Effectiveness of botulinum neurotoxin A, topiramate, and acupuncture in preventive treatment of chronic migraine: a network meta-analysis

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Abstract

Background Botulinum neurotoxin A (BoNT-A) was the primary choice for preventive treatment of chronic migraine. Topiramate and acupuncture showed promising effect for the condition, but their effectiveness relative to BoNT-A was rarely studied. We aimed to perform a network meta-analysis to compare the effectiveness and acceptability between BoNT-A, topiramate, and acupuncture.

Methods We searched OVID Medline, Embase, the Cochrane register of controlled trials (CENTRAL), the Chinese Clinical Trial Register, and clinicaltrials.gov for randomized controlled trials (RCTs) that compared BoNT-A, topiramate, and acupuncture with any of them or placebo in the preventive treatment of chronic migraine. Two independent reviewers screened RCTs, extracted data, and assessed risk of bias. A network meta-analysis was performed by using a frequentist approach and a random-effects model. The primary outcomes were reduction in monthly headache days and monthly migraine days at week 12. Acceptability was assessed by adverse event rate. The effect size of the primary outcomes was measured by using standard mean difference (SMD).

Results We included 15 RCTs (n = 2545). Eleven RCTs were at low risk of bias. The network meta-analyses (n = 2061) showed that acupuncture (2061 participants; SMD - 1.61, 95%CI -2.35 to -0.87) and topiramate (582 participants; SMD - 0.4, 95%CI -0.75 to -0.04) ranked the most effective in the reduction of monthly headache days and migraine days, respectively; but they were not significantly superior over BoNT-A. Topiramate caused the most treatment-related adverse events and the highest rate of dropouts owing to adverse events.

Conclusions Topiramate and acupuncture were not superior over BoNT-A. In terms of acceptability and accessibility of treatments, BoNT-A was still the primary choice for preventive treatment of chronic migraine.

Introduction

Migraine is a recurrent headache usually accompanied with nausea, photophobia, and phonophobia. Migraine affects 12% of the general population and has substantial impact on patient's quality of life and work productivity. Migraine is classified as episodic migraine and chronic migraine. Episodic migraine causes less frequent headache attacks (2–8 attacks per month). Chronic migraine affects 1–3% of the general population[1] and causes more severe socioeconomic impact than episodic migraine. In addition, patients with chronic migraine was usually accompanied with medication overuse headaches, which causes treatment failure in migraine prophylaxis. Few treatment options are available for the preventive treatment of chronic migraine. Botulinum neurotoxin A (BoNT-A) was the first drug that was specifically approved for the prophylactic treatment of chronic migraine by the US Food and Drug Administration [1, 2]. As indicated by several systematic reviews and randomized controlled trials (RCTs), BoNT-A reduced the number of headache days and global pain intensity in patients with chronic migraine[3, 4]. One systematic review indicated that BoNT-A had a relatively higher acceptance rate than other prophylactic agents[5], but the hypothesis was not statistically tested because of the lack of head-to-head comparisons. The efficacy of topiramate in the preventive treatment of chronic migraine was tested in several RCTs and meta-analyses[6–9]. Two multicenter RCTs showed superiority of topiramate over placebo in the reduction of headache days[8, 9], and the findings were further confirmed in a meta-analysis[10]. Acupuncture, a treatment that was efficacious for episodic migraine[11], was also tested for its effectiveness for chronic migraine in two recent RCTs[12, 13]. Owing to the cumulating evidence for the efficacy of topiramate and acupuncture in the treatment of chronic migraine, clinical practitioners might wonder: (1)

which of the 3 treatments—BoNT-A, topiramate, and acupuncture—was relatively more effective; (2) which treatment was relatively safer and more tolerable? The comparative effectiveness between BoNT-A, topiramate, and acupuncture in the treatment of chronic migraine were examined in three RCTs[7, 13, 14], but the three treatments were not compared simultaneously in one RCT.

Network meta-analysis, also known as mixed treatment comparison meta-analysis, combined both direct and indirect evidence to provide a more accurate estimate of a treatment effect[15]. It solves the problem of convention meta-analysis that pairwise comparison between treatments without head-to-head comparison in RCTs, and it therefore saves additional research expenditure and helps the clinical practitioners and participants to select treatment options that are suitable for their condition with data support. Our study primarily aimed to investigate the comparative effectiveness acceptability of BoNT-A, topiramate, and acupuncture in patients with chronic migraine through a network meta-analysis.

Methods

The systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement and PRISMA for network meta-analysis[16]. Additional details of this review were provided in Appendix A-G.

Study source

We searched OVID Medline, Embase, the Cochrane register of controlled trials (CENTRAL), Chinese Clinical Trial Register (ChiCTR), and clinicaltrial.gov for randomized controlled trials (RCTs) that compared BoNT-A, topiramate, and acupuncture with each other or placebo in the preventive treatment of chronic migraine. The literature search was performed from inception to march 1, 2020 without language restriction. Search strategies were provided in Appendix A. We searched google scholar (<https://scholar.google.com>) and Bing scholar (<https://cn.bing.com/academic>) for any missing RCTs.

Study selection

We selected only studies with randomized design to ensure the credibility of the findings. We included: (1) RCTs with parallel design or crossover design with first-phase data, since acupuncture and BoNT-A were reported with effect persisting for even 12 weeks after completion of treatment[17, 18]; (2) RCTs that recruited participants with chronic migraine and with ≥ 15 monthly headache days and ≥ 8 monthly migraine days; (3) RCTs that compared the BoNT-A, topiramate, and acupuncture with each other or placebo interventions; and (4) RCTs that assessed at least one of the following outcomes: monthly headache days, monthly migraine days, headache intensity (assessed with visual analog scale or other scales), responder rate, six-items headache impact test (HIT-6), migraine disability assessment (MIDAS), quality of life scales, or adverse event. We excluded RCTs that examined acupuncture techniques not using filiform needles and RCTs that examined the efficacy of BoNT-A or topiramate at doses outside the licensed range.

We screened the retrieved articles according to PICOS principle—Participants, Interventions, Controls, Outcomes, and Study design. Two reviewers screened titles and abstracts of the retrieved articles in duplicate, and further

screened the full-text copies of the potentially eligible articles. Disagree in study selection was solved by group discussion and arbitrated by a third reviewer.

Data abstraction and risk of bias assessment

Two reviewers independently abstracted trial characteristics, participant's characteristics, risk of bias, and outcome parameters from the included RCTs. The trial characteristics included name of first author, publication year, diagnostic criteria, study settings, participating countries, sample size, interventions, comparisons, and main outcomes. The participant's characteristics included mean age, proportion of female, and disease duration. Dichotomous data for meta-analysis were extracted for the number of participants in each arm, the number of events, the follow-up time points; continuous data were extracted for mean, standard deviation, and the number of participants in each arm. The number of participants was extracted according to the intention-to-treat principle.

Risk of bias was assessed in the following aspects: random sequence generation, allocation concealment, blinding participants, blinding care providers, blinding outcome assessors, unpublished data, selective outcome reporting, and attrition bias. RCTs would be classified as low risk of bias if none of these aspects was rated as high risk of bias and three or fewer were rated as unclear risk of bias; moderate if one was rated as high risk of bias, or none was rated as high risk but four or more were rated as unclear risk; high risk of bias if all other cases were met[19].

Outcome assessments

The primary outcomes were changes in monthly headache days and monthly migraine days measured at week 12. Secondary outcomes included monthly headache days and monthly migraine days measured at other timepoints (week 4, week 8, and week 24), moderate and severe headache or migraine days, responder rate, headache intensity, headache impact test (HIT-6), migraine disability scale (MIDAS), quality of life scales, adverse event rate, and tolerability. A responder was defined a >50% reduction in monthly headache days or monthly migraine days. HIT-6 and MIDAS are scales for testing the impact of migraine on social life, and higher scores indicate larger impact of migraine[20, 21]. Tolerability was defined as the number of dropouts owing to adverse events.

Data synthesis

We performed a network meta-analysis with a frequentist approach through R project (www.r-project.org, version 3.6.0). We calculated the standardized mean difference (SMD) for continuous data and the relative ratio (RR) for dichotomous outcome data, and we estimated their relative 95% confidence intervals (95% CIs). The data were primarily analyzed at week 12. We calculated the pooled estimates by combining both direct and indirect evidence with reference to placebo. We used P-score to rank the treatment by estimating the mean probability of a treatment to be the best treatment for a specific outcome[22]. Higher P-scores in effectiveness outcomes correlate to greater probability in achieving the best treatment effect; higher P-scores in acceptability outcomes (i.e., adverse event rate and tolerability) indicate greater probability in causing more harm. We estimated the

global heterogeneity in each network meta-analysis by using I^2 statistics; an I^2 from 0% to 49% indicates small heterogeneity, an I^2 from 50% to 74% indicates moderate heterogeneity, and an $I^2 \geq 75\%$ indicates large heterogeneity. We checked the consistency of the network by a comparison of the direct estimates and the indirect estimates [23]. We also used a design-by-treatment approach to detect the source of inconsistency in a network meta-analysis by using a method of decomposing Cochran's Q[24]. We performed sensitivity analyses by excluding RCTs with moderate to high risk of bias.

Results

Trial characteristics

We identified 1133 articles, and we finally included 15 RCTs (n=2545) described by 17 articles[14, 25–41]. The process of study screening and selection and the lists of the excluded studies were showed in Appendix B and C. The mean age of the included study ranged from 38.8 to 48.8 years. Female participants constituted 44-91.5% of the total population, and the median proportion was 76.3%. The duration of migraine ranged from 3 to 28.1 years, and the median duration was 16 years. Table 1 shows the details of the included treatments and comparisons. Risk of bias assessment showed that 11 RCTs were at low risk of bias, 3 RCTs at moderate risk of bias, and 1 RCT at high risk of bias. Appendix D shows risk of bias in individual RCTs.

Monthly headache days

Acupuncture was the most effective at week 12 (10 RCTs and 2061 participants; SMD -1.61, 95%CI -2.35 to -0.87; P-score=0.98; global I^2 = 86.2%; Figure 1A). Topiramate was the most effective at week 4 (8 RCTs and 1784 participants; SMD -1.47, 95%CI -2.44 to -0.5; P-score=0.96; global I^2 =96%) and at week 8 (7 RCTs and 1725 participants; SMD -2.54, 95%CI -3.42 to -1.67; P-score=1; global I^2 =88%; Appendix G). BoNT-A was the most effective at week 16 (4 RCTs and 1731 participants; SMD -0.48, 95%CI -0.73 to -0.24; P-score=0.94; global I^2 =72.1%) and week 24 (5 RCTs and 1682 participants; SMD -0.36, 95%CI -0.67 to -0.05; P-score=0.65; global I^2 =83.6%; Appendix G). Acupuncture reduced more monthly headache days than BoNT-A at week 12 (Table 2), but no difference between the three treatments was found at other time points. The design-by-treatment consistency tests showed that inconsistency of the network originated mainly from the comparison between BoNT-A and placebo (Appendix F).

Migraine days

Topiramate was the most effective at week 12 (4 RCTs and 582 participants; SMD -0.4, 95%CI -0.75 to -0.04; P-score=0.96; global I^2 =39.3%; Figure 2B), but no significant difference between treatments was found. Network meta-analysis was not performed at the other time points because of few available data.

Moderate or severe headache days

Acupuncture was more effective than topiramate at week 12 (3 RCTs and 245 participants; SMD -0.83, 95%CI -1.33 to -0.32).

Headache intensity

Acupuncture ranked the most effective at week 12 (3 RCTs and 528 participants; SMD -0.37, 95%CI -1.04 to 0.31; P-score=0.89; Figure 2A); and acupuncture was found more effective than BoNT-A (SMD -0.44, 95%CI -0.82 to -0.05; Table 2). BoNT-A was the most effective at week 4 (1 RCT and 162 participants; SMD -1.03, 95%CI -1.43 to -0.63; P-score=1), and acupuncture was the most effective at week 8 (1 RCT and 162 participants; SMD -0.43, 95%CI -0.81 to -0.05; P-score=0.83).

Responder rate

Acupuncture was the most effective at week 12 (6 RCTs and 726 participants, RR 3.39, 95%CI 0.76 to 15.05; P-score=0.9; global I^2 =66%; Figure 2B). Topiramate was the most effective at week 4 (2 RCTs and participants, RR 8, 95%CI 0.47 to 137.62; P-score=0.83). No difference was found between the three treatments (Table 2).

MIDAS

Acupuncture was the most effective at week 12 (8 RCTs and 826 participants, SMD -1.72, 95%CI -3.69 to 0.25; P-score=0.91; global I^2 =92.9%; Figure 2C). No difference between the three treatments at week 12. Topiramate was more effective than BoNT-A (1 RCT and 60 participants, SMD -0.62, 95%CI -1.14 to -0.1) at week 24.

Frequency of acute medication intake

Acupuncture was the most effective at week 12 (SMD, -1.04, -1.64 to -0.44; P-score=0.94; global I^2 =95.2%; Figure 2D). BoNT-A was the most effective at week 4 (2 RCTs and 164 participants; SMD -2.77, 95%CI -3.52 to -2.02; P-score=1) and week 8 (2 RCTs and 164 participants; SMD 0.15, 95%CI -0.38 to 0.67; P-score=0.46). No difference was observed between the three treatments (Table 2).

Adverse event and tolerability

Topiramate caused the most total adverse events at both week 12 (10 RCTs and 1001 participants, RR 1.51, 95%CI 1.03 to 2.22; P-score=0.94; global I^2 =52.2%; Figure 3A) and week 24 (4 RCTs and 1516 participants, RR 1.34, 95%CI 1.12 to 1.6; P-score=0.96; global I^2 =0%; Figure 3B).

Topiramate also caused the most treatment-related adverse events at both week 12 (4 RCTs and 579 participants; RR 1.51, 95%CI 1.23 to 1.85; P-score=0.98; global I^2 =0%; Figure 3A) and week 24 (3 RCTs and 1444 participants; RR 3.24, 95%CI 2.16 to 4.84; P-score=0.99; global I^2 =0%; Figure 3B). Topiramate caused more treatment-related adverse events than BoNT-A at week 24 (RR 1.39, 95%CI 1 to 1.94; Table 2).

Topiramate had the least tolerability—caused the most drop-outs due to adverse events (4 RCTs and 1500 participants; RR 8.62, 95%CI 2.03 to 36.62; P-score=0.97; global I^2 =0%; Figure 3B). However, no significant difference between topiramate and BoNT-A concerning tolerability (topiramate versus BoNT-A, RR 2.67, 95%CI 0.78 to 9.09; Table 2)

Sensitivity analysis

Eight RCTs (n=2157) were included for sensitivity analysis of the primary outcomes, and topiramate ranked the most effective in monthly headache days (SMD -1.47, 95%CI -2.44 to -0.50; P-score =0.96) and monthly migraine days (SMD -0.28, 95%CI -2.44 to -0.77; P-score =0.20). Six RCTs (n=1874) were included for sensitivity analysis of tolerability, and topiramate had similar tolerability to BoNT-A (RR, 0.29 95%CI 0.29 to 1.77).

Discussion

We performed a network meta-analysis to perform pairwise comparison between BoNT-A, topiramate, and acupuncture in the preventive treatment of chronic migraine. We found that: (1) BoNT-A, topiramate, and acupuncture were effective in reducing headache days and migraine days at week 12. Although acupuncture ranked the most effective, no significant difference was found between the 3 treatments; (2) Other efficacy outcomes showed similar results; (3) topiramate caused higher total adverse event rate, treatment-related adverse event rate, and number of dropouts due to adverse events than acupuncture and BoNT-A, which indicated a lower acceptability of topiramate than BoNT-A and acupuncture.

Several SRs examined the efficacy of acupuncture[11, 42], BoNT-A[5, 43], or topiramate[10, 44, 45] in migraine prophylaxis. Most of the SRs focused on the efficacy of the 3 treatments in episodic migraine; and none of them has compared the 3 treatments by combining both direct and indirect evidence. BoNT-A was the first treatment that was approved by the Food and Drug Administration for the preventive treatment of chronic migraine, and the American neurology society guideline supported the use of topiramate[1]. These two treatments were rarely compared in head-to-head RCTs. One RCT [30] showed that topiramate was similar to BoNT-A in improving outcomes of patients with chronic migraine, which was further confirmed in our study. Our study added that BoNT-A had better effect in reducing headache days and migraine days at week 16. Regarding the similar treatment effect between BoNT-A and topiramate and the lower acceptability of topiramate, BoNT-A should be considered as the first choice for chronic migraine prophylaxis.

Most of the RCTs testing the efficacy of acupuncture focused on its specific effect by comparing it to sham acupuncture. As found in a recent SR[46], we found only 2 trials comparing acupuncture with standard pharmacological treatments in the treatment of chronic migraine[14, 25]. One RCT found acupuncture was superior over BoNT-A and valproate in reducing headache days at week 12[25]; and the other trial found that acupuncture caused more reduction in headache days than topiramate[14]. This explained acupuncture ranking top in causing fewer headache days at week 12. We should interpret this finding with caution, since the two trials were small-scale open-label trials that maybe under the risk of small-study effect, and the inclusion of these two trials brought in between-study heterogeneity. However, the finding might, on the other hand, reflect the true effect of acupuncture in practice. Several trials testing the effect of acupuncture on episodic migraine also showed superiority of acupuncture over standard pharmacological treatments[47–49], and one of our SRs comparing acupuncture with propranolol using indirect evidence also showed similar results[50]. Based on these grounds, a new trial on chronic migraine with larger sample size might also showed similar results. Acupuncture treatment should be given for at least 10 sessions and at least one session per week as suggested by guidelines[51]. Considering the accessibility and cost of acupuncture treatment, BoNT-A should also be considered as the first choice.

Our study had several limitations. First, we did not perform a network meta-analysis of the 3 treatment in long-term assessment (> 24 weeks), because few studies assessed the long-term effect of acupuncture on chronic migraine. Second, we did not perform subgroup analysis for medication overuse migraine because of insufficient data. Third, with-design heterogeneity in BoNT-A versus placebo precludes a firm conclusion based on current evidence. Fourth, cost-effectiveness evaluation was not performed.

Conclusions

Our network meta-analysis showed that all 3 treatments were effective in prophylactic treatment of chronic migraine. Considering the acceptability and accessibility of the treatments, BoNT-A should still be the primary choice for preventive treatment of chronic migraine.

List Of Abbreviations

BoNT-A	Botulinum toxin A
CENTRAL	Cochrane register of controlled trials
HIT-6	Headache impact test
ICHD	International classification of headache disorders
MIDAS	Migraine disability assessment
PRISMA	Preferred reporting items for systematic reviews and meta-analysis
RCTs	Randomized controlled trials
RR	Relative ratio
SMD	Standard mean difference

Declarations

Ethics approval and consent to participate Not applicable.

Consent for publication Not applicable.

Availability of data and materials All data generated or analyzed data in study are included in this article.

Competing interests The authors declare no competing interests.

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Author contributions: All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Hui Zheng and Min Chen designed the study. Shi-Le Huang, Yao-Yao Chen, Tai-Chun Tang, Di Qin acquired the study data. Hui Zheng and Min Chen analyzed the data. Hui Zheng drafted the manuscript, and all authors revised the manuscript and approved it for publication.

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Tables

Table 1. Trial characteristics

Study	Country; sites	Diagnostic criteria	Female (%)	Mean age (year)	Disease duration (year)	Treatment groups	Treatment sessions
Aurora, 2010	USA; 56	ICHD-II	87.5	41.70	20.5	BoNT-A (n=341) versus placebo (n=338)	BoNT-A was administered at 31 injection sites (155U in total). At the investigator's discretion, an additional 40U could be administered. The maximum total dose was 195 U at 39 sites.
Cady, 2011	USA; 3	ICHD-II	91.5	39.60	16.0	Topiramate (n=30) versus BoNT-A (n=29)	BoNT-A was administered at a maximum dose of 200 U. Topiramate dosing was initiated at 25 mg daily and escalated to 100 mg in weekly incremental changes of 25 mg.
Diener, 2007	Europe; NA	ICHD-II	44.0	46.10	NA	Topiramate (n=32) versus placebo (n=27)	Topiramate was titrated from 25mg/day over 4 weeks to 100mg/day and maintained for another 12 weeks
Diener, 2010	Global; 66	ICHD-II	85.4	41.00	18.1	BoNT-A (n=347) versus placebo (n=358)	BoNT-A was administered at 31 injection sites (155U in total). At the investigator's discretion, an additional 40U could be administered.
Freitag, 2007	USA; NA	ICHD-I	73.2	42.30	NA	BoNT-A (n=20) versus placebo (n=21)	BoNT-A was administered at 22 injection sites (100U in total).
Hollanda,	Brazil; 1	NA	76.3	45.30	NA	BoNT-A	BoNT-A was

2014						(n=20) versus placebo (n=18)	administered at 12-24 injection sites (3-5U per injection; 100U in total). BoNT-A was administered during a treatment period of 12 weeks.
Mathew, 2009	USA; 1	ICHD-I	90.0	36.80	17.5	BoNT-A (n=30) versus topiramate (n=30)	BoNT-A was administered at a maximum dose of 200 U. Topiramate was titrated to 100 mg/day for 4 weeks and titrated optionally for another 4 weeks at a dose of 200 mg/day.
Mei, 2006	Italy; 1	ICHD-II	68.5	45.80	5.0	Topiramate (n=30) versus placebo (n=20)	Topiramate was titrated from 25mg/day over 4 weeks to 100mg/day and maintained for another 12 weeks.
Naderinabi, 2017	Iran; 1	ICHD-III	59.3	37.20	9.8	Acupuncture (n=54) versus BoNT-A (n=54) versus Valproate (n=54)	Acupuncture was given for a total of 30 sessions during a 2- month treatment duration. Injection sessions of BoNT-A was unclear. Oral administration of valproate 500mg/day for 3 months.
Ondo, 2004	USA; 1	ICHD-I	81.7	47.00	NA	BoNT-A (n=29) versus placebo (n=29)	BoNT-A was administered following a "follow-the- pain" strategy at a fixed dose of 200 U.

Pijpers, 2019	Netherlands;1	ICHD-III	76.0	45.20	28.1	BoNT-A (n=90) versus placebo (n=89)	BoNT-A was administered at 31 predefined injection sites (5U per injection; 155U in total). BoNT-A was administered during a treatment period of 12 weeks.
Sandrini, 2011	Italy; 3	ICHD-II	80.4	48.75	20.0	BoNT-A (n=27) versus placebo (n=29)	A total of 16 BoNT-A injections (100U) were administered at 8 sites. B
Silberstein, 2007; Silberstein, 2009; Dodick, 2007	USA; 46	ICHD-II	85.2	38.20	9.2	Topiramate (n=153) versus placebo (n=153)	Topiramate was titrated from 25mg/day over 4 weeks to 100mg/day and maintained for another 12 weeks.
Silvestrini, 2003	Italy; 1	ICHD-I	64.2	43.50	3.0	Topiramate (n=14) versus placebo (n=14)	Topiramate was titrated from 25mg/day over one week to 50mg/day.
Yang, 2011	China; 1	ICHD-II	89.3	47.90	13.3	Acupuncture (n=33) versus topiramate (n=33)	Acupuncture was delivered for a total of 24 sessions over 12 weeks. Topiramate was administered from 25mg/day weekly to a maximum of 100mg/day in a 8-week maintenance period

Abbreviations: BoNT-A, botulinum neurotoxin A. ICHD-I, II and III: the first, second, and third version of international classification of headache disorders.

	Topiramate	Acupuncture
Headache days		
12w	SMD, -0.27 [95%CI, -0.79 to -0.25]	SMD, -0.82 [95%CI, -1.48 to -0.16]
Migraine days		
12w	SMD, -0.41 [95%CI, -0.94 to 0.12]	NA
Headache intensity		
12w	SMD, -0.26 [95%CI, -0.77 to 0.25]	SMD, -0.44 [95%CI, -0.82 to -0.05]
Responder		
12w	RR, 0.80 [95%CI, 0.30 to 2.14]	RR, 2 [95%CI, 0.42 to 9.42]
MIDAS		
12w	SMD, 0.23 [95%CI, -0.73 to 1.19]	SMD, -1.01 [95%CI, -2.99 to 0.96]
Frequency of acute medication intake		
12w	SMD, 0.67 [95%CI, 0.07 to 1.27]	SMD, -0.23 [95%CI, -0.74 to 0.29]
Treatment-related adverse event		
12w	RR, 1.46 [95%CI, 0.96 to 2.22]	NA
24w	RR, 1.39 [95%CI, 1 to 1.94]	NA
Tolerability		
12w	RR, 2.67 [95%CI, 0.78 to 9.09]	NA

Table 2. Compared with BoNT-A in the outcomes

Abbreviations: BoNT-A, botulinum neurotoxin A. MIDAS, migraine disability scale.

Footnote: Tolerability was defined as the rate of participants who dropped out because of adverse event.

Figures

A Headache days

B Migraine days

Figure 1

Primary efficacy outcomes Abbreviations: 95%CI, 95% confidence interval. SMD, standard mean difference. Footnote: The network meta-analyses assessed the two primary outcomes at week 12: (A) monthly headache days, (B) monthly migraine days. The left of both (A) and (B) shows the geometry of the networks, and the right shows the forest plots using placebo as a reference comparator. The size of the red nodes corresponds to the number of participants who were allocated to the treatments. Direct comparison was linked by a line between two treatments; the thickness of the lines corresponds to the number of trials that studied the treatment. The blue triangle among treatments indicates a three-arm design of an RCT. The treatments were ranked by P-scores. A P-score is an estimation of the mean probability of a treatment to be the best treatment. A treatment with the highest P-score ranked the most effective. A SMD>0 indicates superiority of a treatment over placebo.

Figure 2

Secondary efficacy outcomes Abbreviations: 95%CI, 95% confidence interval. MIDAS, migraine disability assessment. RR, relative ratio. SMD, standard mean difference. Footnote: The meta-analyses assessed the following outcomes at week 12: (A) mean monthly headache intensity, (B) responder rate, (C) MIDAS, and (D) frequency of acute medication intake. (C) MIDAS scale assesses the impact of migraine headache on daily life and summarizes the total number of days with impact. Higher MIDAS scores indicate worse migraine headaches. The left of plot (A)-(D) shows the geometry of the networks, and the right shows the forest plots using placebo as a reference comparator. The size of the red nodes corresponds to the number of participants

who were allocated to the treatments. Direct comparison was linked by a line between two treatments; the thickness of the lines corresponds to the number of trials that studied the treatment. The blue triangle among treatments indicates a three-arm design of an RCT. The treatments were ranked by P-scores. A P-score is an estimation of the mean probability of a treatment to be the best treatment. A treatment with the highest P-score ranked the most effective. A SMD>0 or an RR>1 indicates superiority of a treatment over placebo.

Figure 3

Safety outcomes Abbreviations: 95%CI, 95% confidence interval. RR, relative ratio. Footnotes: The network meta-analyses assessed adverse events at week 12 and 24. Tolerability was defined as the number of dropouts owing to adverse events. If a treatment had higher RR of dropouts owing to adverse event, it indicates lower tolerability of treatment. The treatments were ranked by P-scores. A P-score is an estimation of the mean probability of a treatment to be the most harmful treatment. An RR>1 indicates superiority of a treatment over placebo.

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