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Efficacy of migraine prophylaxis treatments for treatment-naïve patients and those with prior treatment failure: a protocol for systematic review and network meta-analysis of randomised controlled trials

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ABSTRACT

Introduction Migraine headache is a significant health problem affecting patients' psychological well-being and quality of life. Several network meta-analyses (NMAs) have compared the efficacy of migraine prophylaxis medications. However, some have focused exclusively on oral medications, while others were limited to injectable medications. Moreover, none of these NMAs conducted a stratified analysis between treatment-naïve patients and those with prior treatment failure. Therefore, this systematic review and NMA will compare the efficacy among all treatments for migraine prophylaxis, stratified by the treatment status of patients (ie, treatment-naïve and previous treatment failure).

Methods and analysis Randomised-controlled trials that included patients with chronic or episodic migraine, assessed the efficacy of oral or injectable treatments for migraine prophylaxis and measured the outcomes as monthly migraine day, monthly headache day, migraine-related disability, health-related quality of life or adverse drug events will be eligible for inclusion in this review. Relevant studies will be searched from Medline, Scopus, the US National Institutes of Health Register, and the World Health Organization International Clinical Trials Registry Platform (WHO-ICTRP) databases since inception through 15 August 2023. Risk of bias assessment will be performed using a revised tool for assessing the risk of bias in randomised trials. Two-stage NMA will be applied to compare relative treatment effects among all treatments of migraine prophylaxis. Surface under the cumulative ranking curve will be applied to estimate and rank the probability to be the best treatment. Consistency assumption will be assessed using a design-by-treatment interaction model. Publication bias will be assessed by comparison-adjusted funnel plot. All analyses will be stratified according to patients' status (ie, treatment-naïve and prior treatment failure).

Ethics and dissemination This study is a systematic review protocol collecting data from published literature and does not require approval from an institutional review board. Results from this systematic review will be published in a peer-reviewed journal.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Both published and unpublished studies will be searched to minimise the publication bias.
⇒ The analysis will be stratified according to patient treatment status (ie, treatment-naïve or prior treatment failure).
⇒ Short-term and long-term treatment efficacy will be assessed.
⇒ Heterogeneity between studies may be presented due to differences in patient characteristics, research methodology, definitions of prior treatment failure and study time periods.
⇒ The definition of prior treatment failure may vary depending on the specific criteria used in each study.

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BACKGROUND AND RATIONALE

Migraine is a chronic neurological disease that affects both sexes; one-year prevalence of migraine is estimated at 20.7% and 9.7% in women and men, respectively.[1] Migraine is defined as a moderate to severe intensity throbbing headache that is usually unilateral; it is aggravated by physical activity and can be associated with photophobia, phonophobia, nausea and vomiting. Frequent migraine attacks can worsen a person's performance[2] and also affect psychological well-being and health-related quality of life.[3] Moreover, risks of analgesic medication overuse and associated psychological disorders such as anxiety and depression were significantly higher in patients who had frequent migraine attacks.[4] Therefore, prevention of migraine is important in order to improve patient outcomes and decrease the risk of

medication overuse, headache-related stress and psychological problems.

Indications for preventive treatment usually depend on the frequency of migraine attacks, impairment of the patient's functionality, risk of analgesic medication overuse and patient preference. Normally, migraine prophylaxis is prescribed for patients with chronic migraine, defined as having headaches at least 15 days per month (of which at least 8 days are migraine attacks) or episodic migraine, defined as having attacks >4 days but <15 days per month.[5]

Several conventional treatments are prescribed for migraine prevention including antiepileptic drugs, beta-blockers, calcium channel blockers, antidepressants and angiotensin receptor blockers. However, only antiepileptic drugs, beta-blockers and angiotensin receptor blockers provide evidence of migraine prophylaxis according to the American Headache Society (AHS) consensus statement.[5] Although the efficacy of these oral drugs is favourable in terms of decreasing the frequency of migraine attacks and reducing the severity of symptoms, long-term compliance is suboptimal. Results from previous studies found that approximately 40% of patients with chronic migraine did not adhere to oral preventive treatments because of suboptimal efficacy, adverse events or poor tolerability.[6–8] Moreover, previous studies indicated that up to 78% of patients with migraine encountered treatment failure.[9 10] This failure could be attributed to the fact that conventional treatments were originally developed for other conditions and do not directly address migraine pathophysiology. In addition, most previous trials excluded individuals who had experienced treatment failures, resulting in a significant gap in evidence specifically tailored for this group of patients.

Currently, there are also some injectable preventive treatments available for migraine prophylaxis such as onabotulinumtoxinA and calcitonin gene-related peptide (CGRP) antagonists (eg, fremanezumab, galcanezumab and erenumab). The primary pathogenesis of migraine symptoms is vasodilatation and neurogenic inflammation that result from the binding of CGRP, an important neurotransmitter in the development and progression of migraine,[11] to its receptor. Thus, blocking this interaction, via the inhibition of CGRP receptors, can rapidly terminate and prevent migraine symptoms.[12–14] Therefore, CGRP receptor antagonists are the first mechanism-based and disease-specific class of preventive treatment for migraine prophylaxis.

The efficacy of these treatments is demonstrated from both systematic review (SR)[15 16] and randomised controlled trials (RCTs).[17 18] Moreover, these injectable preventive treatments have additional advantages such as no requirement for dose titration, rapid onset and low incidence of adverse drug reactions, making the tolerability of these treatments high.[19–21]

Although these preventive treatments have been available for many years, there is a scarcity of head-to-head RCTs directly comparing their efficacy and tolerability in patients with naive treatment or prior response to preventive treatment[22–24] and patients with previous preventive treatment failure.[17 25–28] Consequently, to help guide clinical practice, it is necessary to conduct a comprehensive review and network meta-analysis (NMA). Previous SR and NMAs have been limited by focusing exclusively on oral medications[29 30] or anti-CGRP monoclonal antibodies.[31–33] Furthermore, none of these NMAs conducted a stratified analysis between treatment-naïve patients and those with prior treatment failure. The AHS recommends that migraine prophylaxis agents should be selected based on patient characteristics such as prior treatment response, disease severity and duration.[5] Patients who have experienced failure with two or more available preventive treatments (due to reasons such as inadequate efficacy, tolerability issues, comorbidities or poor compliance) should be prioritised for anti-CGRP monoclonal antibody.[34] Combining data from patients with various disease severities and treatment response in a single pooled analysis may not be appropriate for guiding clinical practice.

Therefore, we aim to perform an SR and NMA comparing the efficacy and risk of adverse events among all oral and injectable treatments used for migraine prophylaxis, stratified by two distinct patient groups: those who are treatment-naïve and those with previous treatment failure. Additionally, this study will identify the most effective drugs for both short-term and long-term prevention of migraine symptoms. The findings from our SR and NMA will offer valuable evidence to inform recommendations for migraine prophylaxis in treatment-naïve individuals and those who have previously not responded to conventional preventive treatments.

METHODS

This SR and NMA will be performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and the PRISMA Network Meta-Analysis Extension statement.[35 36]

Type of studies

Parallel or cross-over RCTs that directly compared any pairs of both oral and injectable preventive active treatments, placebo or no intervention will be eligible. Cross-over RCTs will be included if the results of the first administration are reported separately. RCTs that compared different doses of the same drugs will be excluded.

Type of participants

Studies that included participants with chronic or episodic migraine with or without aura will be included. Episodic migraine is defined as headache on at least 5 days (but <15 days) per month that fulfils the International Classification of Headache Disorders (ICHD)-3 criteria (ie, duration of headache is 4–72 hours, if untreated, and characteristics of headache have at least two of the

following: (1) unilateral location, (2) pulsating quality, (3) moderate to severe pain intensity, (4) aggravation by routine physical activity and during headache has at least one of the following: (1) nausea and/or vomiting, (2) photophobia and phonophobia). Chronic headache is defined as headache at least 15 days per month with at least 8 days fulfilling the ICHD-3 criteria.[37]

Prior preventive treatment failure is defined as a history of at least one previously failed preventive treatment or is defined according to the definition specified in each included study. Preventive treatment failure can be an efficacy failure (inadequate reduction in headache frequency after receiving an appropriate therapeutic dose within a sufficient treatment duration) or tolerability failure with drug discontinuation due to adverse events.

Type of interventions and comparators

Oral or injectable treatments for migraine prophylaxis are interventions of interest. Only medications with established efficacy according to the AHS consensus statement will be eligible.[5] This will include (1) antiepileptic drugs (ie, divalproex sodium, valproate sodium and topiramate), (2) beta-blockers (ie, metoprolol, propranolol and timolol), (3) candesartan, (4) triptans (ie, frovatriptan), (5) onabotulinumtoxinA and (6) monoclonal antibodies targeting CGRP or CGRP receptors (ie, fremanezumab, galcanezumab, eptinezumaband erenumab). Studies that directly compared any of these active treatments or compared the active drugs with placebo will be eligible.

Outcomes of interest

The primary outcome will be the frequency of headache, expressed as the monthly average number of migraine days, where a day is defined by:

- A headache that lasts at least 4 hours; meets ICHD-III criteria C and D for migraine without aura (1.1), B and C for migraine with aura (1.2) or ICHD-III criteria for probable migraine (1.6).
- A day with a headache that is successfully treated with a triptan, ergotamine or other migraine-specific acute medication.

Secondary outcomes will be as follows:

- The monthly average number of moderate to severe headache days is defined as a day with moderate or severe pain that lasts at least 4 hours or a day with a headache that is successfully treated by an acute headache medication.
- The proportion of participants who responded to treatment is defined as a 50% reduction in the number of migraine days or number of moderate or severe headache days from baseline.
- Migraine-related disability is measured by the Headache Impact Test or the Migraine Disability Assessment questionnaire or other measurements specified in the studies.
- Health-related quality of life is measured by the Short Form 36-Item Health Survey or other measurements specified in the studies.
- Adverse drug events.

Search strategy

Search terms and search strategies will be constructed to identify relevant studies based on population (ie, episodic or chronic migraine) and prophylaxis intervention (ie, divalproex sodium, valproate sodium, topiramate, metoprolol, propranolol, timolol, frovatriptan, onabotulinumtoxinA and monoclonal antibodies targeting CGRP or CGRP receptors such as fremanezumab, galcanezumab and erenumab). Medical Subject Heading in Medline will also be supplemented with free text terms. Search terms and search strategies are presented as follows.

(((“Migraine Disorders”[Mesh]) OR migraine)) AND ((((((((((((((((((((“Valproic Acid”[Mesh]) OR “Topiramate”[Mesh]) OR “Metoprolol”[Mesh]) OR “Propranolol”[Mesh]) OR “Timolol”[Mesh]) OR frovatriptan) OR “Botulinum Toxins, Type A”[Mesh]) OR “Calcitonin Gene-Related Peptide Receptor Antagonists”[Mesh]) OR divalproex) OR valproate) OR topiramate) OR metoprolol) OR propranolol) OR timolol) OR onabotulinumtoxina) OR fremanezumab) OR galcanezumab) OR erenumab) OR “Calcitonin Gene-Related Peptide Receptor Antagonists”) OR Eptinezumab) OR Gepant)) AND ((Prophylaxis OR prevention)).

Databases

Medline, Scopus and WHO International Clinical Trials Registry Platform databases will be searched since inception through 15 August 2023. The US National Institutes of Health Register (www.clinicaltrials.gov) will be searched to identify ongoing RCTs. Reference lists of all included studies will also be explored where appropriate to identify additional relevant studies.

Study selection

Citations of all studies identified from searching will be exported into EndNote, and duplicate studies will be removed. First, two reviewers will independently select the studies based on titles and abstracts. Full articles will be reviewed according to the inclusion and exclusion criteria after screening titles and abstracts. Disagreement between both reviewers will be resolved by consensus with a third party. Number of included and excluded studies, along with reasons for study exclusion will be recorded to construct a flow chart of study selection according to PRISMA guidelines.

Data extraction

The following data from included studies will be extracted independently and in duplicate using a standardised data record form:

- Characteristics of included study: first author name, year of publication, study design (ie, parallel or crossover RCT), study setting and type of migraine (ie, chronic or episodic migraine).
- Baseline characteristics of study participants: mean age and body mass index, percent male, duration of migraine headache, monthly number of migraine

days at baseline and mean migraine-related disability score at baseline.
- Interventions and controls: type of intervention, dosage, duration of treatment and drug administration.
- Primary and secondary outcomes: method of outcome measurement, time of measurement, number of participants, mean and SD of each continuous outcome and number of participants who did or did not have dichotomous outcomes by treatment groups.

Disagreement between both reviewers will be resolved by consensus with a third party. Corresponding authors of the included studies will be contacted if there is insufficient data.

Risk of bias assessment

Risk of bias of the included studies will be assessed using a revised tool for assessing risk of bias in randomised trials (RoB 2).[38] The revised tool for assessing risk of bias in randomised trials consists of five domains as follows:
- Bias arising from the randomisation process.
- Bias due to deviations from intended interventions.
- Bias due to missing outcome data.
- Bias in the measurement of the outcome.
- Bias in the selection of the reported result.

Each domain has a series of questions where possible response options are 'yes', 'probably yes', 'probably no', 'no' and 'no information'. A 'yes' answer might suggest either lower or higher risk of bias, depending on the framing of the questions. Risk of bias for each domain will be classified as 'low risk of bias', 'some concern' or 'high risk of bias', determined by an algorithm that maps responses to questions. Overall risk of bias will also be classified as 'low risk of bias', 'some concern' or 'high risk of bias'. 'Low risk of bias' will be considered if all domains are 'low risk of bias', otherwise studies will be classified as 'high risk of bias' if at least one domain is 'high risk of bias' or multiple domains are 'some concerns' that might significantly lower confidence in the results.

Two reviewers will perform risk of bias assessments independently. Disagreement between both reviewers will be resolved by consensus through a third party.

Statistical analysis plan

Characteristics of the included studies and baseline characteristics of study participants will be described by mean (or median where appropriate) for continuous outcomes, and frequency and percentage for dichotomous outcomes. Pairwise and network meta-analyses will be performed and will be stratified by two patient groups: (1) those who were treatment-naïve and (2) those who had experienced previous preventive treatment failures, irrespective of the number of prior failures.

Pairwise meta-analysis

Pairwise meta-analysis will be performed if more than two RCTs had similar population, interventions, comparator and outcomes available. For continuous outcomes, mean difference between intervention and control groups will be estimated and pooled using unstandardised mean difference (USMD) if all studies used similar methods for outcome measurement, otherwise, standardised mean difference (SMD) will be applied. For dichotomous outcomes, risk ratio (RR) will be estimated and pooled using the inverse variance method; a random effect model will be applied instead, if heterogeneity is present.

Heterogeneity between studies will be estimated using Q-test and I^2 statistic. Heterogeneity between studies will be considered, if the Q-test p value is <0.10 or I^2 statistic is >25%. Relative treatment effects will be pooled using a fixed effect model, if there is no heterogeneity between studies, otherwise a random effect model will be applied.

Sources of heterogeneity will be explored by meta-regression analysis. Factors that might be the cause of heterogeneity such as mean age, monthly migraine days at baseline, migraine duration, mean migraine-related disability score at baseline and duration of treatment will be fitted in a meta-regression model one by one. Subgroup analyses according to short-term and long-term prevention regimens, and the factors that can decrease tau^2 or I^2 from meta-regression will be further performed. Short-term prevention is defined as 4 weeks after initiation of treatment, while long-term prevention is defined as 6–12 months or beyond after initiation of treatment.

Network meta-analysis

We will apply an NMA to compare relative treatment effects among all treatments of migraine prophylaxis using a two-stage NMA[39 40] as follows. First, relative treatment effect (ie, SMD/USMD or the natural logarithm of the RR) and its variance–covariance will be estimated for each individual study, using placebo as the reference. Second, these relative treatment effects will be pooled across studies by a multivariate meta-analysis with consistency model, and then multiple treatment comparisons will be performed. Surface under the cumulative ranking curve (SUCRA) will be applied to estimate and rank the probability that a treatment will have the highest efficacy and safety. A cluster ranking plot will be constructed to demonstrate the benefit and risk of all treatments by plotting SUCRA for lowest mean monthly migraine days versus lowest adverse events.

Consistency assumption estimates of the agreement between direct and indirect comparisons will be assessed using a design-by-treatment interaction model that incorporates both loop and design inconsistencies.[41 42] If inconsistency is suggested from the model, characteristics of the studies in the loops with an inconsistency factor higher than 2 will be explored. Sensitivity analysis with exclusion of these studies will be further performed.

Publication bias will be assessed by comparison-adjusted funnel plot.[43] The horizontal axis of the comparison-adjusted funnel plot will present the difference between the study-specific effect sizes from the corresponding comparison-specific summary effect and the vertical axis will present the inverse variance of treatment effect.

Publication bias is suggested if there is asymmetrical comparison-adjusted funnel plot around the zero line.

Statistical analyses will be performed using STATA V.18. A p value <0.05 will be applied to establish a level of statistical significance, except for the heterogeneity test as previously indicated.

The certainty of evidence for NMA of primary outcomes considered in cluster ranking plots will be assessed using the Confidence in Network Meta-Analysis (CINeMA) tool.[44] The CINeMA tool consists of six domains: (1) within-study bias, (2) reporting bias, (3) indirectness, (4) imprecision, (5) heterogeneity and (6) incoherence. The confidence of each domain will be graded as no concerns, some concerns or major concerns.

Ethics and dissemination

This study is SR protocol collecting data from published literature and therefore does not require institutional review board approval. Results from this SR and NMA will be published in a peer-reviewed journal.

Patient and public involvement

There was no patient or public involvement in this review protocol.

DISCUSSION

Chronic and episodic migraine headaches represent significant health problems that have a profound impact on patients' daily functioning and overall quality of life. Although there are currently several medications available for the prevention of migraine attacks, the majority of patients with chronic and episodic migraines have experienced treatment failure (77.9%), which greatly affects their personal, social and professional lives.[45] Consequently, the recommended treatment options for patients who have previously failed preventive treatments may differ from those patients who have yet initiated prophylaxis. Unfortunately, previous studies and evidence, including NMAs, have often overlooked this issue by combining both patients with chronic migraine and episodic migraine, irrespective of their prior treatment failure status. Therefore, this study represents the first SR and NMA with the aim of identifying the most suitable migraine prophylaxis treatments for both distinct patient groups: those who are treatment-naïve and those who have experienced previous treatment failure. We expect the findings from this NMA to provide valuable guidance to clinicians and patients in selecting the most appropriate migraine prophylaxis treatment that aligns with the patient's individual needs. This evidence-based approach will assist in making informed decisions for personalised medicine to optimise treatment outcomes for individuals suffering from migraines.

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Contributors PN and TA are the principal investigators. PN, TA, GM, JA and AT designed the study. PN and TA drafted the manuscript. PN, TA, GM, JA and AT critically revised the study protocol and the manuscript. The entire project will be supervised by TA and AT.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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