

# BMJ Open Efficacy and safety of different drug monotherapies for tension-type headache in adults: study protocol for a Bayesian network meta-analysis

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## ABSTRACT

**Introduction** Tension-type headache (TTH) is the most prevalent neurological disease, with an estimated 1.5 billion cases worldwide. Pharmacotherapy should be considered by patients with TTH who have a limited response to non-pharmacological treatment. However, recommendations for the vast array of therapeutic drugs for TTH partially overlap, with conflicting recommendations for strength in different guidelines; these may confuse the decision-making process of clinicians. Hence, the aims of this study are to analyse the available direct and indirect evidence on different drug monotherapies for TTH in adults, and to generate a treatment ranking according to their efficacy and safety outcomes by using a Bayesian network meta-analysis (NMA).

**Methods and analysis** We will systematically search the Cochrane Library, PubMed, Web of Science, Embase, China Biomedical Literature Database, International Clinical Trials Registry Platform and other resources for eligible studies. Randomised controlled trials on different drug monotherapies for TTH will be included. Two review authors (RX and YW) will independently search and select the studies, extract the data and assess the risk of bias. A Bayesian NMA will afterwards be conducted to pool the effect measures across all types of monotherapy drugs. The ranking probabilities of the efficacy and safety of different drug monotherapies will be estimated. Heterogeneity will be quantified using the Q statistic and the I<sup>2</sup> index. Inconsistency between direct and indirect evidence will be assessed by the node-splitting model. In addition, the overall quality of evidence will be assessed using the Grading of Recommendations Assessment, Development and Evaluation approach.

**Ethics and dissemination** No ethical issues are foreseen. The results will be published in a peer-reviewed journal, which will be disseminated electronically and in print.

**PROSPERO registration number** CRD42018090554.

## INTRODUCTION

Over the past 25 years, the burden of neurological disease has increased constantly, and neurological diseases have become a major cause of disability and death worldwide.<sup>1</sup> Tension-type headache (TTH) is the most prevalent neurological disease, with an

## Strengths and limitations of this study

- This Bayesian network meta-analysis will provide a comprehensive summary of the direct and indirect evidence on the efficacy and safety of different drug monotherapies for tension-type headache (TTH) in adults.
- The relative ranking results of the efficacy and safety outcomes will facilitate patients, clinicians and healthcare providers in the selection of the available drug monotherapies by providing the highest level of evidence.
- This protocol is drafted in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols 2015 statement and has been registered with the International prospective register of systematic reviews (PROSPERO).
- The overall quality of evidence will be assessed using the Grading of Recommendations Assessment, Development and Evaluation approach.
- This research will exclude non-English, non-Chinese and non-randomised controlled trials, and the publications investigating combination therapies for TTH will also be limited.

estimated 1.5 billion cases globally.<sup>1,2</sup> TTH is generally a diffuse, mild-to-moderate pain in the head, often described as feeling like a tight band around the head. TTH may be associated with considerable disability, low effectiveness at work, absenteeism or decreased learning ability, and may have a great impact on the patient's quality of life.<sup>2</sup> Pharmacotherapy should be considered or added for patients with TTH who show a limited response to non-pharmacological treatment.<sup>3</sup>

Since 1995, TTHs have been divided into episodic TTH (ETTH) and chronic TTH (CTTH) subtypes; these were introduced in the first edition of the International Classification of Headache Disorders of the International Headache Society (IHS).<sup>4</sup> Our preliminary search found that the

recommendations for therapeutic drugs for patients with ETTH or CTTH varied widely between different guidelines, partially overlapped and exhibited variation in recommended strength (online supplementary appendix 1).<sup>5–15</sup> That is, either the same drug was recommended at different strength in different guidelines, or different guidelines recommended different pharmaceuticals. For example, ibuprofen and ketoprofen were considered to be level A in the European Federation of Neurological Societies guidelines, although the Italian guidelines suggested these two analgesics were at the level II recommendation.<sup>8,14</sup>

Thus far, evidence for the acute treatment of ETTH and the prophylactic treatment of CTTH of direct head-to-head comparison among all treatments is scarce. In addition, conventional pairwise meta-analyses as a means of summarising evidence do not allow for the inclusion of data that have not been direct comparisons. Hopefully, previous studies have shown that the combined results of direct evidence and indirect evidence can improve accuracy for treatments that have been directly evaluated.<sup>16</sup> Therefore, to assess the relationships between all treatments, a network meta-analysis (NMA) will be necessary for the integration of direct and indirect evidence from multiple treatment comparisons.<sup>17</sup>

The relative efficacy and safety among different types of drugs and between different drugs of the same type for the treatment of ETTH and CTTH are not yet clear. Therefore, clinicians may be confused when making decisions on pharmaceuticals. Hence, the aims of this study are to synthesise the available direct and indirect evidence on the different drug monotherapies for ETTH and CTTH in adults, and to generate a treatment ranking based on their efficacy and safety outcomes by using an NMA.

## METHODS AND ANALYSIS

This protocol is drafted in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols 2015 statement.<sup>18</sup> It has been registered with the International prospective register of systematic reviews (PROSPERO).

### Criteria for included studies

#### Participants and settings

The participants studied by this review must be adult patients ( $\geq 18$  years of age) with TTH (either ETTH or CTTH).

The diagnosis criteria for TTH should be developed by professional organisations or agencies (eg, the IHS)<sup>19</sup>; they can clearly classify TTH into ETTH and CTTH and reasonably distinguish TTH from other types of headache.

Only data from participants with ETTH or CTTH will be analysed. Studies and trials including participants with ‘mixed’ or ‘combination’ TTH and other types of headache will be excluded. There will be no limitations on participants’ gender, race and nationality.

### Interventions

In our preliminary studies, we searched the relevant databases, electronic databases and websites for guidelines containing ETTH or CTTH drug monotherapies. These monotherapies were extracted to the ‘ETTH and CTTH drug monotherapies list’ (table 1).

Each intervention from the included studies shall match at least one monotherapy of the ‘ETTH and CTTH drug monotherapies table’. There will be no restriction on dose.

Studies solely investigating on non-pharmacological interventions, or on combinations of drugs instead of monotherapies, will be excluded.

### Comparators

The comparator(s)/control of the included studies shall involve at least one monotherapy from the ‘ETTH and CTTH drug monotherapies list’ or blank/placebo control.

### Outcome measures

#### Primary outcome

The primary efficacy outcomes will be pain-free at 2 hours, sustained freedom from pain at 24 hours and Visual Analogue Scale score. The primary safety outcomes will be the incidence of adverse events, gastrointestinal adverse reactions and addiction to drugs.

#### Secondary outcomes

The possible secondary efficacy outcomes are as follows: (1) changes in patient-reported headache frequency, duration and intensity; and (2) functional health status and health-related quality of life (eg, 36-Item Short Form Survey). The possible secondary safety outcomes are (1) liver-kidney function indicators and (2) faecal occult blood.

### Study design and publication types

Randomised controlled trial (RCT) studies in any setting using different drug monotherapies for ETTH or CTTH in adults will be included. We will exclude publications that were not peer-reviewed, such as letters, comments and conference proceedings.

### Information sources and search strategy

We will develop search strategies for each electronic database, based on the search strategy developed for PubMed (online supplementary appendix 2), with appropriate revisions for each database. The following databases will be searched: Cochrane Library, PubMed, Web of Science, Embase, China Biomedical Literature Database and International Clinical Trials Registry Platform. We will also search other resources for eligible studies. The search dates will be from the establishment of the respective library to 15 March 2018. The languages will be limited to English and Chinese. In addition, we will also hand-search the reference lists of all eligible articles for additional studies if they meet our eligibility criteria.

**Table 1** ETTH and CTTH drug monotherapies list

Subtype of TTH	Drug classification	Drug treatment	
ETTH	Non-steroidal anti-inflammatory drugs	Aspirin/acetylsalicylic acid	
		Acetaminophen/paracetamol	
		Lumiracoxib	
		Ibuprofen	
		Ketoprofen	
		Naproxen	
		Diclofenac	
		Diclofenac-K	
	Analgesics	Metamizole/Dipyrone	
		Codeine	
		Dihydrocodeine	
	Antiemetics	Dextropropoxyphene	
		Metoclopramide	
	Supplementary	Chlorpromazine	
Tiger balm			
CTTH	Antidepressants	Amitriptyline	
		L-5-Hydroxytryptophan	
		Fluvoxamine	
		Venlafaxine	
		Clomipramine	
		Mirtazapine	
		Maprotiline	
		Mianserin	
		Desipramine	
		Fluoxetine	
		Paroxetine	
		Nefazodone	
		Ritanserin	
		Sulpiride	
		Dothiepin/Prothiaden	
		Nortriptyline	
		Protriptyline	
		Antiepileptics	Sodium valproate
			Topiramate
	Gabapentin		
	Levetiracetam		
	Anxiolytics	Diazepam/Valium	
		Alprazolam	
		Buspirone	
	Narcotics	Tizanidine	
		Cyclobenzaprine	
		Botulinum toxin A/	
		OnabotulinumtoxinA	

CTTH, chronic TTH; ETTH, episodic TTH; TTH, tension-type headache.

### Study selection

Two review authors (RX and YW) will independently screen the titles/abstracts of all studies retrieved according to the search strategy and those obtained from additional sources to identify the studies suitable for the inclusion criteria mentioned above. Afterwards, the full text of the remaining studies will also be retrieved and independently assessed for eligibility. Any disagreement between them will be resolved by discussion or by referral to a third reviewer for a final decision.

### Data extraction

We will design a prepiloted data extraction form to extract data from the included studies for study quality assessment and evidence synthesis. Using this form, two authors (RX and YW) will independently extract data from each study. Any disagreement that occurred will be resolved by mutual discussion or by referral to a third reviewer for a final decision. The extracted information will include basic information on the study; characteristics of the study; details of the intervention and control group; outcomes measures and their data; risk of bias (quality) assessment information; and other relevant information.

### Risk of bias assessment

Two review authors (RX and YW) will independently assess the risk of bias in included studies, using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions.<sup>16</sup>

Each study will be assessed on the following aspects:

1. Random sequence generation (to assess the domain of selection bias). We will assess the method used to generate the allocation sequence in sufficient detail as low risk of bias (the investigators describe a random component in the sequence generation process); high risk of bias (the investigators describe a non-random component in the sequence generation process); or unclear risk of bias (insufficient information about the sequence generation process to permit judgement).
2. Allocation concealment (to assess the domain of selection bias). We will assess the method used to conceal the allocation sequence in sufficient detail as low risk of bias (participants and investigators enrolling participants could not foresee assignment); high risk of bias (participants or investigators enrolling participants could possibly foresee assignments and thus introduce selection bias); or unclear risk of bias (insufficient information to permit judgement).
3. Blinding of participants and personnel (to assess the domain of performance bias). We will assess the method used to blind study participants and personnel from knowledge of which intervention a participant received as low risk of bias (the outcome is not likely to be influenced by lack of blinding, or the blinding could not have been broken); high risk of bias (the outcome is likely to be influenced by lack of blinding, or the blinding could have been broken); or unclear

- risk of bias (insufficient information to permit judgement, or the study did not address this outcome).
4. Blinding of outcome assessment (to assess the domain of detection bias). We will assess the method used to blind outcome assessors from the knowledge of which intervention a participant received as low risk of bias (the outcome measurement is not likely to be influenced by lack of blinding, or the blinding could not have been broken); high risk of bias (the outcome measurement is likely to be influenced by lack of blinding, or the blinding could have been broken); or unclear risk of bias (insufficient information to permit judgement, or the study did not address this outcome).
  5. Incomplete outcome data (to assess the domain of attrition bias). We will assess the completeness of outcome data for each main outcome as low risk of bias (no missing outcome data, or missing outcome data unlikely to have a clinically relevant impact on observed effect size); high risk of bias (missing outcome data likely to be related to the true outcome, or missing outcome data sufficient to induce clinically relevant bias in observed effect size); or unclear risk of bias (insufficient reporting of attrition/exclusion to permit judgement, or the study did not address this outcome).
  6. Selective reporting (to assess the domain of reporting bias). We will assess the possibility of selective outcome reporting by the review authors as low risk of bias (the study protocol is available and all of the study outcomes are prespecified, or the study protocol is not available but it is clear that the published reports include all expected outcomes); high risk of bias (not all of the prespecified primary outcomes of the study have been reported, or one or more primary outcomes are reported using measurements, analysis methods or subsets of the data that were not prespecified); or unclear risk of bias (insufficient information to permit judgement).
  7. Other sources of bias (to assess the domain of other bias). We will assess any important concerns about bias not addressed in the other domains in the tool as low risk of bias (the study appears to be free of other sources of bias); high risk of bias (there is at least one important risk of bias); or unclear risk of bias (insufficient information to assess whether an important risk of bias exists, or insufficient rationale or evidence that an identified problem will introduce bias).

### Statistical analysis

We will descriptively summarise the included studies based on the study characteristics, patient characteristics, intervention and outcome measures, and our assessment of the risk of bias. If quantitative synthesis is not appropriate, we will describe the results of the systematic review.

We will calculate the risk ratio and its 95% CIs for dichotomous data, and the mean differences with 95% CIs for continuous data. Weighted mean differences will be used for data measured on the same scale with the same units; otherwise, standardised mean differences will

be used. When lacking head-to-head comparisons, indirect treatment comparison meta-analysis will be retrieved from the available evidence.

We will perform the NMA in the Bayesian framework using the Markov chain Monte Carlo method. In our NMA of TTH treatment efficacy and safety, effect measures across all types of drug monotherapies will be pooled. Convergence of the simulations will be evaluated using trace plots, density plots and Brooks-Gelman-Rubin diagnosis plots.<sup>20</sup> In this study, both fixed-effects and random-effects models in the Bayesian NMA will be considered based on the results of the deviance information criterion. Moreover, the ranking probability of the efficacy and safety of different drug monotherapies will be estimated for the acute treatment of ETTH and the prophylactic treatment of CTTH. The results of rankograms, ranking probabilities plots and evidence network plots will be displayed graphically. Cumulative ranking will be estimated by the surface under the cumulative ranking curve (SUCRA) for each TTH treatment. SUCRA will be 1 when a treatment is certain to be the best and 0 when a treatment is certain to be the worst, with higher values indicating better efficacy or safety.<sup>21</sup>

### Assessment of heterogeneity

Heterogeneity will be quantified with  $Q$  statistic and  $I^2$  index. We will consider  $p < 0.1$  or  $I^2 \geq 50\%$  indicative of at least moderate heterogeneity.<sup>22</sup> Under this circumstance, the random-effect model will be used. Otherwise, the fixed-effect model will be used.

### Assessment of inconsistency

Inconsistency between direct and indirect evidence will be assessed by the node-splitting model, which is a straightforward interpretation, contrasting estimates from both direct and indirect evidence.<sup>23</sup> Values of  $p < 0.05$  indicate inconsistency between direct and indirect estimates in a specific closed loop.

### Assessment of similarity

All indirect analyses are based on the underlying assumption that the study populations in the trials being compared are sufficiently similar to be pooled, akin to meta-analyses.<sup>24</sup> The similarities in the clinical and methodological characteristics, such as baseline data for patients and trial design, between studies will be qualitatively compared.

### Sensitivity analysis

We will 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.

### Assessment of publication bias and small-study effects

We will use funnel plots for each treatment comparison separately to assess for publication bias if there are 10 or more studies reporting on a particular outcome. Small-study effects will be tested within a network

meta-regression model that distinguishes studies based on their size.

### Subgroup analysis

Possible subgroup analyses will be performed based on the age of patients and the route of drug administration.

### Software

The NMA in the Bayesian framework will be conducted using JAGS V.4.2.0, with 'gemtc', 'R2WinBUGS', 'lattice' and 'coda' packages in R V.3.4.4.<sup>25</sup>

### Assessment of quality of evidence

The overall quality of evidence will be assessed using the Grading of Recommendations Assessment, Development and Evaluation approach on the efficacy and safety of different drug monotherapies for TTH in adults. The quality of RCT evidence will be classified into high, moderate, low or very low quality evidence, depending on the presence of these five factors: (1) limitations in the design and implementation; (2) indirectness of evidence; (3) unexplained heterogeneity or inconsistency of results; (4) imprecision of results; and (5) high probability of publication bias.<sup>16</sup>

### Patient and public involvement

There was no patient or public involvement in the development of this manuscript. Following completion of this work, we will disseminate our findings through open-access publications.

## DISCUSSION

Among the different types of headaches, TTH is probably the most prevalent, but the least studied.<sup>3 26</sup> According to the preliminary guideline search results, at minimum of 11 guidelines currently recommend more than 40 different drug monotherapies for the acute treatment of ETTH and the prophylactic treatment of CTTH. However, these recommendations cannot provide a clear answer on the best choice for the initial treatment of ETTH and CTTH owing to a lack of consistency. Therefore, we have proposed an NMA to quantitatively synthesise the available direct and indirect evidence on the different drug monotherapies for ETTH and CTTH. The relative ranking of efficacy and safety outcomes of each competing treatment will be presented. We expect that the results of this research will facilitate the decision making by patients, clinicians and healthcare providers in the treatment of patients with TTH with pharmaceuticals.

The limitations of this research will be noted. First, the exclusion of non-English and non-Chinese studies may cause publication bias. Second, we will exclude non-RCT publications to support our intention to include only higher quality evidence. Finally, this study did not include publications of combination therapy for TTH, which may affect the generalisability of this study.

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**Contributors** RX, JT and HL conceived the study and drafted the manuscript. JT and YW provided search strategies and professional advice. RX and YW implemented a preliminary search. JT and HL provided guidance on the NMA methodology. YC and HL provided expertise on treatments, outcomes and related knowledge on TTH. All authors read, critically reviewed and approved the final manuscript as submitted.

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