INTRODUCTION

Review question / Objective: Which is the most effective treatment among Acupuncture, Flunarizine, anti-CGRP monoclonal antibodies for migraine prophylaxis?

Condition being studied: Migraine, as a chronic neurological disorder, imposes a significant health and financial burdens. Acupuncture is widely used for migraine prophylaxis on account of its proven efficacy. Flunarizine, recommended by the guidelines, is the most commonly used to prevent migraine in clinical practice. Meanwhile, there are some emerging treatments have been proven effective in clinical trials, like anti-CGRP monoclonal antibodies. But comparative effectiveness of these mentioned therapies is unknown.

INPLASY PROTOCOL


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Review Stage at time of this submission: Preliminary searches.

Conflicts of interest: No.

Comparative Efficacy of Acupuncture, Flunarizine and anti-CGRP monoclonal antibodies for migraine prophylaxis: protocol for a Bayesian Network Meta-Analysis

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INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 27 April 2020 and was last updated on 27 April 2020 (registration number INPLASY202040196).
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METHODS

Participant or population: Inclusion: Adult patients diagnosed with episodic migraine and experienced migraine attack for at least 1 year. Exclusion: Adolescents (under 18 years of age) and patients with chronic migraine, chronic daily headache or in which at baseline more than half of participants had more than 15 days with migrainous headache per month.

Intervention: We will include acupuncture and pharmacological treatments for migraine prophylaxis. We will include acupuncture and moxibustion methods used for migraine prophylaxis, which include but not limited to body or head needle insertion on acupoints and electroacupuncture. We will exclude laser acupuncture and noninvasive electrostimulation, as these interventions do not involve the mechanical stimulation of acupoints. We will exclude acupoint injection, because the effect may be confused by the injectant. We will include prophylactic pharmacological treatments, which should be recommended by the guidelines or evidenced with obvious clinical effect (defined as having at least 2 complete phase III RCTs showing the effectiveness of treatment). The treatments are flunarizine and anti-CGRP monoclonal antibodies (fremanezumab, galcanezumab, erenumab).

Comparator: Placebo, sham acupuncture (defined as invasive needle piercing into the sham acupoints, which do not correspond to any true acupuncture points) or one of the intervention treatments.

Study designs to be included: We will include randomized controlled trials of acupuncture and specific pharmacological treatments for migraine prophylaxis.

Eligibility criteria: Studies will be selected according to the PICO S criteria (Participant, Intervention, Comparator, Outcomes, Study design) outlined in the referred sections.

Information sources: We will search MEDLINE (PubMed interface), EMBASE, and the Cochrane Central Register of Controlled Trials for randomized controlled trials (RCTs) about the efficacy of mentioned migraine treatments. Literature search strategies will be developed using medical subject headings (MeSH) and text words related to migraine treatments to search for target RCTs. The electronic database search will be supplemented by searching clinical registries (clinicaltrials.gov) for ongoing RCTs. We will also contact the investigators of these trials to ask for preliminary data if possible. To ensure literature saturation, we will retrieve the relevant systematic reviews and scan their reference lists to find the related RCTs. We will also contact the investigators of these trials to ask for preliminary data if possible. The literature search will be limited to the English language and medical subjects. The search dates to April 2020.

Main outcome(s): We will measure the outcomes at the completion of treatment and at follow-up (closest to six months after randomization) separately[50]. The primary outcome is the change from baseline in the number of monthly migraine days (MMD). Secondary outcome measures will include the frequency of migraine attack (defined as the number of episodes of migraine attack separated by pain-free intervals of at least 48h) and responder rate (defined as a percentage change relative to baseline frequency) as measured by MMD or the frequency of migraine attacks.

Additional outcome(s): The occurrence of adverse events can be reported narratively by qualitative analysis.

Data management: Two reviewers (Chen and Lu) will use Endnote X7 to combine the database searching results and exclude the duplicates. They will independently screen the titles and abstracts of retrieved studies to find the relevant reports. If the 2
reviewers cannot determine whether a study is related to our research, the study will be adjudicated by the third reviewer (Zhao) after examining the full-text of this study. Then, the two reviewers will examine the full-text of relevant reports and decide whether these should be included according to “Intervention and comparisons”. Another 2 reviewers (Wang and Hu) will read the full-text of eligible studies and extract information from them independently with standardized data extraction forms (performed by Excel 2013), consisting of four sheets: (1) General information will include title, the years of publication, authors, country, group allocation (randomized, non-randomized, unknown), blinding (open, single, double, triple), dosing (flexible, fixed) and sample size. (2) Participant characteristic will include sex, age, the number of each group, mean duration of migraine, VAS score before treatments, baseline MMD or the frequency of migraine attack. (3) Interventions will include names of arms, numbers of arms, durations of arms, frequency of arms, duration of treatment and follow-up. (4) Outcome assessment will include the outcome assessment at different times (at the completion of treatment, at follow-up), the values of the outcomes (mean, SD, n), and whether adverse events occur. For cross-over trials, we will only use the data from the first phase for concerning cross-over effects. After extraction, the two reviewers will cross check the extraction forms. Disagreements will be solved by two reviewers’ discussions. Otherwise, these issues will be adjudicated by the other reviewer (Xu).

**Quality assessment / Risk of bias analysis:** We will assess the risk of bias with a tool recommended by the Cochrane collaboration. We will evaluate the risk of bias in sequence generation, allocation concealment, blinding, incomplete outcome, selective outcome report, and another source of bias. We will classify RCTs having a low risk of bias in the first 3 items as high-quality RCTs.

**Strategy of data synthesis:** The network meta-analysis (NMA) will be developed in a Bayesian framework using the Markov chain Monte Carlo (MCMC) simulation implemented through the RStudio software (version v1.2.1335). We will perform the pair-wise meta-analysis to examine the consistency and confirm the results obtained in the framework of the NMA. In the pair-wise meta-analysis, the I² statistic will be used to assess levels of the heterogeneity, fixed effects models will be used if the I² value is <50%, or else a random effects model will be used. For combining direct/indirect-based evidence, we will use Bayesian random effects model and a consistency model. And we will perform the network plot to analysis the association between the included treatments. To convince its appropriateness, we will assess the convergence by using the Gelman-Rubin-Brooks plot, which compares the variation within each chain in simulation to the variation between chains. Inconsistency will be evaluated in a loop which connects three or more treatments. We will perform a node-splitting analysis to evaluate the inconsistency of network model by Rstudio, we will also generate a forest plot of the information above. Then, to generate the network meta-analysis results, we will perform the rankogram and the forest plot of ranking probabilities, which will illustrate the order of interventions for each outcome, and we will calculate the surface under the cumulative ranking (SUCRA) score to support the results. We will analyze three treatment outcomes at different time points separately (MMD, the frequency of migraine attacks and responder rates). Continuous outcomes will be calculated as standardized mean differences (SMDs), and binary outcomes will be calculated as risk ratios (RRs). Both types of effect sizes will be expressed with a 95% confidence intervals (CI) for direct comparisons or expressed with a 95% credible intervals (CrI) for indirect comparisons.

**Subgroup analysis:** The subgroup analysis will include subtypes of migraine (migraine with aura, migraine without aura), the ways
of treatment (acupuncture, oral medication, subcutaneous injection), blinding method (open trial, single blind, double blind), quality of evidence (high risk, unclear of the risk and low risk).

**Sensibility analysis:** We will use sensibility analysis to assess the impact on the overall treatment effects of inclusion of trials: we will exclude low-quality RCTs, which do not report an intention to treat analysis, have high rates of participant attrition, or with other missing data, then we will re-run the meta-analysis.

**Language:** Chinese; English.

**Country(ies) involved:** China.

**Keywords:** Migraine; Bayesian Network Meta-Analysis; Acupuncture; Flunarizine; anti-CGRP monoclonal antibodies.