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The 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 to TTH patients who has limited response to non-pharmacological treatment. However, the recommended therapeutic drugs for TTH were wide variety, partially overlapped and divergent recommended strength between different guidelines, which may be confused clinicians about medical decision-making. Hence, the aims of this study are to synthesise the available direct and indirect evidence on different drug monotherapies of TTH in adults, and to generate a treatment ranking according to their efficacy and safety outcomes using a Bayesian network meta-analysis (NMA).

Methods and analysis We will systematically search Cochrane Library, PubMed, Web of Science, Embase, CBM, ICTRP and other resource for eligible studies. RCTs on different drug monotherapies for TTH will be included. Two review authors (RX and YW) will independently search the studies, select the studies, extract the data and assess the risk of bias. A Bayesian NMA will be conducted to pool effect measures across all types of monotherapies drug. The ranking probabilities of the efficacy and safety of different drug monotherapies will be estimated. Heterogeneity will be quantified with Q statistic and I^2 index. Inconsistency between direct and indirect evidence will be assessed by the node-splitting model. The overall quality of evidence will be assessed by using the GRADE 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.

Strengths and limitations of this study

► This Bayesian network meta-analysis will provide a comprehensive summary of direct and indirect evidence on the efficacy and safety of different drug monotherapies for TTH in adults.

► The relative ranking results of efficacy and safety outcomes will facilitate patients, clinicians and healthcare providers for decision-making from among the many available drug monotherapies in treatment process by using the highest level of evidence.

► This protocol is drafted in accordance with PRISMA-P 2015 statement and has been registered with the International Prospective Register of Systematic Reviews (PROSPERO).

► The overall quality of evidence will be assessed by using the GRADE approach.

► This research will exclude non-English, non-Chinese and non-RCT studies, and the publications of combination therapy for TTH will also be limited.

INTRODUCTION

Over the past 25 years, the burden of neurological disease has increased constantly, and neurological diseases have become major cause of disability and death worldwide.[1] Tension-type headache (TTH) is the most prevalent neurological disease, with an estimated 1.5 billion cases globally.[1 2] A TTH is generally a diffuse, mild to moderate pain in the head that's often described as feeling like a tight band around the head. TTH can be associated with considerable disability, low work effectiveness, absenteeism, or decreased learning ability, and may have a great impact on the quality of life.[2] Pharmacotherapy should be considered or added to TTH patients who has limited response to non-pharmacological treatment.[3]

Since 1995, TTH have bend divided into episodic TTH (ETTH) and chronic TTH (CTTH) subtypes, introduced in the first edition of International Classification of Headache Disorders (ICHD-I) of International Headache Society (IHS).[4] After our previous search, we found that the recommended therapeutic drugs for the ETTH or CTTH patients were wide variety, partially overlapped and divergent recommended strength between different guidelines (Appendix 1).[5-15] That is, the same drugs are recommended differently in different guidelines, and different guidelines recommended different drugs. For example, the recommendation of ibuprofen and ketoprofen were considered as level A in the EFNS guidelines while the Italian guidelines suggested these two drugs with a level of recommendation II.[8 14]

Thus far, the evidence for the acute treatment of ETTH and prophylactic treatment of CTTH of direct head-to-head comparison between all treatments are rarely seen or not available. Moreover, using the conventional pairwise meta-analyses to summarise evidence would not allow for the inclusion of data that have not been compared head-to-head. Previous studies show that the results from direct combined with indirect evidence can improve accuracy for treatments that have been directly evaluated.[16] Therefore, to assess the interrelations across all treatments, a network meta-analysis (NMA) is necessary to be conducted to integrate direct and indirect evidence from multiple treatment comparisons.[17]

As the relative efficacy and safety among different drug types and between different drugs in the same type on the treatment of ETTH and CTTH are not yet clear, clinicians may be confused about medical decision-making. Hence, the aims of this study are to synthesise the available direct and indirect evidence on different drug monotherapies of ETTH and CTTH in adults, and to generate a treatment ranking according to their efficacy and safety outcomes using a NMA.

METHODS AND ANALYSIS

This protocol is drafted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses protocols (PRISMA-P) 2015 statement.[18] It has been registered with PROSPERO (registration number: CRD42018090554).

Criteria for included studies

Participants and settings

The participants being studied by this review must be adult patients (at least 18 years of age or older) with TTH (ETTH or CTTH).

The diagnosis criteria of TTH should be developed by relevant professional organizations or agencies (e.g. International Headache Society)[19]. It can clearly separate TTH into ETTH and CTTH and reasonably distinguish TTH from other headache types.

We will analyse data only for participants with ETTH or CTTH. The studies/trials including participants with 'mixed' or 'combination' TTH and other headache types would be excluded. The participants' gender, race, and nationality are not limited.

Interventions

We have searched relevant guideline database, electronic database and websites in the previous period. After we obtained the guidelines containing ETTH or CTTH drug monotherapies, these monotherapies were extracted to form the "ETTH and CTTH drug monotherapies list" (Table 1).

The interventions of included studies must have at least one monotherapy of the "ETTH and CTTH drug monotherapies table". There will be no restriction on dose.

We will exclude studies only with non-pharmacological interventions. We will also exclude studies which only reported on combinations of any of these pharmacological interventions.

Comparators

The comparator(s)/control of included studies must have at least one monotherapy of the "ETTH and CTTH drug monotherapies list" or blank control or 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. The primary safety outcomes will be the incidence of serious adverse events, gastrointestinal adverse reactions and addiction to drugs.

Secondary outcomes

The possible secondary efficacy outcomes are listed as follows: (1) Change in patient-reported headache frequency, duration and intensity; (2) Functional health status and health related quality of life (e.g. SF-36). The possible secondary safety outcomes are listed as follows: (1) Liver-kidney functions effects; (2) fecal occult blood.

Study designs and publication types

We will only include randomised controlled trial (RCT) studies in any setting using different drug monotherapies for ETTH or CTTH in adults. We will exclude the publications which 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 (Appendix 2), revised appropriately for each database. Databases to be searched include the following: Cochrane Library, PubMed, Web of Science, Embase, China Biomedical Literature Database(CBM), International Clinical Trials Registry Platform (ICTRP). We will also search other resource for eligible studies. The search dates are from the library established to 15 March 2018. Language is 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.

Study selection

Two review authors (RX and YW) will independently screen the titles/abstracts of all studies retrieved using the search strategy and those from additional sources to identify those studies suitable for the inclusion criteria mentioned above. The full text of the remaining studies will also be retrieved and independently assessed for eligibility by them. 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 pre-piloted data extraction form to extract data from the included studies for assessment of study quality and evidence synthesis. Two authors (RX and YW) will independently extract data from each study using this form. Any disagreement between them will be resolved by mutual discussion or by referral to a third reviewer for a final decision. Extracted information will include: basic information of study; characteristics of study; details of the intervention and control conditions; outcomes measures and its data; risk of bias (quality) assessment information; other 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.[16] We will assess the following characteristics:

1. Random sequence generation (assessing 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); Unclear risk of bias (insufficient information about the sequence generation process to permit judgement).

2. Allocation concealment (assessing 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); Unclear risk of bias (insufficient information to permit judgement).

3. Blinding of participants and personnel (assessing 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); Unclear risk of bias (insufficient information to permit judgement, or the study did not address this outcome).

4. Blinding of outcome assessment (assessing the domain of Detection bias). We will assess the method used to blind outcome assessors from 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); Unclear risk of bias (insufficient information to permit judgement, or the study did not address this outcome).

5. Incomplete outcome data (assessing 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 true outcome, or missing outcome data enough to induce clinically relevant bias in observed effect size); Unclear risk of bias (insufficient reporting of attrition/exclusions to permit judgement, or the study did not address this outcome).

6. Selective reporting (assessing the domain of Reporting bias). We will assess the possibility of selective outcome reporting was examined by the review authors as: low risk of bias (the study protocol is available and all of the study's pre-specified, 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 study's pre-specified primary outcomes have been reported, or one or more primary outcomes is reported using measurements, analysis methods or subsets of the data that were not pre-specified); Unclear risk of bias (insufficient information to permit judgement).

7. Other sources of bias (assessing 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); 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 summarize the included studies based on study characteristics, patient characteristics, interventions and outcomes measures, and our assessment of risk of bias. If quantitative synthesis is not appropriate, we will describe the results of systematic review.

We will calculate risk ratio (RR) with its 95% CIs for dichotomous data and mean differences (MD) with its 95% CIs for continuous data. Weighted mean differences (WMD) will be used for data measured on the same scale and for which the same units are used. Otherwise, standardised mean differences (SMD) will be used. When lacking head-to head evidence, indirect treatment comparison meta-analysis will be retrieved from available evidence.

We will carry out the NMA in the Bayesian framework using the Markov Chains Monte Carlo (MCMC) method. In our NMA of TTH treatment efficacy and safety, we will pool effect

measures across all types of monotherapies drug. Convergence of the simulations will be evaluated with the trace plots, density plots and Brooks-Gelman-Rubin diagnosis plots.[20] We
In this study, we will consider both fixed-effects and random-effects models in the Bayesian NMA, and then will choose the final models according to the results of deviance information criterion (DIC). We will also estimate the ranking probability of the efficacy and safety of different drug monotherapies for acute treatment of ETTH and prophylactic treatment of CTTH. The results of rankograms, ranking probabilities plots and evidence network plots will be shown in graphically. Cumulative ranking will be estimate the surface under the cumulative ranking curve (SUCRA) for each TTH treatment. SUCRA would 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.[21]

Assessment of heterogeneity

Heterogeneity will be quantified with Q statistic and I^2 index. We will consider p <0.1 or $I^2 \geqslant 50\%$ indicative of at least moderate heterogeneity.[22] Under the circumstances, 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 straightforward interpretation, contrasting estimates from both direct and indirect evidence. [23] P <0.05 indicates that there is 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 similar enough to be pooled, akin to meta-analyses.[24] The similarities in clinical and methodological characteristics between studies will be qualitatively compared (e.g. baseline data for patients, trial design, etc.).

Sensitivity analysis

We will assess the robustness of our results through a series of sensitivity analysis. By excluding trials at high risk of bias, removing 1 study at a time iteratively, and using 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 age and route of administration.

Software

The NMA in the Bayesian framework will be conducted using JAGS V.4.2.0, with 'gemtc', 'R2WinBUGS', 'lattice' and 'coda' package in R V.3.4.4.[25]

Assessment of quality of evidence

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

DISCUSSION

Among the different headaches, probably TTH is the most prevalent but the least studied type.[3 26] According to the preliminary search results of guidelines, at least 11 guidelines currently recommend more than 40 different drug monotherapies for the acute treatment of ETTH and prophylactic treatment of CTTH. However, these recommendations cannot provide a clear answer regarding the best choice for initial treatment of ETTH and CTTH due to lack of consistency. Therefore, we have proposed a network meta-analysis to quantitatively synthesise the available direct and indirect evidence on different drug monotherapies of ETTH and CTTH. The relative ranking of efficacy and safety outcomes for each competing treatment will also be presented. We expect that the results of this research could facilitate patients, clinicians and healthcare providers for decision-making in treatment process.

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

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

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Competing interests The authors declare that they have no competing interests.

Patient consent Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Abbreviations

AAN: American academy of neurology; BASH: British association for the study of headache; CBM: China Biomedical Literature Database; CTTH: Chronic tension-type headache; DIC: Deviance information criterion; EFNS: European federation of neurological societies; EHF: European headache federation; ETTH: Episodic tension-type headache; GRADE: Grading of Recommendations Assessment, Development and Evaluation; ICHD: International classification of headache disorders; ICSI: Institute for clinical systems improvement; ICTRP: International Clinical Trials Registry Platform; IHS: International headache society; MCMC: Markov Chains Monte Carlo; MD: Mean differences; NICE: National institute for health and clinical excellence; NMA: Network meta-analysis; RR: Risk ratio; SIGN: Scottish intercollegiate guidelines network; SISC: Italian society for the study of headaches; SMD: Standardised mean differences; SUCRA: Surface under the cumulative ranking curve; TOP: Toward optimized practice; TTH: Tension-type headache; WMD: Weighted mean differences.

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Table 1 ETTH and CTTH drug monotherapies list

Subtype of TTH	Drug Classification	Drug treatment
ETTH	Non-steroidal anti-inflammatory drugs (NSAIDs)	Aspirin/acetylsalicylic acid
		Acetaminophen/paracetamol
		Lumiracoxib
		Ibuprofen
		Ketoprofen
		Naproxen
		Diclofenac
		Diclofenac-K
		Metamizole/ dipyrone
	Analgesics	Codeine
		Dihydrocodeine
		Dextropropoxyphene
	Antiemetics	Metoclopramide
		Chlorpromazine
	Supplementary	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

Appendix 1 The recommended TTH therapeutic drugs among guidelines

No.	Drug treatment	AAN[Err] or! Reference source not found.	BASH[Err] or! Reference source not found.	Croatian[Err] or! Reference source not found.	EFNS[Err] or! Reference source not found.	EHF[Err] or! Reference source not found.	French[Err] or! Reference source not found.	ICSI[Err] or! Reference source not found.	NICE[Err] or! Reference source not found.	SIGN[Err] or! Reference source not found.	SISC[Err] or! Reference source not found.	TOP[Err] or! Reference source not found.
1	Aspirin/acetylsalicylic acid		√	√	√	√		√	√	√	√	√
2	Acetaminophen/paracetamol		√	√	√	√		√	√	√	√	√
3	Lumiracoxib										√	
4	Ibuprofen		√	√	√	√	√				√	√
5	Ketoprofen		√	√	√		√				√	
6	Naproxen		√	√	√						√	√
7	Diclofenac			√	√							
8	Diclofenac-K										√	
9	Metamizole/ dipyrone										√	
10	Codeine		×			×						
11	Dihydrocodeine		×			×						
12	Dextropropoxyphene					×						
13	Metoclopramide										√	
14	Chlorpromazine										√	
15	Tiger balm										√	
16	Amitriptyline		√	√	√	√		√		√	√	√
17	L-5-hydroxytryptophan										√	
18	Fluvoxamine										√	
19	Venlafaxine			√	√			√			√	√

No.	Drug treatment	AAN[Err] or! Reference source not found.	BASH[Err] or! Reference source not found.	Croatian[Err] or! Reference source not found.	EFNS[Err] or! Reference source not found.	EHF[Err] or! Reference source not found.	French[Err] or! Reference source not found.	ICSI[Err] or! Reference source not found.	NICE[Err] or! Reference source not found.	SIGN[Err] or! Reference source not found.	SISC[Err] or! Reference source not found.	TOP[Err] or! Reference source not found.
20	Clomipramine				√						√	
21	Mirtazapine			√	√						√	√
22	Maprotiline				√						√	
23	Mianserin				√						√	
24	Desipramine										√	
25	Fluoxetine										√	
26	Paroxetine										√	
27	Nefazodone										√	
28	Ritanserin										√	
29	Sulpiride										√	
30	Dothiepin/prothiaden		√									
31	Nortriptyline		√			√						√
32	Protriptyline		√									
33	Sodium valproate			√								
34	Topiramate			√							√	
35	Gabapentin			√								
36	Levetiracetam			√								
37	Diazepam/valium										√	
38	Alprazolam										√	
39	Buspirone										√	

No.	Drug treatment	AAN[Err] or! Reference source not found.	BASH[Err] or! Reference source not found.	Croatian[Err] or! Reference source not found.	EFNS[Err] or! Reference source not found.	EHF[Err] or! Reference source not found.	French[Err] or! Reference source not found.	ICSI[Err] or! Reference source not found.	NICE[Err] or! Reference source not found.	SIGN[Err] or! Reference source not found.	SISC[Err] or! Reference source not found.	TOP[Err] or! Reference source not found.
40	Tizanidine										√	
41	Cyclobenzaprine										√	
42	Botulinum toxin A/OnabotulinumtoxinA	×	×			×				×		

Abbreviations: AAN, American academy of neurology; BASH, British association for the study of headache; EFNS, European federation of neurological societies; EHF, European headache federation; ICSI, Institute for clinical systems improvement; NICE, National institute for health and clinical excellence; SIGN, Scottish intercollegiate guidelines network; SISC, Italian society for the study of headaches; TOP, Toward optimized practice; "√" indicates recommendation; "×" indicates not recommendation;

Appendix 2 PubMed Search Strategy (illustrated by the example of aspirin)

#1 " aspirin " [Title/Abstract]

#2 " Aspirin "[Mesh]

#3 " acetylsalicylic acid " [Title/Abstract]

#4 " Acetylsalicylic acid "[Mesh]

#5 #1 OR #2 OR #3 OR #4

#6 "Tension-Type Headache"[Mesh]

#7 Psychogenic Headache[Title/Abstract]

#8 Tension-TypeHeadache*[Title/Abstract]

#9 Stress Headache*[Title/Abstract]

#10 Tension Headache*[Title/Abstract]

#11 PsychogenicHeadache*[Title/Abstract]

#12 Tension-VascularHeadache*[Title/Abstract]

#13 #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12

#14 (randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR clinical trials as topic [mesh: noexp] OR randomly [tiab] OR trial [ti]) NOT (animals [mh] NOT humans [mh])

#15 #5 AND #13 AND #14

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Information reported	Page number(s)
ADMINISTRATIVE INFORMATION				
Title:				
Identification	1a	Identify the report as a protocol of a systematic review	√	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	×	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	√	1
Authors:				
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	√	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	√	7
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	×	N/A
Support:				
Sources	5a	Indicate sources of financial or other support for the review	√	7
Sponsor	5b	Provide name for the review funder and/or sponsor	√	7
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	√	7
INTRODUCTION				
Rationale	6	Describe the rationale for the review in the context of what is already known	√	1-2
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	√	1-2
METHODS				
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	√	3-4
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	√	4
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such	√	4;

		that it could be repeated		Appendix 2
Study records:				
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	√	3
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	√	4
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	√	4
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	√	3-5
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	√	3
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	√	4-5
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	√	5
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	√	6
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	√	6
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	√	5
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	√	6
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	√	7

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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The 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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Keywords:	Tension-type headache, Monotherapies, Efficacy, Network meta-analysis

The 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 TTH patients who have limited response to non-pharmacological treatment. However, recommendations about the vast array therapeutic drugs for TTH were partially overlapped and of divergent recommended strength among different guidelines, which may confuse clinicians in medical decision-making. Hence, the aims of this study are to synthesise the available direct and indirect evidence on different drug monotherapies of TTH in adults, and generate a treatment ranking according to their efficacy and safety outcomes using a Bayesian network meta-analysis (NMA).

Methods and analysis We will systematically search Cochrane Library, PubMed, Web of Science, Embase, CBM, ICTRP and other resources for eligible studies. RCTs 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 be conducted afterwards to pool effect measures across all types of monotherapies drug. The ranking probabilities of the efficacy and safety of different drug monotherapies will be estimated. Heterogeneity will be quantified with Q statistic and I^2 index. Inconsistency between direct and indirect evidence will be assessed by the node-splitting model. Additionally, the overall quality of evidence will be assessed by using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) 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.

Strengths and limitations of this study

► This Bayesian network meta-analysis will provide a comprehensive summary of direct and indirect evidence on the efficacy and safety of different drug monotherapies for TTH in adults.

► The relative ranking results of efficacy and safety outcomes will facilitate patients, clinicians and healthcare providers in choosing among the available drug monotherapies by providing the highest level of evidence.

► This protocol is drafted in accordance with PRISMA-P 2015 statement and has been registered with the International Prospective Register of Systematic Reviews (PROSPERO).

► The overall quality of evidence will be assessed by using the GRADE approach.

► This research will exclude non-English, non-Chinese and non-RCT studies, and the publications on combination therapies for TTH will also be limited.

INTRODUCTION

Over the past 25 years, the burden of neurological disease has increased constantly, and neurological diseases have become major cause of disability and death worldwide.[1] Tension-type headache (TTH) is the most prevalent neurological disease, with an estimated 1.5 billion cases globally.[1 2] A TTH is generally a diffuse, mild to moderate pain in the head that's often described as feeling like a tight band around the head. TTH can be associated with considerable disability, low work effectiveness, absenteeism, or decreased learning ability, and may have great impact on the quality of life. [2] Pharmacotherapy should be considered or added to TTH patients who have limited response to non-pharmacological treatment.[3]

Since 1995, TTH have bend divided into episodic TTH (ETTH) and chronic TTH (CTTH) subtypes, introduced in the first edition of International Classification of Headache Disorders (ICHD-I) of International Headache Society (IHS).[4] Our preliminary search found that the recommendations of therapeutic drugs for the ETTH or CTTH patients among different guidelines were wide variety, partially overlapped and of divergent recommended strength (Appendix 1).[5-15] That is, either a same drug was recommended at different strength among guidelines, or different guidelines recommended different pharmaceuticals. For example, ibuprofen and ketoprofen were considered as level A in the EFNS guidelines, however the Italian guidelines suggested these two analgesics at a level of recommendation II. [8 14]

Thus far, the evidence for the acute treatment of ETTH and prophylactic treatment of CTTH of direct head-to-head comparison among all treatments are scarce. Additionally, the conventional pairwise meta-analyses as a mean of summarising evidence would not allow for the inclusion of data that have not been compared head-to-head. Hopefully, previous studies showed that the results from direct evidence combined with indirect can improve accuracy for treatments that have been directly evaluated.[16] Therefore, to assess the interrelations across all treatments, a network meta-analysis (NMA) will be necessary for integration of direct and indirect evidence from multiple treatment comparisons.[17]

The relative efficacy and safety among different types of drugs and between different drugs in the same type on the treatment of ETTH and CTTH are not yet clear. Because of that, clinicians may be confused when making decision on pharmaceuticals. Hence, the aims of this study are to synthesise the available direct and indirect evidence on different drug monotherapies of ETTH and

CTTH in adults, and to generate a treatment ranking according to their efficacy and safety outcomes using a NMA.

METHODS AND ANALYSIS

This protocol is drafted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses protocols (PRISMA-P) 2015 statement.[18] It has been registered with PROSPERO (registration number: CRD42018090554).

Criteria for included studies

Participants and settings

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

The diagnosis criteria of TTH should be developed by professional organizations or agencies (e.g. International Headache Society)[19]. It 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. The studies/trials including participants with 'mixed' or 'combination' TTH and other types of headache will be excluded. Besides, the participants' genders, races, and nationalities will not be limited.

Interventions

In our preliminary studies, we have searched in relevant guideline database, electronic database and websites for guidelines containing ETTH or CTTH drug monotherapies. These monotherapies were extracted to form the "ETTH and CTTH drug monotherapies list" (Table 1).

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

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

Comparators

The comparator(s)/control of 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. The primary safety outcomes will be the incidences of serious adverse events, gastrointestinal adverse reactions and addiction to drugs.

Secondary outcomes

The possible secondary efficacy outcomes are listed as follows: (1) Change in patient-reported headache frequency, duration and intensity; (2) Functional health status and health related quality of life (e.g. SF-36). The possible secondary safety outcomes are listed as follows: (1) Liver-kidney functions indicators; (2) fecal occult blood.

Study designs 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 the publications which 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 (Appendix 2), and revised appropriately for each database. Databases to be searched are as follows: Cochrane Library, PubMed, Web of Science, Embase, China Biomedical Literature Database(CBM), International Clinical Trials Registry Platform (ICTRP). We will also search other resource for eligible studies. The search dates are from the establishment of the respective library to 15 March 2018. Language 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.

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 from additional sources to identify those 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 pre-piloted data extraction form to extract data from the included studies for of the study quality assessment and evidence synthesis. Two authors (RX and YW) will independently extract data from each study using this form. Any disagreement occurred will be resolved by mutual discussion or by referral to a third reviewer for a final decision. Extracted information will include: basic information of study; characteristics of study; details of the intervention and control group; outcomes measures and its 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.[16] Each study will be assessed in the following aspects:

1. Random sequence generation (assessing 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); Unclear risk of bias (insufficient information about the sequence generation process to permit judgement).
2. Allocation concealment (assessing 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); Unclear risk of bias (insufficient information to permit judgement).

3. Blinding of participants and personnel (assessing 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); Unclear risk of bias (insufficient information to permit judgement, or the study did not address this outcome).

4. Blinding of outcome assessment (assessing the domain of Detection bias). We will assess the method used to blind outcome assessors from 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); Unclear risk of bias (insufficient information to permit judgement, or the study did not address this outcome).

5. Incomplete outcome data (assessing 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 true outcome, or missing outcome data enough to induce clinically relevant bias in observed effect size); Unclear risk of bias (insufficient reporting of attrition/exclusions to permit judgement, or the study did not address this outcome).

6. Selective reporting (assessing the domain of Reporting bias). We will assess the possibility of selective outcome reporting was examined by the review authors as: low risk of bias (the study protocol is available and all of the study's pre-specified, 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 study's pre-specified primary outcomes have been reported, or one or more primary outcomes is reported using measurements, analysis methods or subsets of the data that were not pre-specified); Unclear risk of bias (insufficient information to permit judgement).

7. Other sources of bias (assessing 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); 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 summarize the included studies based on study characteristics, patient characteristics, interventions and outcomes measures, and our assessment of risk of bias. If quantitative synthesis is not appropriate, we will describe the results of systematic review.

We will calculate risk ratio (RR) with its 95% CIs for dichotomous data and mean differences (MD) with its 95% CIs for continuous data. Weighted mean differences (WMD) will be used for data measured on the same scale under same units are used. Otherwise, standardised mean differences (SMD) will be used. When lacking head-to head evidence, indirect treatment comparison meta-analysis will be retrieved from available evidence.

We will carry out the NMA in the Bayesian framework using the Markov Chains Monte Carlo (MCMC) 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 with the trace plots, density plots and Brooks-Gelman-Rubin diagnosis plots.[20] In this study, both fixed-effects and random-effects models in the Bayesian NMA will be considered according to the results of deviance information criterion (DIC). Moreover, the ranking probability of the efficacy and safety of different drug monotherapies will be estimated for acute treatment of ETTH and prophylactic treatment of CTTH. The results of rankograms, ranking probabilities plots and evidence network plots will be shown in graphically. Cumulative ranking will be estimate by the surface under the cumulative ranking curve (SUCRA) for each TTH treatment. SUCRA would 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.[21]

Assessment of heterogeneity

Heterogeneity will be quantified with Q statistic and I^2 index. We will consider p <0.1 or $I^2 \geqslant 50\%$ indicative of at least moderate heterogeneity.[22] Under the circumstances, 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 straightforward interpretation, contrasting estimates from both direct and indirect evidence. [23] P <0.05 indicates that there is 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 similar enough to be pooled, akin to meta-analyses.[24] The similarities in clinical and methodological characteristics between studies will be qualitatively compared (e.g. baseline data for patients, trial design, etc.).

Sensitivity analysis

We will assess the robustness of our results through a series of sensitivity analysis. By excluding trials at high risk of bias, removing 1 study at a time iteratively, and using 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 age and route of administration.

Software

The NMA in the Bayesian framework will be conducted using JAGS V.4.2.0, with 'gemtc', 'R2WinBUGS', 'lattice' and 'coda' package in R V.3.4.4.[25]

Assessment of quality of evidence

The overall quality of evidence will be assessed by using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach on the efficacy and safety of different drug monotherapies for TTH in adults. 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; (5) high probability of publication bias.[16]

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 headaches, probably TTH is the most prevalent but the least studied one.[3 26] According to the preliminary search results of guidelines, at least 11 guidelines currently recommend more than 40 different drug monotherapies for the acute treatment of ETTH and prophylactic treatment of CTTH. However, these recommendations cannot provide a clear answer regarding the best choice for initial treatment of ETTH and CTTH due to lack of consistency. Therefore, we have proposed a network meta-analysis to quantitatively synthesise the available direct and indirect evidence on different drug monotherapies of 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 would facilitate patients', clinicians' and healthcare providers' decision-making when treating TTH patients with pharmaceuticals.

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

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

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Disclaimer The funders had no role in the protocol design; the writing of the protocol; or the decision to submit the protocol for publication.

Competing interests The authors declare that they have no competing interests.

Patient consent Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Abbreviations

AAN: American academy of neurology; BASH: British association for the study of headache; CBM: China Biomedical Literature Database; CTTH: Chronic tension-type headache; DIC: Deviance information criterion; EFNS: European federation of neurological societies; EHF: European headache federation; ETTH: Episodic tension-type headache; GRADE: Grading of Recommendations Assessment, Development and Evaluation; ICHD: International classification of headache disorders; ICSI: Institute for clinical systems improvement; ICTRP: International Clinical Trials Registry Platform; IHS: International headache society; MCMC: Markov Chains Monte Carlo; MD: Mean differences; NICE: National institute for health and clinical excellence; NMA: Network meta-analysis; RR: Risk ratio; SIGN: Scottish intercollegiate guidelines network; SISC: Italian society for the study of headaches; SMD: Standardised mean differences; SUCRA: Surface under the cumulative ranking curve; TOP: Toward optimized practice; TTH: Tension-type headache; WMD: Weighted mean differences.

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Table 1 ETTH and CTTH drug monotherapies list

Subtype of TTH	Drug Classification	Drug treatment
ETTH	Non-steroidal anti-inflammatory drugs (NSAIDs)	Aspirin/acetylsalicylic acid
		Acetaminophen/paracetamol
		Lumiracoxib
		Ibuprofen
		Ketoprofen
		Naproxen
		Diclofenac
		Diclofenac-K
		Metamizole/ dipyrone
	Analgesics	Codeine
		Dihydrocodeine
		Dextropropoxyphene
	Antiemetics	Metoclopramide
		Chlorpromazine
	Supplementary	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

Appendix 1 The recommended TTH therapeutic drugs among guidelines

No.	Drug treatment	AAN[1]	BASH[2]	Croatian[3]	EFNS[4]	EHF[5]	French[6]	ICSI[7]	NICE[8]	SIGN[9]	SISC[10]	TOP[11]
1	Aspirin/acetylsalicylic acid		√	√	√	√		√	√	√	√	√
2	Acetaminophen/paracetamol		√	√	√	√		√	√	√	√	√
3	Lumiracoxib										√	
4	Ibuprofen		√	√	√	√	√				√	√
5	Ketoprofen		√	√	√		√				√	
6	Naproxen		√	√	√						√	√
7	Diclofenac			√	√							
8	Diclofenac-K										√	
9	Metamizole/ dipyrone										√	
10	Codeine		×			×						
11	Dihydrocodeine		×			×						
12	Dextropropoxyphene					×						
13	Metoclopramide										√	
14	Chlorpromazine										√	
15	Tiger balm										√	
16	Amitriptyline		√	√	√	√		√		√	√	√
17	L-5-hydroxytryptophan										√	
18	Fluvoxamine										√	
19	Venlafaxine			√	√			√			√	√
20	Clomipramine				√						√	
21	Mirtazapine			√	√						√	√
22	Maprotiline				√						√	

No.	Drug treatment	AAN[1]	BASH[2]	Croatian[3]	EFNS[4]	EHF[5]	French[6]	ICSI[7]	NICE[8]	SIGN[9]	SISC[10]	TOP[11]
23	Mianserin				√						√	
24	Desipramine										√	
25	Fluoxetine										√	
26	Paroxetine										√	
27	Nefazodone										√	
28	Ritanserin										√	
29	Sulpiride										√	
30	Dothiepin/prothiaden		√									
31	Nortriptyline		√			√						√
32	Protriptyline		√									
33	Sodium valproate			√								
34	Topiramate			√							√	
35	Gabapentin			√								
36	Levetiracetam			√								
37	Diazepam/valium										√	
38	Alprazolam										√	
39	Buspirone										√	
40	Tizanidine										√	
41	Cyclobenzaprine										√	
42	Botulinum toxin A/OnabotulinumtoxinA	×	×			×				×		

Abbreviations: AAN, American academy of neurology; BASH, British association for the study of headache; EFNS, European federation of neurological societies; EHF, European headache federation; ICSI, Institute for clinical systems improvement; NICE, National institute for health and clinical excellence; SIGN, Scottish intercollegiate guidelines network; SISC, Italian society for the study of headaches; TOP, Toward optimized practice; "√" indicates recommendation; "×" indicates not recommendation;

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Appendix 2 PubMed Search Strategy (illustrated by the example of aspirin)

#1 " aspirin " [Title/Abstract]

#2 " Aspirin "[Mesh]

#3 " acetylsalicylic acid " [Title/Abstract]

#4 " Acetylsalicylic acid "[Mesh]

#5 #1 OR #2 OR #3 OR #4

#6 "Tension-Type Headache"[Mesh]

#7 Psychogenic Headache[Title/Abstract]

#8 Tension-TypeHeadache*[Title/Abstract]

#9 Stress Headache*[Title/Abstract]

#10 Tension Headache*[Title/Abstract]

#11 PsychogenicHeadache*[Title/Abstract]

#12 Tension-VascularHeadache*[Title/Abstract]

#13 #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12

#14 (randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR clinical trials as topic [mesh: noexp] OR randomly [tiab] OR trial [ti]) NOT (animals [mh] NOT humans [mh])

#15 #5 AND #13 AND #14

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Information reported	Page number(s)
ADMINISTRATIVE INFORMATION				
Title:				
Identification	1a	Identify the report as a protocol of a systematic review	√	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	×	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	√	1
Authors:				
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	√	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	√	7
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	×	N/A
Support:				
Sources	5a	Indicate sources of financial or other support for the review	√	7
Sponsor	5b	Provide name for the review funder and/or sponsor	√	7
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	√	7
INTRODUCTION				
Rationale	6	Describe the rationale for the review in the context of what is already known	√	1-2
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	√	1-2
METHODS				
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	√	3-4
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	√	4
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such	√	4;

		that it could be repeated		Appendix 2
Study records:				
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	√	3
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	√	4
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	√	4
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	√	3-5
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	√	3
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	√	4-5
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	√	5
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	√	6
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	√	6
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	√	5
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	√	6
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	√	7

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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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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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 analyze 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, CBM, ICTRP, and other resources for eligible studies. RCTs 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 by using the Q statistic and the I^2 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 by using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) 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.

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 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 PRISMA-P 2015 statement and has been registered with the International prospective register of systematic reviews (PROSPERO).

► The overall quality of evidence will be assessed by using the GRADE approach.

► This research will exclude non-English, non-Chinese and non-RCT studies, and the publications investing combination therapies for TTH will also be limited.

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.[1] Tension-type headache (TTH) is the most prevalent neurological disease, with an estimated 1.5 billion cases globally.[1 2] 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 patient quality of life.[2] Pharmacotherapy should be considered or added for patients with TTH who show a limited response to non-pharmacological treatment.[3]

Since 1995, TTHs have been divided into episodic TTH (ETTH) and chronic TTH (CTTH) subtypes; these were introduced in the first edition of International Classification of Headache Disorders (ICHD-I) of International Headache Society (IHS).[4] Our preliminary search found that the recommendations for therapeutic drugs for patients with ETTH or CTTH variety widely between different guidelines, partially overlapped, and exhibited variation in recommended strength (Appendix 1).[5-15] 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 (EFNS) guidelines, although the Italian guidelines suggested these two analgesics were at the level recommendation II.[8 14]

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 summarizing evidence do not allow for the inclusion of data that have not been included 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.[16] 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.[17]

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 synthesize 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 Reviews and Meta-Analyses Protocols (PRISMA-P) 2015 statement.[18] It has been registered with PROSPERO (registration number: CRD42018090554).

Criteria for included studies

Participants and settings

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

The diagnosis criteria for TTH should be developed by professional organizations or agencies (e.g., the International Headache Society)[19]; 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 analyzed. Studies and trials including participants with “mixed” or “combination” TTH and other types of headache will be excluded. There will be no limitations on the participants’ genders, races, and nationalities.

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 form 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 (VAS). The primary safety outcomes will be the incidence of serious 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; (2) Functional health status and health-related quality of life (e.g., SF-36). The possible secondary safety outcomes are: (1) Liver-kidney function indicators; (2) fecal occult blood.

Study designs and publication types

Randomized 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 (Appendix 2), with appropriately revisions for each database. The following databases will be searched: Cochrane Library, PubMed, Web of Science, Embase, China Biomedical Literature Database (CBM), International Clinical Trials Registry Platform (ICTRP). 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.

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 pre-piloted data extraction form to extract data from the included studies for the study quality assessment of the study and evidence synthesis. Using this form, two authors (RX and YW) will independently extract data from each study. Any disagreement 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 study; details of the intervention and control group; outcomes measures and its 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.[16]

Each study will be assessed for 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 pre-specified, 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 pre-specified primary outcomes of the study have been reported, or one or more primary outcomes are reported by using measurements, analysis methods or subsets of the data that were not pre-specified); 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 summarize 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 (RR) and its 95% CIs for dichotomous data, and the mean differences (MD) with 95% CIs for continuous data. Weighted mean differences (WMD) will be used for data measured on the same scale with the same units; otherwise, standardized mean differences (SMD) 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 by using the Markov Chains Monte Carlo (MCMC) 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 by using trace plots, density plots, and Brooks-Gelman-Rubin diagnosis plots.[20] 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 (DIC). 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.[21]

Assessment of heterogeneity

Heterogeneity will be quantified with Q statistic and I^2 index. We will consider $p < 0.1$ or $I^2 \geqslant 50\%$ indicative of at least moderate heterogeneity.[22] 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 straightforward interpretation, contrasting estimates from both direct and indirect evidence. [23] 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.[24] 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 by using JAGS (Version 4.2.0), with 'gemtc', 'R2WinBUGS', 'lattice', and 'coda' packages in R (Version 3.4.4).[25]

Assessment of quality of evidence

The overall quality of evidence will be assessed by using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) 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.[16]

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.[3 26] 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 a network meta-analysis to quantitatively synthesize 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 the publications of combination therapy for TTH, which may affect the generalizability of this study.

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

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Abbreviations

AAN: American academy of neurology; BASH: British association for the study of headache; CBM: China Biomedical Literature Database; CTTH: Chronic tension-type headache; DIC: Deviance information criterion; EFNS: European federation of neurological societies; EHF: European headache federation; ETTH: Episodic tension-type headache; GRADE: Grading of Recommendations Assessment, Development and Evaluation; ICHD: International classification of headache disorders; ICSI: Institute for clinical systems improvement; ICTRP: International Clinical Trials Registry Platform; IHS: International headache society; MCMC: Markov Chains Monte Carlo; MD: Mean

differences; NICE: National institute for health and clinical excellence; NMA: Network meta-analysis; RR: Risk ratio; SIGN: Scottish intercollegiate guidelines network; SISC: Italian society for the study of headaches; SMD: Standardised mean differences; SUCRA: Surface under the cumulative ranking curve; TOP: Toward optimized practice; TTH: Tension-type headache; VAS: Visual analogue scale; WMD: Weighted mean differences.

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Table 1 ETTH and CTTH drug monotherapies list

Subtype of TTH	Drug Classification	Drug Treatment
ETTH	Non-steroidal anti-inflammatory drugs (NSAIDs)	Aspirin/acetylsalicylic acid
		Acetaminophen/paracetamol
		Lumiracoxib
		Ibuprofen
		Ketoprofen
		Naproxen
		Diclofenac
		Diclofenac-K
		Metamizole/ dipyrone
	Analgesics	Codeine
		Dihydrocodeine
		Dextropropoxyphene
	Antiemetics	Metoclopramide
		Chlorpromazine
	Supplementary	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

Appendix 1 The recommended TTH therapeutic drugs among guidelines

No.	Drug treatment	AAN[1]	BASH[2]	Croatian[3]	EFNS[4]	EHF[5]	French[6]	ICSI[7]	NICE[8]	SIGN[9]	SISC[10]	TOP[11]
1	Aspirin/acetylsalicylic acid		√	√	√	√		√	√	√	√	√
2	Acetaminophen/paracetamol		√	√	√	√		√	√	√	√	√
3	Lumiracoxib										√	
4	Ibuprofen		√	√	√	√	√				√	√
5	Ketoprofen		√	√	√		√				√	
6	Naproxen		√	√	√						√	√
7	Diclofenac			√	√							
8	Diclofenac-K										√	
9	Metamizole/ dipyrone										√	
10	Codeine		×			×						
11	Dihydrocodeine		×			×						
12	Dextropropoxyphene					×						
13	Metoclopramide										√	
14	Chlorpromazine										√	
15	Tiger balm										√	
16	Amitriptyline		√	√	√	√		√		√	√	√
17	L-5-hydroxytryptophan										√	
18	Fluvoxamine										√	
19	Venlafaxine			√	√			√			√	√
20	Clomipramine				√						√	
21	Mirtazapine			√	√						√	√
22	Maprotiline				√						√	

No.	Drug treatment	AAN[1]	BASH[2]	Croatian[3]	EFNS[4]	EHF[5]	French[6]	ICSI[7]	NICE[8]	SIGN[9]	SISC[10]	TOP[11]
23	Mianserin				√						√	
24	Desipramine										√	
25	Fluoxetine										√	
26	Paroxetine										√	
27	Nefazodone										√	
28	Ritanserin										√	
29	Sulpiride										√	
30	Dothiepin/prothiaden		√									
31	Nortriptyline		√			√						√
32	Protriptyline		√									
33	Sodium valproate			√								
34	Topiramate			√							√	
35	Gabapentin			√								
36	Levetiracetam			√								
37	Diazepam/valium										√	
38	Alprazolam										√	
39	Buspirone										√	
40	Tizanidine										√	
41	Cyclobenzaprine										√	
42	Botulinum toxin A/OnabotulinumtoxinA	×	×			×				×		

Abbreviations: AAN, American academy of neurology; BASH, British association for the study of headache; EFNS, European federation of neurological societies; EHF, European headache federation; ICSI, Institute for clinical systems improvement; NICE, National institute for health and clinical excellence; SIGN, Scottish intercollegiate guidelines network; SISC, Italian society for the study of headaches; TOP, Toward optimized practice; "√" indicates recommendation; "×" indicates not recommendation;

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Appendix 2 PubMed Search Strategy (illustrated by the example of aspirin)

#1 " aspirin " [Title/Abstract]

#2 " Aspirin "[Mesh]

#3 " acetylsalicylic acid " [Title/Abstract]

#4 " Acetylsalicylic acid "[Mesh]

#5 #1 OR #2 OR #3 OR #4

#6 "Tension-Type Headache"[Mesh]

#7 Psychogenic Headache[Title/Abstract]

#8 Tension-TypeHeadache*[Title/Abstract]

#9 Stress Headache*[Title/Abstract]

#10 Tension Headache*[Title/Abstract]

#11 PsychogenicHeadache*[Title/Abstract]

#12 Tension-VascularHeadache*[Title/Abstract]

#13 #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12

#14 (randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR clinical trials as topic [mesh: noexp] OR randomly [tiab] OR trial [ti]) NOT (animals [mh] NOT humans [mh])

#15 #5 AND #13 AND #14

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Information reported	Page number(s)
ADMINISTRATIVE INFORMATION				
Title:				
Identification	1a	Identify the report as a protocol of a systematic review	√	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	×	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	√	1
Authors:				
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	√	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	√	7
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	×	N/A
Support:				
Sources	5a	Indicate sources of financial or other support for the review	√	7
Sponsor	5b	Provide name for the review funder and/or sponsor	√	7
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	√	7
INTRODUCTION				
Rationale	6	Describe the rationale for the review in the context of what is already known	√	1-2
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	√	1-2
METHODS				
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	√	3-4
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	√	4
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such	√	4;

		that it could be repeated		Appendix 2
Study records:				
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	√	3
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	√	4
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	√	4
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	√	3-5
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	√	3
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	√	4-5
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	√	5
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	√	6
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	√	6
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	√	5
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	√	6
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	√	7

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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