INPLASY PROTOCOL

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Review Stage at time of this submission: **Formal screening of search results against eligibility criteria.**

Conflicts of interest:
None.

Unveiling the comparative efficacy and tolerability of comprehensive treatments for migraine: a protocol of systematic review and Bayesian network-meta analysis

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Review question / Objective: **We conduct this systematic review and Bayesian network-meta analysis (NMA) as the first attempt to synthesis quantitative and comparative evidence on the efficacy and tolerability of all the known pharmacological and non-pharmacological interventions for treating patients with migraine. P: The participants included in this NMA are all diagnosed as migraine according to the recognized criteria: International Classification of Headache Disorders (ICHD) for migraine headaches. I: All the available treatments both pharmacological or non-pharmacological strategies. C: usual care, placebo or another included pharmacological or nonpharmacological treatment strategy for migraine. O: . Our primary outcomes are as follow. i). The number of participants with pain-free response at 2 hours (complete resolution of headache pain). ii). The number of participants with headache pain reduction from moderate/severe to mild or none at 2 hours. iii). The number of participants with sustained relief for 24 hours. Our secondary outcomes of efficacy included Migraine disability assessment (MIDAS) questionnaire, Headache impact test (HIT-6), Mindfulness attention awareness scale (MAAS), 36-item short form survey (SF-36), headache frequency per month, headache severity and headache duration. Our primary outcomes of safety include the total adverse events, restlessness, drowsiness, nausea, vomiting. Other side effects such as tingling, numbness, swelling and any other adverse events would also be analyzed as the secondary outcomes. S: Only randomized controlled trials (RCTs) will be included in our systematic review and NMA.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 24 May 2020 and was last updated on 24 May 2020 (registration number INPLASY202050089).

INTRODUCTION

Review question / Objective: **We conduct this systematic review and Bayesian network-meta analysis (NMA) as the first attempt to synthesis quantitative and comparative evidence on the efficacy and tolerability of all the known**

pharmacological and non-pharmacological interventions for treating patients with migraine. P: The participants included in this NMA are all diagnosed as migraine according to the recognized criteria: International Classification of Headache Disorders (ICHD) for migraine headaches. I: All the available treatments both pharmacological or non-pharmacological strategies. C: usual care, placebo or another included pharmacological or nonpharmacological treatment strategy for migraine. O: . Our primary outcomes are as follow. i). The number of participants with pain-free response at 2 hours (complete resolution of headache pain). ii). The number of participants with headache pain reduction from moderate/severe to mild or none at 2 hours. iii). The number of participants with sustained relief for 24 hours. Our secondary outcomes of efficacy included Migraine disability assessment (MIDAS) questionnaire, Headache impact test (HIT-6), Mindfulness attention awareness scale (MAAS), 36-item short form survey (SF-36), headache frequency per month, headache severity and headache duration. Our primary outcomes of safety include the total adverse events, restlessness, drowsiness, nausea, vomiting. Other side effects such as tingling, numbness, swelling and any other adverse events would also be analyzed as the secondary outcomes. S: Only randomized controlled trials (RCTs) will be included in our systematic review and NMA.

Rationale: Migraine seriously endangers health of human worldwide ranking as the third most prevalent medical condition and the second most disabling neurological disorder.However, there are still no comprehensive estimates of treatments for migraine no matter the pharmacological or the non-pharmacological, let alone the quantitative comparative efficacy and safety.Therefore, taking an overall consideration of both the efficacy and the safety of the treatments is significantly important.

Condition being studied: Although previous studies have provided some recommendations on the effective class of medications, they didn't reach a consensus and all of them were based on limited on the limited number of clinical trials with biases. Besides, all the previous reviews only focus on some specific fields of pharmacological treatments such as parenteral drugs, Chinese herbal medicine, steroids ,or other specific medications, which results in numerous and sophisticated assessments without concluding a comprehensive guideline of pharmacotherapeutics for migraine.

METHODS

Search strategy: We conduct this systematic review and Bayesian network-meta analysis (NMA) as the first attempt to synthesis quantitative and comparative evidence on the efficacy and tolerability of all the known pharmacological and non-pharmacological interventions for treating patients with migraine. P: The participants included in this NMA are all diagnosed as migraine according to the recognized criteria: International Classification of Headache Disorders (ICHD) for migraine headaches. I: All the available treatments both pharmacological or non-pharmacological strategies. C: usual care, placebo or another included pharmacological or nonpharmacological treatment strategy for migraine. O: . Our primary outcomes are as follow. i). The number of participants with pain-free response at 2 hours (complete resolution of headache pain). ii). The number of participants with headache pain reduction from moderate/severe to mild or none at 2 hours. iii). The number of participants with sustained relief for 24 hours. Our secondary outcomes of efficacy included Migraine disability assessment (MIDAS) questionnaire, Headache impact test (HIT-6), Mindfulness attention awareness scale (MAAS), 36-item short form survey (SF-36), headache frequency per month, headache severity and headache duration. Our primary outcomes of safety include the total adverse events, restlessness, drowsiness, nausea, vomiting. Other side effects such as tingling, numbness, swelling and any other adverse events

would also be analyzed as the secondary outcomes. S: Only randomized controlled trials (RCTs) will be included in our systematic review and NMA.

Participant or population: The participants included in this NMA are all diagnosed as migraine according to the recognized criteria: International Classification of Headache Disorders (ICHD) for migraine headaches. We excluded the studies and trials which recruited participants with 'mixed' or 'combination' migraine and other types of headache such as tension-type headache. There were no restrictions of gender, age, ethnicity, nationality or duration of disease.

Intervention: All the available treatments both pharmacological or non-pharmacological strategies for migraine will be considered in this NMA being accessing efficacy and safety.

Comparator: Eligible comparator groups within this NMA includes usual care, placebo or another included pharmacological or nonpharmacological treatment strategy for migraine.

Study designs to be included: Only randomized controlled trials (RCTs) will be included in our systematic review and NMA in order to provide high quality of evidence.

Eligibility criteria: P: The participants included in this NMA are all diagnosed as migraine according to the recognized criteria: International Classification of Headache Disorders (ICHD) for migraine headaches. I: All the available treatments both pharmacological or non-pharmacological strategies. C: usual care, placebo or another included pharmacological or nonpharmacological treatment strategy for migraine. O: . Our primary outcomes are as follow. i). The number of participants with pain-free response at 2 hours (complete resolution of headache pain). ii). The number of participants with headache pain reduction from moderate/severe to mild or none at 2 hours. iii). The number of participants with sustained relief for 24 hours. Our secondary outcomes of efficacy included Migraine disability assessment (MIDAS) questionnaire, Headache impact test (HIT-6), Mindfulness attention awareness scale (MAAS), 36-item short form survey (SF-36), headache frequency per month, headache severity and headache duration. Our primary outcomes of safety include the total adverse events, restlessness, drowsiness, nausea, vomiting. Other side effects such as tingling, numbness, swelling and any other adverse events would also be analyzed as the secondary outcomes. S: Only randomized controlled trials (RCTs) will be included in our systematic review and NMA.

Information sources: We will perform the systematic electronic search of the literature utilizing MEDLINE, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), CINAHL, PsycINFO and CENTRAL.

Main outcome(s): Our primary outcomes are as follow. i). The number of participants with pain-free response at 2 hours (complete resolution of headache pain). ii). The number of participants with headache pain reduction from moderate/severe to mild or none at 2 hours. iii). The number of participants with sustained relief for 24 hours. Our primary outcomes of safety include the total adverse events, restlessness, drowsiness, nausea, vomiting. Other side effects such as tingling, numbness, swelling and any other adverse events would also be analyzed as the secondary outcomes.

Additional outcome(s): Our secondary outcomes of efficacy included Migraine disability assessment (MIDAS) questionnaire, Headache impact test (HIT-6), Mindfulness attention awareness scale (MAAS), 36-item short form survey (SF-36), headache frequency per month, headache severity and headache duration.

Data management: Two of us will perform the data extraction independently and once the discrepancies come up, the final decision would be made by a third reviewer. Initially, the baseline

characteristics of the included studies as potential effects modifiers will be abstracted roundly, and the information collected are as follow. 1) Study characteristics: publication date, authorship, location of study, journal of publication, study sponsorships, etc. 2) Patient characteristics: average age, proportion of female patients, occupations, etc. 3) Intervention characteristics: intervention director, intervention protocol, medication dosing schedule, duration of medication, etc. Secondly, the primary and secondary outcomes of safety and efficacy illustrated before will be extracted from included RCTs. The doses of drugs, methods of drug delivered, and schedules of drug administration will all be recognized from included studies.

Quality assessment / Risk of bias analysis: The risk of bias of the selected RCTs will be accessed strictly following the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions. By this Cochrane bias tools, two reviewers should independently evaluated the bias and quality of included RCTs from six aspects including random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias) and other bias. Once there is any controversy, a third reviewer would give the final assessment and finally assign a level of risk of bias (high risk, unclear risk, low risk) for each item.

Strategy of data synthesis: We will cautiously assume the transitivity and similarity based on that the clinical and methodological characteristics described above are balanced on average across treatment comparisons. This assumption was set after reviewing all data of studies' and participants' characteristics and examining potential efficacy modifiers such as age, timing of exposure, risk-of-bias, etc. And all these effect modifiers will be judged and reported before the network meta-analysis is conducted. We will carefully evaluate the treatment groups received comparative interventions (usual care or placebo) to make sure they are similar across pairwise comparisons.

Subgroup analysis: Subgroup analysis will be processed to further demonstrate the efficacy and safety for different groups of patients, and which would include adolescent group, pregnancy group, elder group, etc.

Sensibility analysis: Sensitivity analyses would be processed incorporating only the RCTs at low risk of bias into the network estimates. And then we would assess the robustness of our results through a series of sensitivity analyses: the exclusion trials with a high risk of bias, the iterative removal of one study at a time, and the use of both fixed and random-effects models.

Language: Only English-language articles published as full-text would be included.

Other relevant information: Migraine; pharmacological treatments; non-pharmacological treatments; Systematic review; Bayesian network-meta analysis.

Keywords: migraine; pharmacological treatments; non-pharmacological treatments; Systematic review; Bayesian network-meta analysis.

Contributions of each author:

Author 1 - Boru Jin - The author contributed to research screening, data extraction,risk of bias assessment, data analysis and draft the manuscript.

Author 2 - Huayan Liu - The author contributed to the preliminary searches, piloting of the study selection process and formal screening of search results against eligibility criteria.

Author 3 - Lei Qiao - The author contributed to protocol design, quality accessment, research screening and manuscript revision.