias will be calculated with Egger-Regression.

i. Bias arising from the randomization process
ii. Bias due to deviation from intended interventions
iii. Bias due to missing outcome data (loss to follow up)
iv. Bias in measurement of the outcome (blinding of outcome assessment)
v. Bias in selection of the reported result (reporting outcomes compared with a published protocol)
vi. Other risks of bias

Data synthesis

The aim of the evidence synthesis in this review is to estimate the clinical effectiveness of the three selected preventive treatments for individuals who fulfilled the combination of CM and MOH diagnosis from the identified study. Evidence synthesis will be done based on available data and type of data in the included studies. We plan to do a summary of evidence (systematic review) and quantitative synthesis of outcome (meta-analysis). Protocol will be followed during the evidence synthesis, any changes will be reported with the explanations. The evidence synthesis will be presented based on the information collected from each included studies as outlined in Table 3.

Narrative synthesis. The summary of the studies will be presented in the text and in the tables. Studies will be grouped by preventive treatments as topiramate, botulinum toxin type A and CGRP (eptinezumab or erenumab or fremanezumab or galcanezumab). Any important differences between the studies in terms of patient characteristics, interventions (dosing, frequency, duration), outcomes including assessment methods, study quality will be noted. Some of the key information synthesized in this systematic review will include patient characteristics, migraine/headache days among individuals with MOH and CM, preventive treatments, and outcome definitions.

Quantitative synthesis /meta-analysis. Analysis will be conducted based upon the type and quality of the evidence. For each outcome and each subgroup (by preventive treatments), methodological and clinical characteristics reporting effect estimates for the set of included studies will be reviewed. We will re-express the reported outcome measure if required (e.g., if studies reporting only mean migraine days at baseline and at follow-up, then this will be converted by calculating a change by subtracting mean migraine days in two groups). The primary outcome for the efficacy analysis is the change in headache/migraine frequency. We plan to analyze change in mean headache/migraine days from baseline in the monthly average and will be reported as mean difference (MD). If required, standardized mean difference (SMD) will be converted to MD. Odds ratio (OR) will be calculated for achieving $\geq$50% response rate (reduction in headache frequency) across studies using random effect meta-analysis. We will attempt to obtain adequate data from the study authors. The equation for calculating MD is as follow,[26]

$\mathrm{MD} = \mathrm{SMD} \times \sigma$ (σ is a standard deviation based on either or both populations)

In situations where mixed intervention effects estimates (dichotomous and continuous) are reported, we will use statistical approach that will re-express ORs to MDs and vice versa.[26] Assuming different duration for preventive treatments in different included studies, specific time points will be determined after evaluating the narrative synthesis (e.g., 4 weeks, 8 weeks, 12 weeks etc.). A point estimate for log odds ratio can be obtained by equation as follow,

$$\ln\ \mathrm{OR} = -\frac{\pi}{\sqrt{3}} \times \mathrm{SMD} \approx -1.81 \times \mathrm{SMD}$$

Table 4. Timeline.

Activity	2021		2022		
	October–December	January–March	April–June	July–September	October–December
Conceptualization and protocol writing					
Protocol register					
Information sources – Run the search strategy in multiple database – Collect references and abstract – Eliminate duplicates					
Data management and selection process – Screen title and abstract by two reviewers – Collect, compare and select for retrieval – Apply selection criteria and retrieve full text					
Contact experts/authors and search for additional trials/studies					
Final selection list and draw flow diagram (two reviewers)					
Data Extraction – Develop data extraction forms – Apply data collection forms (two reviewers)					
Evaluate study quality and risk of Bias (two reviewers)					
Data Synthesis					
GRADE assessment (two reviewers)					
Update and submit for publication					

Meta-analysis is done in two steps. At first, a summary statistic with 95% CI (ORs for dichotomous and mean difference for continuous data) will be calculated for each study in the same way that describes the observed intervention effect. Second, a combined intervention effect estimate will be calculated that provides a total effect for each medication. The results including both individual study's effect estimate and pooled effect will be presented in a forest plot. Assuming that intervention effect varies across the studies, we will conduct random-effect pairwise meta-analysis or network meta-analyses where feasible.[27–29] Random-effect meta-analysis involves an assumption that effects being measured in different studies are estimating different yet related intervention effects, and address heterogeneity that cannot be explained by other factors. Sensitivity analysis will be done when appropriate (e.g. differences in drug doses).

Heterogeneity across studies will be assessed using the Cochrane I^2 statistics and Chi^2 test and will be displayed in the forest plot. I^2 values from 0–40% represent minimal level of heterogeneity, 30–60% moderate heterogeneity, 50–90% substantial heterogeneity, and 75–100% considerable heterogeneity. A low p value (<0.05) provides evidence of heterogeneity of intervention effects (variation in effect estimate beyond chance). Publication bias will be demonstrated by funnel plots[30] or in an illustrative figure with color codes.

GRADE assessment

The quality of evidence for outcomes across included studies will be rated according to the five factors outlined in Cochrane GRADE approach: risk of bias (study design and limitations), heterogeneity or consistency of effects/results, directness (generalizability), precision (sufficient data), and publication bias (reporting of the results across all studies that measure that particular outcome).[31] Four levels of certainty will be provided for evidence for a planned outcome: high, moderate, low and very low. Two independent authors will assess certainty of evidence and provide their judgments (high or moderate or low or very low) based on five GRADE criteria. The authors will use Cochrane GRADEpro tool[32] as it ensures that the authors are accessing the same information to inform their judgments, and is free to use. The quality rating starts at high when high quality RCTs provide required results and downgrade the quality by one level for each of the factors not met upto a maximum of three levels for all factors. Review authors will report justification for downgrading or upgrading the evidence for each outcomes included.

Timeline and resource use

We plan to register the planned systematic review protocol by March 2022, followed by selection of the study based on inclusion ad exclusion criteria (June), data extraction

(September), data synthesis and finalization of the review by the end of December 2022 (Table 4).

Public health relevance

- Migraine results in substantial disability that affect social life and healthcare cost.
- Patients with migraine, particularly chronic migraine often tend to overuse medications to alleviate the symptoms of primary headaches, whereby the medications specified for the headache treatment becomes the cause of medication overuse headache (MOH).
- Comparing the effects of preventive treatment of topiramate, botulinum toxin type A, and CGRP-antibodies and its receptor in chronic migraine patients with MOH will be beneficial to clinicians and patients.

Authors Note

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Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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