PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Efficacy and safety of different drug monotherapies for tension-type headache in adults: Study protocol for a Bayesian network meta-analysis
AUTHORS	Xie, Runsheng; Tian, Jinhui; Wang, Yangyang; Cai, Yefeng; Li, Hui

VERSION 1 – REVIEW

REVIEWER	Wei WANG Dept Clinical Psychology and Psychiatry, Zhejiang University College of Medicine, Hangzhou, China
REVIEW RETURNED	08-May-2018

GENERAL COMMENTS	The authors would like to analyze the efficacy and safety of different monotherapies for tension-type headaches, using available published data and a Bayesian model. The idea is nice but it is less than clinically-needed in practice. 1. Tension-type headache patients not only suffer from head pain, but were from psychiatric/ psychological comorbidities or consequences. Therefore, monotherapy does rarely work well, and pain relief medication has connection with addiction and somatic (GUT) dysfunctions. 2. In clinics, prophylactic therapies and pain-reliefs can be delivered to patients as combination. The authors might design the comparisons of these mixed therapies with different monotherapies. In the treatments of CTTH, cognitive-behavioral therapy is one excellent management. 3. For the diagnoses, CTTH should be compared with episodic tension-type headache and migraine or other primary headaches. The efficacy and safety of these therapies might be compared with these primary headaches.

REVIEWER	Jeffrey L Jackson Medical College of Wisconsin, USA
REVIEW RETURNED	18-May-2018

GENERAL COMMENTS	The problem with the author's suggested approach is the dearth of studies on tension-type headache. I several systematic reviews that I have conducted, the number of studies that focus on tension-type headache are too few to support a network meta-analysis. My publication of a network meta-analysis for migraine headaches was not followed up by a network meta-analysis on tension-type headache because there were simply too few studies. (Jackson JL, Cogbill E, Santana-Davila R, Eldredge C, Gradall A, Sehgal N, Collier W, Kuester J. A comparative effectiveness meta-analysis of commonly prescribed drugs for the prophylaxis of migraine

	headache. Plos One. 2015 Jul 14;10(7):e0130733. doi: 10.1371/journal.pone.0130733). Consequently I am pessimistic that the authors will be able to conduct this study. The process they outline is fine, the methods are sound and the writing clear.

VERSION 1 – AUTHOR RESPONSE

Response to the reviewers' comments:

Thanks for your valuable suggestions on our paper. We have carefully read through the comments and made proper revisions. Our responses to the reviewer's comments are listed below. Several repetitive presentations were deleted, grammar and spelling errors corrected.

Reviewer #1

Comment 1: Tension-type headache patients not only suffer from head pain, but were from psychiatric/ psychological comorbidities or consequences. Therefore, monotherapy does rarely work well, and pain relief medication has connection with addiction and somatic (GUT) dysfunctions.

***Response*:** Thank you for your comment. Previous studies showed that different drug monotherapies had a certain headache relief effect on the treatment of ETTH and CTTH patients (e.g. ibuprofen, acetaminophen, ketoprofen and amitriptyline).[1-4] Moreover, these drugs are also the recommended drugs for the therapy of TTH in some guidelines.[5] Although TTH patients may manifest other concomitant symptoms, relieving headaches are a more urgent concern for TTH patients. Hence, the comparison and selection of different analgesic drugs is particularly important. Taking pain relief medications on the long-term may cause addiction and other adverse events in TTH patients, which are also one of the pharmaceutical safety issue we plan to look into in our research. From a different perspective, reducing the number of treatments, and more rational administration of analgesics, both of which monotherapy encourages, may help to reduce addiction.

1. Packman E, Leyva R, Kellstein D. Onset of analgesia with ibuprofen sodium in tension-type headache: a randomized trial. *J Pharm Health Care Sci* 2015;2:1-13.
2. Prior MJ, Cooper KM, May LG, Bowen DL. Efficacy and safety of acetaminophen and naproxen in the treatment of tension-type headache. A randomized, double-blind, placebo-controlled trial. *Cephalalgia* 2002;22:740-8.
3. Steiner TJ, Lange R. Ketoprofen (25 mg) in the symptomatic treatment of episodic tension-type headache: double-blind placebo-controlled comparison with acetaminophen (1000 mg). *Cephalalgia* 1998;18:38-43.
4. Göbel H, Hamouz V, Hansen C, Heininger K, Hirsch S, Lindner V, Heuss D, Soyka D. Chronic tension-type headache: amitriptyline reduces clinical headache-duration and experimental pain sensitivity but does not alter pericranial muscle activity readings. *Pain* 1994;59:241-9.
5. Bendtsen L, Evers S, Linde M, *et al*. EFNS guideline on the treatment of tension-type headache - report of an EFNS task force. *Eur J Neurol* 2010;17:1318-25.

Comment 2: In clinics, prophylactic therapies and pain-reliefs can be delivered to patients as combination. The authors might design the comparisons of these mixed therapies with different monotherapies. In the treatments of CTTH, cognitive-behavioral therapy is one excellent management.

***Response*:** Thank you for your comment. According to the recommendations of the guidelines, non-pharmacologic treatments are also helpful to TTH patients (e.g. regular exercise, physiotherapy and meditation).[1 2] Moreover, cognitive therapies and acupuncture may be worth trying if all else fails.[2] In our opinion, it is a relatively complicated and challenging task to study the comparisons of mixed therapies with different monotherapies, since the relative efficacy and safety among different monotherapies are clear yet. Therefore, the aims of this study are focused on clarifying the relationship between different monotherapies treatments of TTH. Above all, we would like to thank you again for providing these important ideas for our future research.

1. Bendtsen L, Evers S, Linde M, *et al*. EFNS guideline on the treatment of tension-type headache - report of an EFNS task force. *Eur J Neurol* 2010;17:1318-25.
2. British Association for the Study of Headache (BASH). *Guidelines for all healthcare professionals in the diagnosis and management of migraine, tension-type, cluster and medication-overuse headache*. 3rd ed. 2007.

Comment 3: For the diagnoses, CTTH should be compared with episodic tension-type headache and migraine or other primary headaches. The efficacy and safety of these therapies might be compared with these primary headaches.

***Response*:** Thank you for your suggestion. The relevant guidelines and studies have shown that the drugs involved in this study have a certain effect on a variety of primary headaches. Therefore, it is a good research idea to compare the efficacy and safety of these drugs treating different primary headaches. However, due to limited time and resources, we prioritize TTH patients in our studies. As the manuscript mentioned, the diagnosis criteria of TTH should clearly separate TTH into ETTH and CTTH and reasonably distinguish TTH from other headache types.

Reviewer #2

Comment 1: The problem with the author's suggested approach is the dearth of studies on tension-type headache. I several systematic reviews that I have conducted, the number of studies that focus on tension-type headache are too few to support a network meta-analysis. My publication of a network meta-analysis for migraine headaches was not followed up by a network meta-analysis on tension-type headache because there were simply too few studies. (Jackson JL, Cogbill E, Santana-Davila R, Eldredge C, Gradall A, Sehgal N, Collier W, Kuester J. A comparative effectiveness meta-analysis of commonly prescribed drugs for the prophylaxis of migraine headache. Plos One. 2015 Jul

14;10(7):e0130733. doi: 10.1371/journal.pone.0130733). Consequently I am pessimistic that the authors will be able to conduct this study. The process they outline is fine, the methods are sound and the writing clear.

***Response*:** Thank you for your comments and recognitions. Based on your experience, it seems that it is difficult to carry out a network meta-analysis for studies focusing on tension-type headache are too few. However, our preliminary searches found nearly 3000 articles, which brought possibility that we may be able to continue this study.

Considering the number of final articles that may be eligible for inclusion exclusion is uncertain. As was stated in our manuscript, we will take some countermeasures (Page 5, line 46-47, 52-53). When head-to head evidence is in lack, indirect treatment comparison meta-analysis will be performed basing on available evidence. If quantitative synthesis is not appropriate, we will alternatively describe the results of systematic review.