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Research article

Efficacy and safety of Chinese patent medicines for tension-type headache: Systematic review and network meta-analysis

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ABSTRACT

Objective: The high incidence of Tension-type headache (TTH) has led to significant social and economic challenges. Given the widespread use of Chinese patent medicines (CPM) for TTH patients, this study aim to evaluate the efficacy of different CPMs in treating TTH by network meta-analysis.
Methods: Eight databases were conducted to identify CPMs-related randomized controlled trials (RCTs) from database inception date to August 2023. The primary outcome was clinical efficiency rate. The secondary outcomes were numerical rating scale (NRS), frequency of headache, duration of headache, hamilton anxiety scale (HAMA), hamilton depression Scale (HAMD) and adverse reactions. ROB 2.0 were used for quality evaluation. Stata 15.1 and R 3.5.3 software were used for Bayesian network meta-analysis.
Results: A total of forty-one RCTs were included, involving 3,996 patients and 8 CPMs. The network meta-analysis revealed that Shugan Jieyu capsule plus western medicine (WM) was the best choice of CPM for improving clinical efficiency rate [vs. WM: relative risk (RR) = 7.31, 95 % confidence interval (CI): (1.65, 56.71)]. Yangxue Qingnao granule plus WM was superior to other therapeutic combinations in reducing duration of headache [vs. WM: MD = 1.05, 95%CI(0.74, 1.40)]. Jieyu pill plus WM might have best effect in reducing HAMD [vs. WM: MD = 7.15, 95%CI (-3.77, 18.14)], HAMA scores [vs. WM: MD = −7.41, 95%CI(-13.39, −1.42)], and NRS scores [vs. WM: mean difference (MD) = 2.01, 95%CI(1.47, 2.55)]. In terms of the frequency of headache, although Yangxue Qingnao granule plus WM and Toutong-ning capsule plus WM performed best, the optimal CPMs in reducing the frequency of headache remain to be further explored. Furthermore, due to the limited safety evidence available, reliable safety conclusions could not be drawn.
Conclusion: CPM can effectively improve headache symptoms, clinical efficiency, and quality of life in patients with TTH. However, research with high quality and large sample sizes is needed for further investigation due to the limitations of this study.

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1. Introduction

Tension-type headache (TTH) is one of the most prevalent headache type, which affect about 1.89 billion people each year [1]. Patients with TTH usually suffer from a mild to moderate sensation of constriction or tightness on both sides of the head, and are often accompanied by photophobia or phonophobia [2,3]. Available data indicated that the global prevalence of TTH is about 42 % in adults and 30 %–78 % in the general population [4]. In particular, the incidence of TTH among women is higher than that of men, and women's average course of disease is longer than that of men. In the Global Burden of Disease Survey, headache is listed as a key reason for the increasing global burden of disease [4]. Furthermore, A study on the global burden of disease showed that of the eight major chronic diseases affecting the world's population, tension headaches ranked second [5]. It is worth noting that the global prevalence of TTH has increased at a rate of 15.3 % over the past decade. In addition, TTH places a heavy economic burden on society and disrupts daily work and life activities, greatly affecting physical and mental health, such as emotion, sleep and cognition [6]. In view of the high incidence and high economic burden, TTH has become one of the most important diseases threatening human health.

The pathogenesis of TTH may be related to psychological factors, peripheral and central mechanisms, but its specific pathophysiological mechanism needs to be further explored [7]. The incomplete understanding of the pathophysiology may explain the limited pharmacological options for TTH. Symptomatic treatment remains the mainstay of TTH management, such as improving emotional burden and reducing headache frequency, intensity, and duration. Commonly used treatments include nonsteroidal anti-inflammatory drugs (NSAIDs) (e.g., ibuprofen), tricyclic antidepressants (e.g., amitriptyline), and muscle relaxants (e.g., epiloxone) [8,9]. Although the use of these drugs has a certain effect on the treatment of TTH, the side effects of long-term use are obvious, and it is easy to relapse or even worsen after stopping the drug [6]. Notably, the survey revealed that TTH patients who experienced frequent headache, were more prone to take medication in excess, and increased the risk of developing medication overuse headache [10]. In this sense, it is of great clinical significance to explore additional therapies in the treatment of TTH.

In the theory of traditional Chinese medicine, TTH belongs to the category of "headache" or "head wind", which is divided into external headache or internal injury headache. With thousands of years of practical, traditional Chinese medicine has accumulated rich clinical experience in treatment of TTH, and has created many effective and safe therapeutic methods [11]. CPM is a kind of traditional Chinese medicine preparation based on the theory of traditional Chinese medicine, which has good therapeutic effect in treating TTH [12,13]. The main CPMs include Toutong-ning (TTN) capsule and Yangxue Qingnao (YXQN) granule, which have good therapeutic effect on alleviating TTH headache [14,15]. However, the lack of direct comparative evidence among different CPMs is not conducive to clinical drug selection, which significantly limits their reliability and popularization in clinical practice [11].

This study will strictly follow the Preferred Reporting Program of systematic review and meta-analysis (PRISMA) [16] (Supplementary Table S1), and use Bayesian network meta-analysis (NMA) to evaluate the effects of CPMs on headache parameters and quality of life in TTH patients, so as to provide evidence for clinical treatment.

2. Methods

This systematic review has been registered in the International Prospective Register of Systematic Reviews (PROSPERO) (number CRD42023399606).

2.1. Search strategy

A comprehensive search for all relevant studies was performed in China Biomedical Literature Service System, the Chinese Science and Technology Journals Database (VIP), China National Knowledge Infrastructure (CNKI), Wanfang Data, PubMed, Embase, CENTRAL, and Web of Science from database inception date to August 2023 by two researchers (Menglong Shi and Yazi Zhang). No language or geographical areas restrictions were put in place. The search strategy is provided in Supplementary Table S2.

2.2. Inclusion criteria

2.2.1. Types of participants

Patient with TTH meeting accepted diagnostic criteria were included [17–20] without age, sex, race, complications, or type of dyslipidemia restriction.

2.2.2. Types of interventions

Patients in the experimental group were treated with CPM based on routine western medicine (WM) treatment. Patients in control group were treated with WM, or another CPM different from the experiment group. The WMs including NSAIDs, tricyclic antidepressants, and muscle relaxants were consistent between groups. CPMs need to be approved by China's National Medical Products Administration.

2.2.3. Outcomes measures

The primary outcome was clinical efficiency rate. The secondary outcomes were numerical rating scale (NRS), headache frequency, headache duration, hamilton anxiety scale (HAMA), hamilton depression scale (HAMD) and adverse reactions.

2.2.4. Studies design

Randomized control trials (RCTs).

2.3. Exclusion criteria

[1] Any study which is not RCTs, such as case reports, animal studies, or reviews [2]; Patients received other traditional Chinese treatments such as acupuncture or cupping [3]; Studies that contained incomplete data [4]; Duplicate published studies [5]; Secondary headache from other causes.

2.4. Research screening and data extraction

Based on the inclusion and exclusion criteria, two authors (Menglong Shi and Yazi Zhang) independently screened studies and extracted the following information [1]: basic information: author, and publication year [2]; sample characteristics: sample size, average age, duration of treatment [3]; outcomes measures: clinical efficiency rate, NRS, headache frequency, headache duration, HAMA, HAMD and adverse reactions. Any disagreements were resolved through discussion with the third researcher (Lujia Cao).

2.5. Risk of bias

The assessment of the risk of bias was conducted using the revised Cochrane risk of bias tool for randomized trials 2.0 (ROB 2.0) by two researchers (Menglong Shi and Tianye Sun). This scale evaluated six domains: randomization process, deviations from the intended interventions, missing outcome data, measurement of the outcome, selection of the reported outcome, and overall bias. Any disagreements were resolved through discussion with the third researcher (Lujia Cao).

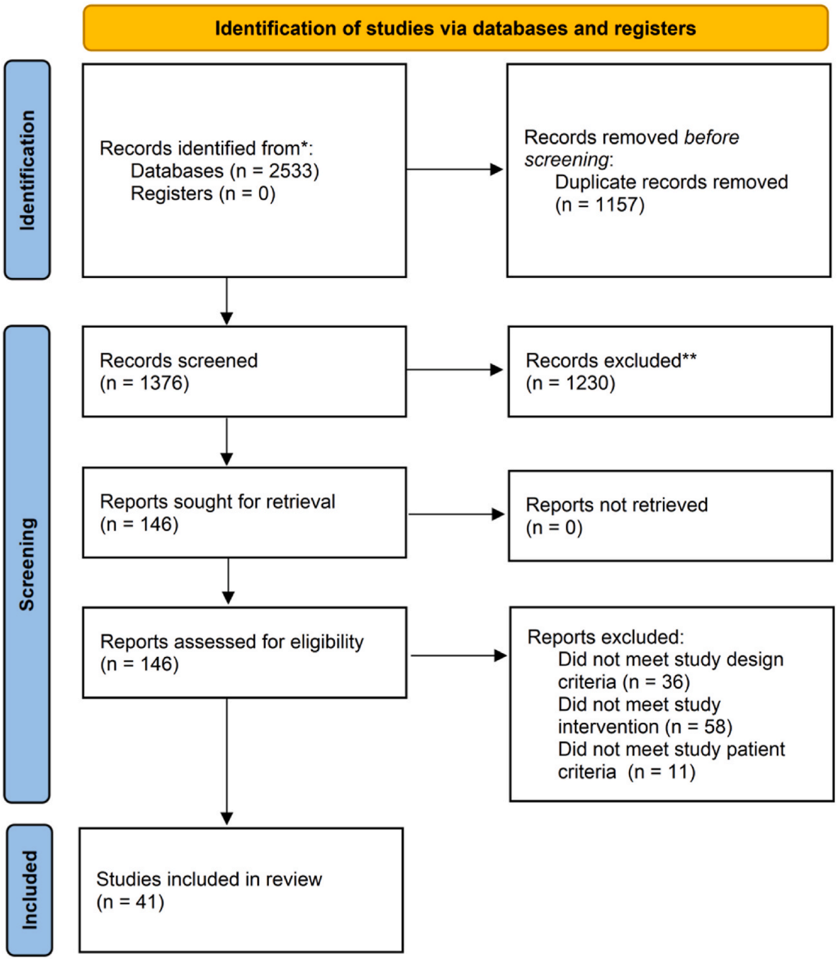

Fig. 1. Flow diagram of study selection process.

2.6. Data synthesis and analysis

R 3.5.3 and Stata 15.1 were used for statistical analysis. The effect value of dichotomous data was calculated by relative risk (RR), and the effect value of continuous data was calculated by mean difference (MD). Confidence intervals (CIs) were set at 95 %. This study was carried out using a Bayesian framework and a Monte Carlo Markov Chain (MCMC) model. The number of model chains was 4, the number of initial iterations was 20,000, the number of updated iterations was 50,000. The model convergence was suggested to be satisfactory when the potential scale reduction factor (PSRF) tended to 1. Stata15.1 was used to construct Network diagrams. Surface under the cumulative ranking curve (SUCRA) were used to predict and assess the efficiency and safety of each CPM. Important principles in NMA included transitivity, homogeneity and consistency. Transitivity was estimated by comparing the basic information of included studies. The consistency of NMA was evaluated locally (node-splitting approach) or globally (design-by-treatment model). Furthermore, heterogeneity was assessed using the inconsistency index (I^2) and Cochran Q test. If $I^2 > 50$ % and $p < 0.05$, the random-effects model would be selected for result synthesis; otherwise, the fixed-effects model was selected. The funnel plot was drawn to assess the small sample effects and publication bias. In addition, sensitivity analysis was performed to assess the stability of network meta-analysis results.

3. Results

3.1. Literature selection

A total of 2533 studies were initially searched. Among them, 1157 duplicate literature were removed, and 1230 literature were removed after reading the title or abstract. The remaining 146 literature were reviewed in full-text, of which 105 were excluded, and 41 studies [21–61] were included in the final review. The process of literature selection is presented in Fig. 1.

3.2. Studies characteristics

In total, 41 studies involving 3996 patients were included, with 2013 patients in the treatment group and 1983 patients in the control group, all participants were Chinese. The treatment duration for all studies spanned from 1 to 12 weeks, and the age of participants spanned from 18 to 68 years old. Furthermore, all the studies employed a two-arm design. Eight types of CPMs were incorporated, including Yangxue Qingnao (YXQN) granules, Danzhen Toutong (DZ) capsules, Duliang-ruan (DL) capsules, Shugan Jieyu (SGJY) capsules, Tianshu (TS) capsules, JeYu (JY) pills, Wuling (WL) capsules and Toutong-ning (TTN) capsules. The characteristics of the included studies were indicated in Table 1. Supplementary Table S3 presents the specific information of all included CPMs.

Fig. 2. Risk of bias assessment for included studies. (A) Risk of bias summary. (B) Risk of bias graph.

3.3. Quality assessment

As shown in Fig. 2A and B. Among the 41 studies included, 11 RCTs [21–24,39,41,43,48,50,52,53] reported details about the randomization methods; while 3 RCTs [34,36,55] were evaluated as high risk because patients may have been grouped according to physician preferences. In addition, The remaining studies had inadequately reported methods of random sequence generation and were evaluated as unclear. Notable, all studies did not provide details of allocation concealment and outcome assessment. 1 study [32] implemented a double-blind method and was evaluated as low risk. Furthermore, 4 RCTs [25,27,55,60] described withdrawals and dropouts, of which 3 RCTs [25,27,55] did not give the reason of dropout and were evaluated as unclear, 1 RCT [60] was evaluated as high risk because of the data missing percentage exceeding 10 %. All studies published complete data regarding the outcomes.

3.4. Evidence network and transitivity assessment

The network diagrams were shown in Fig. 3. A total of 8 interventions constituted the analysis network for clinical efficiency rate (Fig. 3A). A total of 7 interventions constituted the analysis network for NRS (Fig. 3B), HAMD (Fig. 3F) and HAMA (Fig. 3E), respectively. Furthermore, the analysis of headache frequency involved 5 interventions (Fig. 3C), and the analysis of headache duration involved 4 interventions (Fig. 3D). In terms of transitivity, no significant difference were found in the characteristics of all studies. The measurement methods of all outcome indicators were adequate to the statistical pool except for the adverse reactions. Comprehensive networks could be built for outcomes.

3.5. Heterogeneity and inconsistency assessment

The heterogeneity of the clinical efficiency rate was small and the fixed-effects model was chosen for analysis. However, due to the high heterogeneity, the random-effects model was used to analysis NRS, headache frequency, headache duration, HAMA and HAMD. The results of heterogeneity test were illustrated in Supplementary Fig. S1. A closed-loop was found in the network diagrams of clinical efficiency rate, and we used node-splitting method to evaluate the inconsistency. As shown in Supplementary Fig. S2, all p-values were greater than 0.05, indicating that there was no inconsistency between the direct and indirect estimates. Furthermore, the results of PSRF indicating a good convergence of this NMA (Supplementary Fig. S3).

3.6. Primary outcomes

3.6.1. Clinical efficiency rate

A total of 34 studies including 9 interventions and 3,366 patients reported clinical efficiency rate. The results were shown in Table 2. In terms of the clinical efficiency rate, SGJY plus WM (RR = 7.31, 95%CI:1.65 to 56.71), TTN plus WM(RR = 4.50, 95%CI: 3.11 to 6.62), YXQN plus WM (RR = 4.48, 95%CI: 2.94 to 6.97), TS plus WM (RR = 3.83, 95%CI: 1.01 to 19.77), DZ plus WM (RR = 3.63, 95%CI: 1.61 to 8.85), and DL plus WM (RR = 2.93, 95%CI: 1.75 to 4.96) were better than WM group. Statistical differences were also found in the CPM groups, and TTN plus WM (RR = 2.36, 95%CI: 1.03 to 5.34) was better than Wuling capsule group. According to the ranking probability and SUCRA values (Fig. 4A and Table 3), the SGJY plus WM (SUCRA 81.9 %) group performed best in improving clinical efficiency rate, followed by TTN plus WM (SUCRA 70.5 %), YXQN plus WM (SUCRA 69.8 %), TS plus WM (SUCRA 58.1 %), DZ plus WM (SUCRA 55.6 %), DL plus WM (SUCRA 40.9 %), and WL plus WM (SUCRA 22.3 %), while the WM group had the

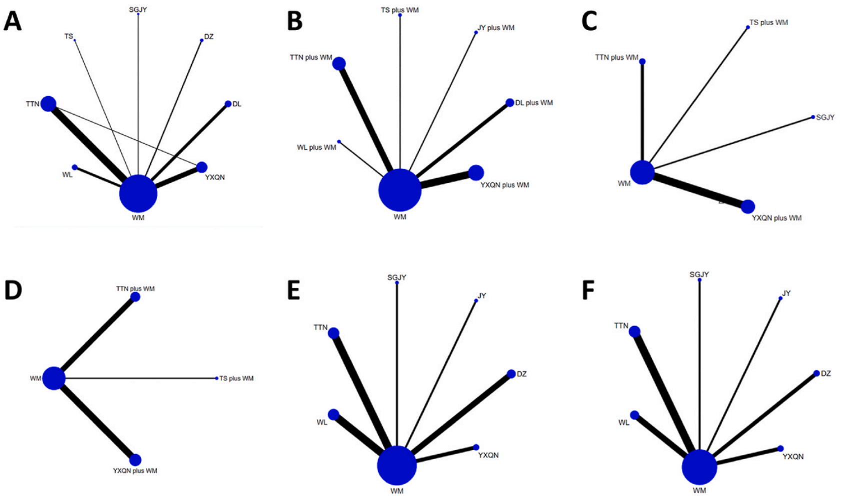

Fig. 3. Network graph of different interventions for outcomes. (A) Clinical efficiency rate; (B) Numerical rating scale (NRS); (C) Headache frequency; (D) Headache duration; (E) Hamilton Anxiety Scale (HAMA); (F) Hamilton depression scale (HAMD).

Table 1
Characteristics of the included studies.

1st author	Sample size		Gender (M/F)		Age (Mean ± SD)		Interventions	Diaereses duration	Outcomes
	T	C	T	C	T	C			
Zhan et al. (2019)	30	30	17/13	16/14	40.38 ± 6.57	41.25 ± 7.03	DZ 2g/tid plus WM *vs.* WM	4 weeks	①⑤⑥⑦
Ji et al. (2017)	75	63	36/39	30/33	48.0 ± 5.8	46.0 ± 6.3	DZ 2g/tid plus WM *vs.* WM	4 weeks	①⑥⑦
Yue et al. (2021)	47	47	27/20	29/18	67.38 ± 6.11	66.17 ± 5.87	DZ 2g/tid plus WM *vs.* WM	4 weeks	⑥
Peng et al. (2016)	40	40	18/22	16/24	50.0 ± 6.2	52.0 ± 5.6	DL 1.12g/tid plus WM *vs.* WM	3 weeks	①②⑤
Gong et al. (2010)	43	42	19/24	16/26	52 ± 5.8	50 ± 6.4	DL 1.12g/tid plus WM *vs.* WM	2 weeks	①②⑤
Yuan et al. (2016)	49	48	19/30	20/28	38–69	36–64	DL 1.12g/tid plus WM *vs.* WM	15 days	①②⑤
Mei et al. (2011)	32	32	11/21	12/20	18–65	18–64	DL 1.12g/tid plus WM *vs.* WM	12 weeks	①⑤
Mao et al. (2022)	40	41	13/27	15/26	45.13 ± 5.01	45.53 ± 5.16	DL 1.12g/tid plus WM *vs.* WM	1 month	①⑤
Zhu et al. (2014)	47	46	17/30	15/31	36.3 ± 10.23	36 ± 9.59	SGJY 0.72g/bid plus WM *vs.* WM	4 weeks	①③⑤
Li et al. (2018)	59	59	35/24	34/25	36.49 ± 4.06	36.31 ± 3.68	SGJY 0.72g/bid plus WM *vs.* WM	4 weeks	⑤⑥⑦
Qu et al. (2019)	72	74	23/49	26/48	18–67	24–68	WL 0.99g/tid plus WM *vs.* WM	8 weeks	①②⑥
Liu et al. (2010)	31	31	13/18	15/16	37.47 ± 8.49	33.37 ± 9.17	WL 0.99g/tid plus WM *vs.* WM	6 weeks	①⑤⑥
He et al. (2013)	48	48	NR	NR	NR	NR	WL 0.99g/tid plus WM *vs.* WM	12 weeks	①⑥⑦
Yuan et al. (2014)	34	34	13/21	11/23	30.5 ± 4.2	32.1 ± 4.5	WL 0.99g/tid plus WM *vs.* WM	4 weeks	①⑤⑥⑦
Zhu et al. (2019)	34	34	15/19	14/20	43.16 ± 5.78	44.58 ± 6.35	YXQN 4g/tid plus WM *vs.* WM	8 weeks	②⑤⑥⑦
Wang et al. (2017)	60	60	28/32	29/31	42.15 ± 5.93	43.22 ± 4.89	YXQN 4g/tid plus WM *vs.* WM	4 weeks	①②⑤
Zhang et al. (2020)	45	45	23/22	24/21	36.37 ± 6.92	37.13 ± 6.80	YXQN 4g/tid plus WM *vs.* WM	15 days	①②③④⑤
Zhang et al. (2019)	63	63	30/33	29/34	35.26 ± 7.32	36.03 ± 7.69	YXQN 4g/tid plus WM *vs.* WM	4 weeks	①②③④⑤
Luo et al. (2012)	50	50	19/31	22/28	30 ± 2.75	28 ± 3.2	YXQN 4g/tid plus WM *vs.* WM	2 weeks	①
Ying et al. (2018)	63	63	23/40	25/38	35.1 ± 7.3	35.8 ± 7.6	YXQN 4g/tid plus WM *vs.* WM	4 weeks	①②③④⑤
Liu et al. (2021)	40	40	15/25	16/24	17.02 ± 0.76	17.17 ± 0.79	YXQN 4g/tid plus WM *vs.* WM	2 weeks	①②③④
Gao et al. (2021)	25	25	15/10	14/11	45.01 ± 2.11	44.03 ± 2.1	YXQN 4g/tid plus WM *vs.* WM	4 weeks	⑤
Yan et al. (2014)	50	50	NR	NR	NR	NR	YXQN 4g/tid plus WM *vs.* WM	4 weeks	⑥⑦
Cao et al. (2013)	63	60	26/37	22/38	18–63	19–65	YXQN 4g/tid plus WM *vs.* WM	4 weeks	①③④⑤
Long et al. (2019)	43	42	18/25	19/23	33.8 ± 4.1	34.1 ± 3.9	YXQN 4g/tid plus WM *vs.* WM	2 weeks	①
Xu et al. (2016)	48	48	21/27	19/29	47.6 ± 4.5	46.0 ± 5.1	TTN 1.2g/tid plus WM *vs.* WM	4 weeks	①②③④⑤
Wang et al. (2016)	40	40	17/23	15/25	40.2 ± 11.12	39.22 ± 9.68	TTN 1.2g/tid plus WM *vs.* WM	8 weeks	①②⑥⑦
Song et al. (2020)	40	40	NR	NR	NR	NR	TTN 1.2g/tid plus WM *vs.* WM	4 weeks	⑤
Li et al. (2021)	67	65	30/37	31/34	48.56 ± 4.28	49.74 ± 4.66	TTN 1.2g/tid plus WM *vs.* WM	4 weeks	①⑤
Gao et al. (2017)	37	37	14/23	17/20	47.4 ± 10.3	46.3 ± 9.7	TTN 1.2g/tid plus WM *vs.* WM	4 weeks	①⑤
Liu et al. (2017)	70	70	26/44	28/42	22–48	23–50	TTN 1.2g/tid plus WM *vs.* WM	3 weeks	①②⑤
Yang et al. (2017)	60	60	24/36	22/38	34.07 ± 3.26	34.37 ± 4.17	TTN 1.2g/tid plus WM *vs.* WM	4 weeks	①⑥⑦
Ye et al. (2015)	90	90	35/55	34/56	33.6 ± 8.2	34.2 ± 6.9	TTN 1.2g/tid plus WM *vs.* WM	4 weeks	①②③④⑤⑥⑦
Li et al. (2014)	55	55	NR	NR	NR	NR	TTN 1.2g/tid plus WM *vs.* WM	2 weeks	①⑤
Shan et al. (2014)	64	59	28/36	25/34	37.3	36.8	TTN 1.2g/tid plus WM *vs.* WM	4 weeks	①

(*continued on next page*)

Table 1 (*continued*)

1st author	Sample size		Gender (M/F)		Age (Mean ± SD)		Interventions	Diaereses duration	Outcomes
	T	C	T	C	T	C			
Li et al. (2011)	55	50	15/40	14/36	35.2 ± 12.8	36.1 ± 11.5	TTN 1.2g/tid plus WM *vs.* WM	4 weeks	①⑤⑥⑦
Niu et al. (2011)	30	30	10/20	12/18	20–58	25–53	TTN 1.2g/tid plus WM *vs.* WM	4 weeks	①②④
Zhang et al. (2010)	31	29	14/17	12/17	34.2 ± 8.83	35.8 ± 9.0	TTN 1.2g/tid plus WM *vs.* WM	4 weeks	①④⑤
Tan et al. (2015)	40	40	22/18	23/17	45.5 ± 5.5	46.5 ± 5.5	TTN 1.2g/tid plus WM *vs.* YXQN 4g/tid plus WM	2 weeks	①⑤
Zhang et al. (2017)	60	60	29/31	30/30	47.6 ± 4.8	45.9 ± 5.72	JY 4g/tid plus WM *vs.* WM	4 weeks	②⑥⑦
Zhang et al. (2013)	43	43	21/24	20/25	37.5 ± 3.43	36.3 ± 3.57	TS 1.46g/tid plus WM *vs.* WM	8 weeks	①②③④⑤

C, control group; DL, Duliang-ruan capsules; DZ, Danzhen Toutong capsules; JY, Jieyu pills; NR, not reported; SGJY, Shugan Jieyu capsules; T, treatment group; TS, Tianshu capsules; TTN, Toutong-ning capsules; WL, Wuling capsules; WM, western medicine; YXQN, Yangxue Qingnao granules; ① clinical efficiency rate; ② NRS; ③, headache frequency; ④ duration of headache; ⑤ adverse reactions; ⑥ HAMA; ⑦ HAMD.

lowest SUCRA (1.0 %).

3.7. *Secondary outcomes*

3.7.1. *NRS*

A total of 17 studies including 8 interventions and 1,780 patients reported NRS. The results were shown in Table 2. In terms of the NRS, JY plus WM (MD = 2.01, 95%CI: 1.47 to 2.55), YXQN plus WM (MD = 1.71, 95%CI: 1.48 to 1.94), WL plus WM (MD = 1.16, 95% CI: 0.53 to 1.79), DL plus WM (MD = 1.01, 95%CI: 0.61 to 1.40), and TTN plus WM (MD = 0.96, 95%CI: 0.69 to 1.19) were better than WM group. Statistical differences were also found in the CPM groups, JY plus WM was significantly effective in decreasing NRS than WL plus WM (MD = 0.85, 95%CI: 0.02 to 1.66), DL plus WM (MD = 1.01, 95%CI: −0.32 to 1.67), TTN plus WM (MD = 1.06, 95%CI: 0.47 to 1.66), and TS plus WM (MD = 1.38, 95%CI: 0.42 to 2.37). Furthermore, YXQN plus WM was significantly effective in decreasing NRS than DL plus WM (MD = 0.71, 95%CI: 0.24 to 1.16), TTN plus WM (MD = 0.76, 95%CI: 0.43 to 1.10), and TS plus WM (MD = 1.08, 95%CI: 0.25 to 1.93). According to the SUCRA values (Fig. 4B and Table 3), the JY plus WM (SUCRA 97.0 %) group performed best in decreasing NRS, followed by YXQN plus WM (SUCRA 84.8 %), WL plus WM (SUCRA 55.4 %), DL plus WM (SUCRA 45.9 %), TTN plus WM (SUCRA 40.9 %), and TS plus WM (SUCRA 24.9 %), while the WM group had the lowest SUCRA (1.0 %).

3.7.2. *Headache frequency*

A total of 9 studies including 5 interventions and 1,000 patients reported headache frequency. The results were shown in Table 4. In terms of the headache frequency, TTN plus WM (MD = −1.06, 95%CI: −1.49 to −0.62) and YXQN plus WM (MD = −1.05, 95%CI: −1.26 to −0.74) were better than WM group. Statistical differences were also found in the CPM groups, TTN plus WM (MD = −1.06, 95%CI: −1.88 to −0.23) and YXQN plus WM (MD = −1.04, 95%CI: −1.76 to −0.26) were significantly effective in decreasing headache frequency than Shugan Jieyu capsule group. According to the SUCRA values (Fig. 4C and Table 3), the TTN plus WM (SUCRA 84.6 %) group performed best in decreasing headache frequency, followed by YXQN plus WM (SUCRA 84.1 %), TS plus WM (SUCRA 52.5 %), and SGJY plus WM (SUCRA 15.4 %), while the WM group had the lowest SUCRA (13.5 %).

3.7.3. *Headache duration*

A total of 10 studies including 4 interventions and 1,027 patients reported headache duration. The results were shown in Table 4. In terms of the headache duration, YXQN plus WM (MD = 1.05, 95%CI: 0.74 to 1.40), TS plus WM (MD = 0.89, 95%CI: 0.01 to 1.76), and TTN plus WM (MD = 0.58, 95%CI: 0.20 to 1.00) were better than WM group. According to the SUCRA values (Fig. 4D and Table 3), the YXQN plus WM (SUCRA 87.5 %) group performed best in decreasing headache duration, followed by TS plus WM (SUCRA 68.6 %), and TTN plus WM (SUCRA 42.9 %), while the WM group had the lowest SUCRA (1.0 %).

3.7.4. *HAMA*

Anxiety and depression are common complications of TTH and are regarded as the causes of frequent headaches in TTH patients. Surveys have shown that the prevalence rate of mental illness complications of TTH is 45 %–56 %, and TTH patients with anxiety and depression have a higher frequency of headaches under pressure, which seriously affects the quality of life (Bera et al., 2014 [62]; Janke et al., 2004 [63]).

A total of 15 studies including 7 interventions and 1,555 patients reported HAMA. The results were shown in Table 5. In terms of the HAMA, JY plus WM (MD = −7.41, 95%CI: −13.39 to −1.42), WL plus WM (MD = −5.21, 95%CI: −8.27 to −2.11), and TTN plus WM (MD = −4.19, 95%CI: −7.24 to −1.14) were better than WM group. According to the SUCRA values (Fig. 4E and Table 3), the JY plus WM (SUCRA 88.4 %) group performed best in decreasing headache duration, followed by WL plus WM (SUCRA 73.6 %), TTN plus WM (SUCRA 60.1 %), SGJY plus WM (SUCRA 46.6 %), YXQN plus WM (SUCRA 44.8 %), and DZ plus WM (SUCRA 31.0 %), while the WM

Table 2
League table of Clinical efficiency rate and NRS.

Comparisons for clinical efficiency rate (bottom left) and NRS (upper right) of interventions								
SGJY + WM	-	-	-	-	-	-	-	-
1.62 (0.35,13.11)	TTN + WM	**0.76 (0.43,1.10)**	0.32 (−0.52,1.17)	-	0.05 (−0.40,0.52)	0.20 (−0.89,0.46)	**1.06 (0.47,1.66)**	**0.96 (0.69,1.19)**
1.64 (0.35,13.15)	1.01 (0.57,1.76)	YXQN + WM	**1.08 (-1.93,-0.25)**	-	**0.71 (0.24,1.16)**	0.55 (−0.13,1.21)	−0.30 (−0.29,0.89)	**1.71 (1.48,1.94)**
1.92 (0.21, 21.46)	1.17 (0.22,4.7)	1.17 (0.21,4.75)	TS + WM	-	0.38 (−0.51,1.30)	0.53 (−0.50,1.56)	**1.38 (0.42,2.37)**	0.63 (−0.18,1.43)
2.03 (0.35,17.9)	1.24 (0.47,3.06)	1.23 (0.46,3.12)	1.05 (0.21, 6.55)	DZ + WM	-	-	-	-
2.51 (0.51,20.36)	1.54 (0.81,2.92)	1.53 (0.78,3.01)	1.05 (0.21,6.55)	1.24 (0.47,3.47)	DL + WM	0.15 (−0.58,0.89)	**1.01 (0.32,1.67)**	**1.01 (0.61,1.40)**
3.86 (0.72,33.29)	**2.36 (1.03,5.34)**	2.35 (0.99,5.45)	2.03 (0.43,11.95)	1.91 (0.63,5.97)	1.54 (0.62,3.75)	WL + WM	**0.85 (0.02,1.66)**	**1.16 (0.53,1.79)**
-	-	-	-	-	-	-	JY + WM	**2.01 (1.47,2.55)**
7.31 (1.65,56.71)	**4.50 (3.11,6.62)**	**4.48 (2.94,6.97)**	**3.83 (1.01,19.77)**	**3.63 (1.61,8.85)**	**2.93 (1.75,4.96)**	1.90 (0.93,4.04)	-	WM

DL, Duliang-ruan capsules; DZ, Danzhen Toutong capsules; JY, Jieyu pills; SGJY, Shugan Jieyu capsules; TS, Tianshu capsules; TTN, Toutong-ning capsules; WL, Wuling capsules; WM, western medicine; YXQN, Yangxue Qingnao granules. The 95 % confidence interval which does not range across 0 favors the column-defining treatment and is shown in bold.

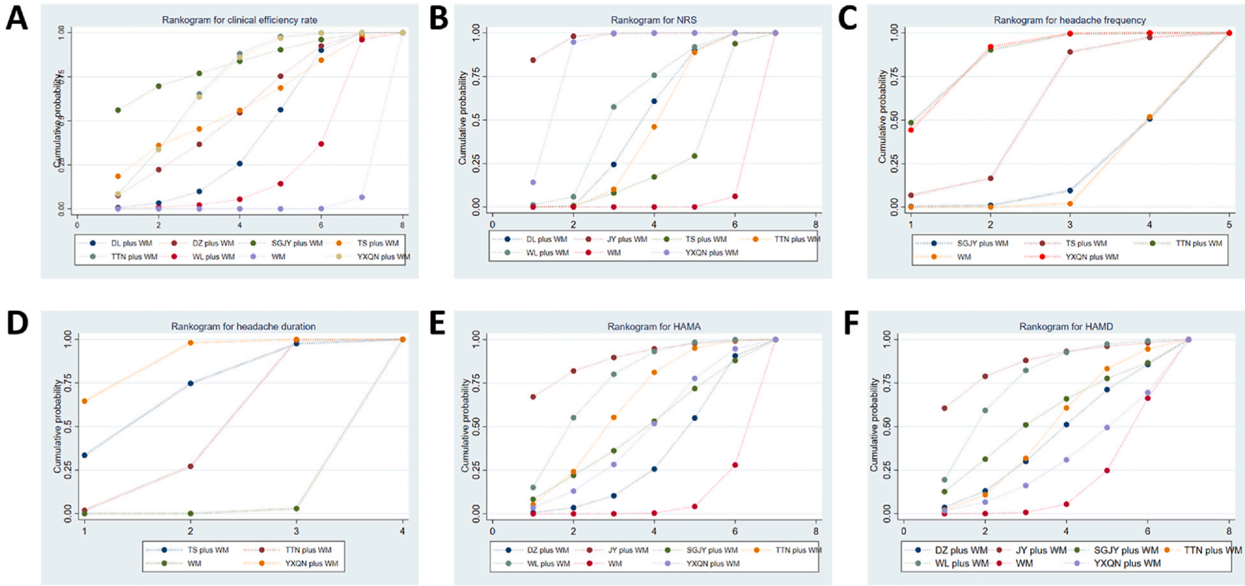

Fig. 4. The cumulative ranking probability plot of comparisons on different outcomes of each CPMs for patients with TTH. (A) Clinical efficiency rate; (B) NRS; (C) Headache frequency; (D) Headache duration; (E) HAMA; (F) HAMD.

Table 3
SUCRA of the outcomes.

Treatments	SUCRA(%)					
	Clinical efficiency rate	NRS	Headache frequency	Headache duration	HAMA	HAMD
SGJY + WM	82.5	-	15.4	-	46.6	54.2
TTN + WM	70.5	40.9	84.6	42.9	60.1	47.2
YXQN + WM	69.8	84.8	84.1	87.5	44.8	29.1
TS + WM	58.1	24.9	52.5	68.6	-	-
DZ + WM	55.6	-	-	-	31.0	42.5
DL + WM	40.9	45.9	-	-	-	-
WL + WM	22.3	55.4	-	-	73.6	75.0
JY + WM	-	97.0	-	-	88.4	85.8
WM	1.0	1.0	13.5	1.0	5.4	16.2

DL, Duliang-ruan capsules; DZ, Danzhen Toutong capsules; JY, Jieyu pills; SGJY, Shugan Jieyu capsules; TS, Tianshu capsules; TTN, Toutong-ning capsules; WL, Wuling capsules; WM, western medicine; YXQN, Yangxue Qingnao granules; HAMA, Hamilton Anxiety Scale; HAMD, Hamilton Depression Scale; NRS, Numerical Rating Scale.

Table 4
League table of headache frequency and headache duration.

Comparisons for headache frequency (bottom left) and headache duration (upper right) of interventions				
TTN + WM	0.47 (−0.05,0.98)	0.30 (−0.68,1.24)	-	**0.58 (0.20,1.00)**
−0.01 (−0.56,0.46)	YXQN + WM	0.17 (−0.75,1.12)	-	**1.05 (0.74,1.40)**
−0.45 (−1.26,0.36)	−0.43 (−1.14,0.33)	TS + WM	-	**0.89 (0.01,1.76)**
−1.06 (-1.88,-0.23)	**−1.04 (-1.76,-0.26)**	−0.61 (−1.59,0.37)	SGJY + WM	-
−1.06 (-1.49,-0.62)	**−1.05 (-1.26,-0.74)**	−0.61 (−1.3,0.08)	0.00 (−0.70,0.70)	WM

SGJY, Shugan Jieyu capsules; TS, Tianshu capsules; TTN, Toutong-ning capsules; WM, western medicine; YXQN, Yangxue Qingnao granules.

group had the lowest SUCRA (5.4 %).

3.7.5. HAMD

A total of 13 studies including 7 interventions and 1,399 patients reported headache HAMD. The results were shown in Table 5. In terms of the HAMD, WL plus WM (MD = 5.47, 95%CI: 0.25 to 10.74) was better than WM group. According to the SUCRA values (Fig. 4F and Table 3), the JY plus WM (SUCRA 85.8 %) group performed best in decreasing headache duration, followed by WL plus WM (SUCRA 75.5 %), SGJY plus WM (SUCRA 54.2 %), TTN plus WM (SUCRA 47.2 %), DZ plus WM (SUCRA 42.5 %), and YXQN plus WM (SUCRA 29.1 %), while the WM group had the lowest SUCRA (16.2 %).

Table 5
League table of HAMA and HAMD.

Comparisons for HAMA (bottom left) and HAMD (upper right) of interventions						
JY + WM	2.45 (−7.95,12.82)	5.41 (−4.64,15.42)	4.53 (−8.18,17.14)	7.15 (−3.77,18.14)	5.85 (−5.11,16.74)	7.15 (−3.77,18.14)
−2.20 (−8.93,4.51)	WL + WM	−2.95 (−3.94,9.84)	−2.06 (−8.29,12.46)	−4.71 (−3.48,12.93)	−3.39 (−4.85,11.63)	**5.47 (0.25,10.74)**
−3.22 (−9.93,3.51)	−1.03 (−5.34,3.33)	TTN + WM	0.90 (−9.10,10.90)	1.76 (−6.05,9.56)	0.43 (−7.32,8.20)	2.52 (−1.95,7.02)
−4.23 (−12.77,4.26)	−2.04 (−8.87,4.79)	−1.01 (−7.81,5.78)	SGJY + WM	2.65 (−8.31,13.52)	1.34 (−9.61,12.23)	3.41 (−5.54,12.36)
−4.35 (−11.60,3.03)	−2.15 (−7.35,3.12)	−1.13 (−6.32,4.13)	−0.12 (−7.48,7.38)	YXQN + WM	1.32 (−7.66,10.27)	0.76 (−5.60,7.12)
−5.43 (−12.28,1.5)	−3.23 (−7.81,1.46)	−2.21 (−6.79,2.45)	−1.19 (−8.12,5.88)	−1.08 (−6.57,4.41)	DZ + WM	2.08 (−4.23,8.41)
−7.41 (-13.39,-1.42)	**−5.21 (-8.27,-2.11)**	**−4.19 (-7.24,-1.14)**	−3.17 (−9.26,2.95)	−3.06 (−7.33,1.15)	−1.98 (−5.49,1.45)	WM

DZ, Danzhen Toutong capsules; JY, Jieyu pills; SGJY, Shugan Jieyu capsules; TTN, Toutong-ning capsules; WL, Wuling capsules; WM, western medicine; YXQN, Yangxue Qingnao granules.

3.7.6. Adverse reactions

A total of 28 syudies reported adverse reactions. Of these, no adverse reactions were observed in one study [56]. In addition, one study [51] showed no adverse reactions in experimental group, but adverse reactions such as pruritus was observed in control group. The main adverse reactions in fifteen studies [22,24–26,28,35,38–40,43,45,53,55,58,60] were nausea, dizziness, and gastrointestinal reactions. Eleven studies [27,29–31,33,36,37,48–50,61] reported other adverse reactions such as rashes, xerostomia, chest distress, and insomnia, but there was no significant difference between groups. (The details of adverse reactions were shown in Supplement Table S4).

3.8. Sensitivity analysis

Sensitivity analysis was conducted to evaluate the influence of the including study on the summary estimate. In terms of clinical efficacy rate, NRS, headache duration, HAMA, and HAMD, sensitivity analysis showed that there was no change in the overall effect when any study with high degree of overall bias were removed, indicating that the results of NMA were robust. However, in terms of headache frequency, the NMA results shifted when studies with a higher risk of overall bias were excluded. TTN plus WM became the best intervention in improving headache frequency. The details of sensitivity analysis were shown in Supplement Fig. S4 and Table S5.

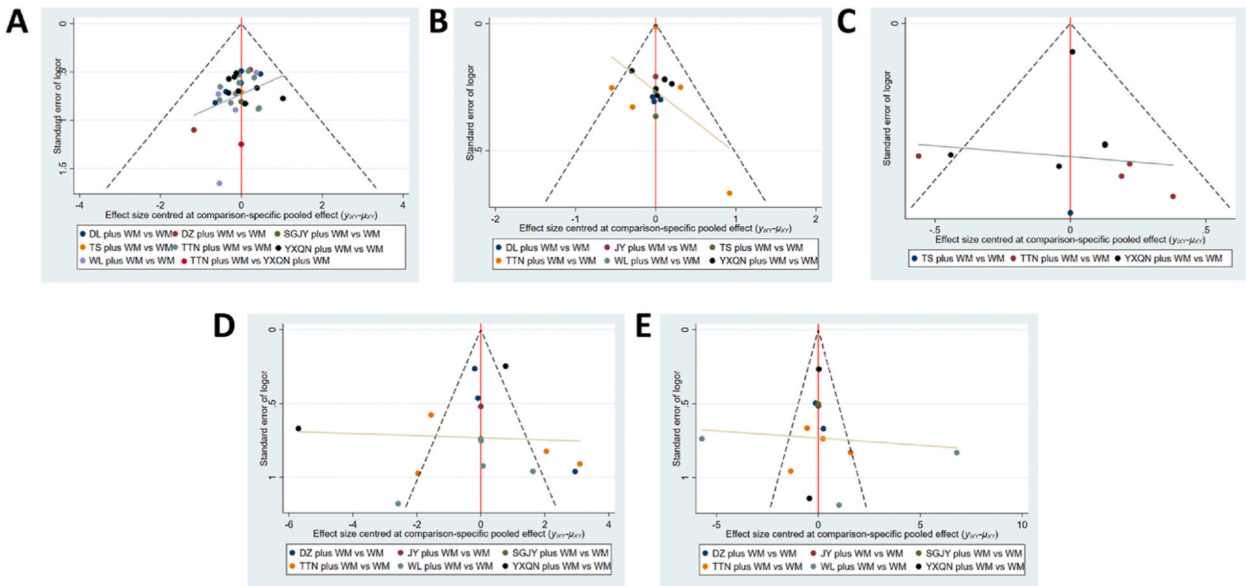

Fig. 5. Funnel plots of outcomes. (A) Clinical efficiency rate; (B) NRS; (C) Headache duration; (D) HAMA; (E) HAMD.

3.9. Publication bias

Funnel plots were used to evaluate the publication bias. As shown in Fig. 5, points of different colors indicate comparisons among various interventions. The funnel plots for clinical efficiency rate (Fig. 5A), headache duration (Fig. 5C), HAMA (Fig. 5D), and HAMD (Fig. 5E) showed that the points were symmetrical, and the angle between the centerline and the adjusted auxiliary line was small, indicating that the risk of publication bias were low. However, the funnel plot for NRS was not symmetrical (Fig. 5B), and the adjusted auxiliary line was not perpendicular to the centerline, indicating a potential publication bias among these studies. Notably, the Egger's test ($p = 0.003$) of NRS indicated the presence of potential publication bias (Supplementary Fig. S5).

3.10. Cluster analysis

Cluster analysis was conducted to assess the best interventions for TTH. In the primary outcome indicators, SGJY plus WM and JY plus WM may be the best treatments in improving clinical efficiency and reducing NRS scores. In terms of headache parameters, YXQN plus WM and TTN plus WM may be the best treatments in improving headache parameters. As for patients' quality of life, TTN plus WM and SGJY plus WM can obviously improve the mood of patients (Fig. 6A and B, and Fig. 6C).

4. Discussion

4.1. Summary of evidence

This network meta-analysis was performed to assess the effect of different CPMs on clinical efficiency rate, headache parameters and quality of life in patients with TTH, including Yangxue Qingnao (YXQN) granules, Danzhen Toutong (DZ) capsules, Duliang-ruan (DL) capsules, Shugan Jieyu (SGJY) capsules, Tianshu (TS) capsules, JeYu (JY) pills, Wuling (WL) capsules and Toutong-ning (TTN) capsules. A total of 41 studies were reviewed for qualitative synthesis, involving 3,996 patients and eight types of CPMs. We found that SGJY plus WM might be the optimum selection, being ranked first for improving clinical efficacy rate over other treatment regimens. Furthermore, YXQN plus WM showed the highest effectiveness in reducing headache duration. It is worth mentioning that TTN plus WM showed the highest effectiveness in reducing headache frequency. In improving patients' quality of life and NRS scores, JY plus WM was demonstrated to be among the most effective intervention to significantly improve the HAMD, HAMA, and NRS score. Although no serious adverse reactions were induced by CPMs, reliable conclusions on CPM safety cannot be drawn due to the inconsistent description of adverse reactions in various studies. The sensitivity analysis indicated that the results of clinical efficiency,

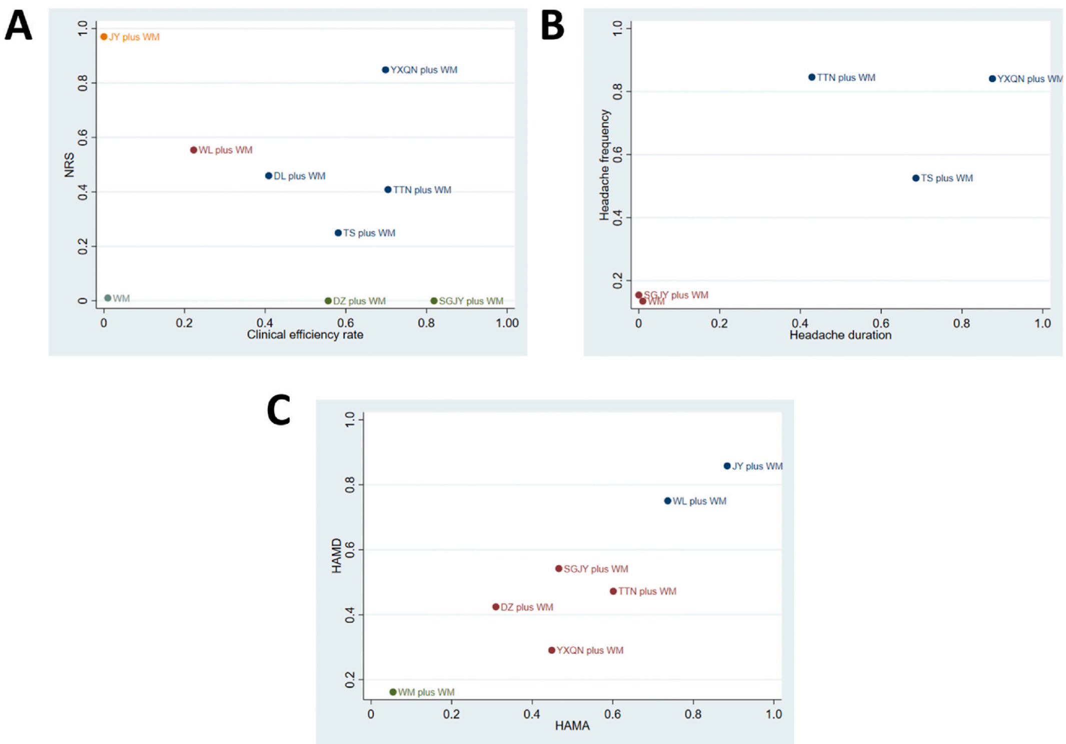

Fig. 6. Cluster analysis plots. (A) Cluster analysis for clinical efficiency rate (X axis) and NRS (Y axis). (B) Cluster analysis for headache duration (X axis) and headache frequency (Y axis). (C) Cluster analysis for HAMA (X axis) and HAMD (Y axis).

NRS, headache duration, HAMA and HAMD were robust, but the best treatment of CPMs for headache frequency requires further research.

4.2. Applicability of evidence

As far as the results of this NMA were concerned, Shugan Jieyu capsule was the best choice of CPMs for improving clinical efficiency rate. It is composed of *Eleutherococcus senticosus* [*Rupr. & Maxim.] Maxim* and *Hypericum perforatum* L. [*Hypericaceae*], which has the effect of soothing liver, relieving depression, and invigorating spleen according to the traditional Chinese medicine principals. Modern research showed that SGJY can improve the function of dopamine, 5-hydroxytryptamine, glutamic acid and gamma-aminobutyric acid (GABA) transmitter systems in the prefrontal cortex and hippocampus to achieve anti-anxiety and anti-depression effects [64]. As we have described, TTH patients with anxiety and depression have a higher frequency of headaches under pressure. Therefore, we believe that Shugan Jieyu capsule may improve the clinical effect by improving the emotional state of patients.

The secondary outcomes included NRS, duration of headache, frequency of headache, HAMA, and HAMD. CPMs plus WM were significantly better than WM alone in these outcomes. Among them, Yangxue Qingnao granules play important roles in reducing headache duration. The main components of YXQN are *Radix angelicae sinensis*, *Rhizoma Chuanxiong*, White peony root, and Ramulus Uncariae cum uncis, which are effective in nourishing Yin and blood and tonifying liver and kidney. *Radix angelicae sinensis* comprises angelica polysaccharide and volatile oil, which exert an analgesic effect by inhibiting the release of pain-induced substances such as chemokines or blocking the amplification of pain sensation in the cascade reaction [65]. Ligusticum contains ligusticum alkaloids, which exert an analgesic effect by the upregulation of the 5-hydroxytryptamine [66]. Paeoniflorin consists of albiflorin and paeoniflorin, which achieves an analgesic effect by increasing the level of Β-endorphin (β-EP) in serum and cerebral cortex [67]. Notably, Jieyu pill ranked first in HAMA, HAMD and NRS scores as the best choice. Jieyu pill was developed on the basis of Xiaoyao decoction and Ganmai Dazao decoction, and is composed of Paeoniae Radix Alba, Radix Bupleuri, Angelicae Sinensis Radix, Curcumae Radix, Poria cocos, and Jujubae Fructus. Wang reviewed the results of previous studies and found that Jieyu pills could increase the levels of monoamine neurotransmitters in the brain, adjust the hypothalamic–pituitary–adrenal axis (HPA) axis, and produce anti-inflammatory effects and other regulatory effects on energy and substance metabolism pathways to synergistically exert antidepressant effects [68].

In addition, Toutong-ning capsule and Yangxue Qingnao granule were the best in improving headache frequency, indicating that their curative effect in improving headache frequency was significantly higher than that of other therapies. The main components of TTN are Aresoil poria, Gastrodia elata, Polygonum multiflorum, Scorpion, Forsnuff, etc., which have the effect of removing blood stasis, relieving pain, expelling phlegm and stopping wind. It has been confirmed that TTN is favorable to inhibiting platelet aggregation, improving local cerebral blood circulation, and regulating the central endogenous analgesic system, thus relieving pain and anxiety in patients [69], which was also confirmed in our study. Although the Wuling capsule was not the best intervention for each outcome index, it was also superior to WM alone. WL powder, the main component of WL capsules, can increase the content of glutamic acid and GABA in the brain, improve the activity of glutamic acid decarboxylase and activate GABA receptors and is often used to relieve anxiety and depression in patients [70].

4.3. Advantages and limitations

Consistent with the results in this study, previous SRs have shown that CPMIs are effective in treating TTH. However, this study has the following advantages over previous studies. First, this study is the first to evaluate the effectiveness of different CPMs in TTH patients using the Bayesian NMA and to rank the advantage of each outcome index of different CPMs to guide clinical use. Second, it strictly follows the important principles of NMA (transitivity, homogeneity, and consistency). The similarity of the included studies, the heterogeneity and the consistency between comparisons were assessed separately, increasing the credibility of the evidence. Third, clinical efficiency, headache parameters (headache frequency, and headache duration), quality of life (HAMA and HAMD) and safety are considered outcome indicators to evaluate the efficiency of CPMs in treating TTH from multiple dimensions. Finally, the findings can provide clinicians with a new idea for the clinical treatment of TTH.

However, this study is associated with several weaknesses. First, although this study conducted a comprehensive literature search, the included studies were all conducted in China, and most of the studies were small sample studies, which may lead to low efficiency of statistical test. Second, although the transitivity of NMA was assessed, differences existed in WM treatments of different studies, which may affect the conclusions. Third, although the consistency of NMA was assessed, no direct comparisons of CPMs were found among the majority of treatment approaches, and the comparison results of different CPMs were obtained through indirect comparisons, which reduced the credibility of the evidence. Fourth, no mid-term or long-term results were assessed quantitatively, which may affect the effective evaluation of CPMs. Finally, although safety is a crucial indicator for the application of CPMs, no reliable conclusions can be reached due to the varying description of adverse reactions in studies. In this sense, more rigorous and higher-quality RCTs are required for validating CPMs in combination with WM in the treatment of patients with TTH.

4.4. Implications for practice and research

We propose some useful and feasible suggestions for future research based on the conclusions and some findings of this NMA. Given the inconsistent evaluation criteria for outcome indicators, the results of some RCTs could not be combined and analyzed, which decreasing the available data in this study. Therefore, future studies should pay more attention to standardizing the measurement of outcome indicators. In addition, future studies should standardize the monitoring and recording of adverse reactions. CPMs were found to reduce headache frequency in patients with TTH. However, limited by the unstable results of this study revealed by sensitivity analysis, the best treatment of CPMs for headache frequency was not reliable in this study. Therefore, the best treatment of CPMs for headache frequency need to be further investigated.

Due to the general methodological quality of the included studies, we put some recommendations for future research. More high-quality and long-period trials are necessary in the future to ensure scientific rigor. Moreover, it is crucial to conduct reasonable sample size estimation and implement random allocation, allocation concealment, and blinding methods in future studies, which increase the research transparency and methodological quality. At the same time, appropriate outcome indicators should be selected according to the core outcome set of TTH.

5. Conclusion

This NMA performed a comprehensive assessment of CPM treatments for TTH on different clinical outcomes and confirmed that the combinations of CPM and WM provides an additional benefit for TTH treatment. Our results indicated that SGJY plus WM was the best choice of CPM for improving clinical efficiency rate. YXQN plus WM was superior to other therapeutic combinations in reducing headache duration. JY plus WM might have best effect in reducing HAMD, HAMA, and NRS scores. In addition, TTN plus WM might have best effect in reducing headache frequency. The results of this study were limited to secondary analysis of existing clinical data, and the quality of evidence included in the studies was low, so it could not fully explain the clinical efficacy of CPMs in the treatment of TTH. The results should be interpreted with caution until further confirmation by rigorous designs RCTs.

Ethics approval and consent to participate

Review and/or approval by an ethics committee was not needed for this study because this Meta-analysis data came from published articles.

Data availability statement

Data included in article/suppmaterial/referenced in article.

CRediT authorship contribution statement

Menglong Shi: Writing – review & editing, Writing – original draft, Validation, Software, Methodology, Investigation, Data curation, Conceptualization. **Tianye Sun:** Methodology, Data curation, Conceptualization. **Yazi Zhang:** Investigation, Data curation. **Fengwen Yang:** Writing – review & editing, Resources, Investigation. **Hui Wang:** Writing – review & editing, Supervision, Resources, Conceptualization. **Bo Pang:** Investigation. **Zhaochen Ji:** Software, Data curation. **Lujia Cao:** Writing – original draft, Resources, Methodology.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e32798.

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