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Comparative efficacy and safety of different pharmacological therapies to medication overuse headache: a network meta-analysis

Fanyi Kong[1], Dawn C. Buse[2], Guoliang Zhu[3] and Jingjing Xu[4*]

Abstract

Background Controversy exists whether prophylactic drugs are necessary in the treatment of medication overuse headache (MOH).

Objectives To determine comparative benefits and safety of available drugs for the treatment of MOH including elimination of medication overuse (MO).

Methods We systematically reviewed randomized controlled trials though an extensive literature search comparing different drug effects on MOH. A random-effect network meta-analysis was conducted to rank comparative effects of interventions. Outcome improvements from baseline include responder rate defined as ≥ 50% reduction of headache frequency, proportion of patients who revert to no acute medication overuse (nMO), and reduction in monthly headache and acute medication intake frequency. Certainty of evidence was classified using the Grading of Recommendations, Assessment, Development & Evaluation (GRADE).

Results Of 8,248 screened publications, 28 were eligible for analysis. Topiramate was found to be beneficial based on its responder rate (odds ratios [OR] 4.93), headache frequency (weighted mean difference [WMD] -5.53) and acute medication intake frequency (WMD − 6.95), with fewer safety issues (i.e., tolerability, or more adverse events) than placebo (OR 0.20). Fremanezumab, galcanezumab and botulinum toxin type A (BTA) were beneficial for increased responder rates (OR 3.46 to 3.07, 2.95, and 2.57, respectively). For reversion to nMO, eptinezumab, fremanezumab and BTA were superior to placebo (OR 2.75 to 2.64, 1.87 to1.57, and 1.55, respectively). Eptinezumab, fremanezumab, erenumab 140 mg, and BTA were more efficacious than erenumab 70 mg (OR 3.84 to 3.70, 2.60 to 2.49, 2.44 and 2.16, respectively) without differences in safety and tolerability.

Conclusion Despite lower safety and greater intolerability issues, topiramate has large beneficial effects *probably* on increasing responder rates, reducing headache frequency, and *might* reduce monthly medication intake frequency. Fremanezumab, galcanezumab, and eptinezumab are promising for increasing responder rates. For reversion to nMO, eptinezumab has large beneficial effects, fremanezumab has a smaller effect. BTA *might* have a moderate effect on responder rates and *probably* has a small effect on reversion to nMO.

Trial registration PROSPERO, CRD42021193370.

Keywords Medication overuse headache, Medication overuse, Efficacy, Tolerability, Systematic review, Network meta-analysis

*Correspondence:
Jingjing Xu
jingsusan123@163.com
Full list of author information is available at the end of the article

Introduction

As defined in the International Classification of Headache Disorders-3rd edition (ICHD-3), medication overuse headache (MOH) refers to monthly headache days of ≥15 per month resulting from acute "medication overuse" defined as the frequent consumption of acute pain medications above a certain threshold (e.g. 10 or 15 days per month depending on the medication type) for ≥three months [1]. The prevalence of MOH is uncertain [2] and estimates vary dramatically from 2% in a recent population-based study [3] to 60% among patients with chronic headache in the Global Burden of Disease Study [4]. Rates of medication overuse among patients with migraine in two US population based studies were reported to be 15% in the MAST study [5] and 17.7% in the CaMEO study [6]. MOH is associated with many negative outcomes. MOH is a predictor of inefficacy of a first preventive drug for migraine [7] and is associated with dependence or abuse of psychoactive substances other than analgesics or acute migraine drugs [8]. Whether MOH is a cause or consequence of frequent acute medication intake has been debated for years and there is likely a bidirectional relationship along with influences of shared underlying mechanisms [9, 10].

Addressing medication overuse is a very important aspect of good clinical care due to its association with increased risk of chronic headache [11] and chronic migraine among people with episodic migraine [12, 13]. And managing MOH is a very important task in clinical care. The optimal management of MOH was a hotly debated topic without clear empirical guidance until the Medication Overuse Treatment Strategy (MOTS) trial compared the efficacy of migraine preventive therapy in chronic migraine with medication overuse (CMMO), with or without switching the overused medication to a restricted acute alternative (≤2 days per week) [14]. In the trial, 720 adults were randomized to continue their overused medication or switch, while receiving pharmacologic preventive treatment. Results showed no significant difference in moderate to severe headache days between groups at 12 weeks (9.3 vs. 9.1 days; $p=0.75$) or during the first two weeks (6.6 vs. 6.4 days; $p=0.57$). While this important study determined that preventive therapy without switching is not inferior, the study did not assess the relative efficacy and tolerability of the various preventive medication options.

Patients with MOH experience severe headache and migraine-related impact on function and worse quality of life [15]. Results from a former systematic review [16] and a randomized clinical trial [17] support a program of prophylaxis treatment together with abrupt withdrawal of acute analgesics when treating MOH. However, due to an insufficient number of randomized controlled trials that make a direct comparison between drug versus placebo, a previous systematic review did not find an acceptable level of evidence for recommending the use of any of particular prophylactic medications [18].

Therefore, we conducted a network meta-analysis (NMA), also known as a multiple-treatments meta-analysis [19], to assess the comparative effects of current available pharmacological therapies for patients with MOH. NMA enables data integration from direct comparisons of treatments within trials and from indirect comparisons when treatments are compared to a common comparator between different trials [20]. By using the analytic approach of NMA to compare and rank multiple interventions based on their relative estimated effects in each outcome [21], we will also provide a summary of comparative effectiveness and safety or tolerability between multiple drugs.

Methods

We followed the PRISMA guidelines for reporting systematic reviews incorporating network meta-analyses [22]. The protocol of the present review has been registered with the international prospective register of systematic reviews (PROSPERO, CRD 42021193370).

Eligibility criteria

Inclusion and exclusion criteria followed the PICOS (patients, intervention, comparison, outcome, and study design) framework. We included patients that fulfilled ICHD-3 diagnostic criteria for MOH with or without other types of primary headache (e.g., migraine, tension-type headache, chronic daily headache) and who were studied in randomized or quasi-randomized controlled trials comparing the efficacy of a drug therapy with a placebo control, blank control, or positive control. The positive control drug needed to be recommended by guidelines for primary headache treatment or prevention to avoid a false positive control therapy being analyzed. The following types of publications were excluded: conference abstracts, retrospective studies, duplications, and unavailable articles [23]. Studies were requited to be published in English or Chinese.

Literature search

We conducted a comprehensive medical literature search from inception through December, 2023 in PubMed, EMBASE, Ovid and the Cochrane Controlled Trials Register for randomized, controlled trials published in English. We also searched the China Biological Medicine Database (CBM-disc), the Chinese National Knowledge Infrastructure (CNKI), and Wan Fang Med for articles published in Chinese. The reference lists of all related manuscripts (e.g., reviews and guidelines) and relevant

articles cited by published reviews were also checked. Full details on search strategies are provided in Supplemental 1.

Study selection

Three reviewers (FK, JX and GZ) independently conducted an electronic search and screened titles and abstracts for consideration. Full texts were obtained from potentially relevant studies when the information given in the title or abstract met the aforementioned eligibility criteria. References included in systematic reviews of the same topic were also manually checked.

Data collection

We extracted baseline data from the included studies using a structured data-abstraction form including research country, published year and date including the elements outlined in Cochrane reviews using the acronym PICOS. PICOS stands for Population (the group being studied), Intervention (the treatment or procedure being investigated), Comparison (a control or alternative treatment for comparison), Outcome (the effects or results measured), and Study Design (the type of study, such as randomized controlled trials or cohort studies). We contacted authors of included studies if data provided were insufficient for synthesis.

Outcome measures of interest

As there are not guidelines for reporting results from clinical trials treating MOH, we adopted Hagen et al.'s suggestions for endpoints for MOH studies follow-up including headache days/month, medication days/month, and responder rate defined as $\geq 50\%$ reduction of headache frequency from baseline [24]. We also extracted outcomes on reversion to no medication overuse when reported. In order to rank the comparative effectiveness of multiple interventions, mean change on monthly headache day frequency and monthly acute medication day intake frequency from baseline were retrieved or calculated where needed. Formulas for data conversion on mean change from baseline are provided in Supplemental 2. Following the International Headache Society guideline [25], responder rate was regarded as the primary outcome. Safety/tolerability evaluation refers to the documentation of any adverse events occurring during the study period.

Geometry of the network

The geometry of the network characterizes the relationships and precision of direct comparisons. At the level of intervention classes, we analyzed head-to-head comparisons between different agents with placebo or other controlled interventions. The geometry of the network was assessed by generating network graphs [26]. Each type of drug intervention represents a node in the network. Randomized comparisons between interventions are shown as links between the nodes. The thickness of the line in the network graphs represents the number of studies included for this comparison. The color of the lines discriminates between open-label trials and blind trials. When a multi-arm trial compares the same intervention given at different dosage, they are treated as different interventions and represented as different nodes in the network. Lumping interventions of different dosages in NMA could break the randomization principle of the original studies. We did not merge treatment regimens that have similar effects (e.g., corticosteroids, calcitonin gene-related peptide, antiepileptics) in pooled analyses as there is scarce strong evidence on recommendations for treatment of MOH [27].

Risk of bias assessment

Risk of bias in the included studies was accomplished using the modified Cochrane risk of bias tool for quality assessment [28] in terms of selection bias, performance bias, attrition bias, and detection bias. Level of bias was determined by assessment of sequence generation, allocation concealment, blinding, incomplete outcome data, and selective reporting within each study and finally graphed by the Cochrane Risk of Bias Scale.

Publication bias assessment

A funnel plot would be used to assess publication bias if the minimum number of included studies reporting on the same outcome is larger than 10 [26].

Statistical analysis

First we conducted a standard pair-wise meta-analysis with a random-effects model [29] for comparisons of the same interventions. Data on continuous outcomes were expressed as standardized mean difference (SMD). Dichotomous data on outcomes were expressed as odds ratios (OR) with 95% confidence intervals (CI). ORs > 1 indicated positive efficacy of a study intervention. Statistical heterogeneity in these analyses was assessed with calculation of an I^2 value. An I^2 value of $\geq 50\%$ or a $\chi 2$ test < 0.1 level indicated significant heterogeneity.

We assessed patient baseline characteristics (age, headache duration, monthly headache day frequency, and headache severity) as potential baseline modifiers to ensure similarity among included study populations and to investigate the potential effect of heterogeneity on effect estimates using meta-regression if any difference was found.

Then we conducted random-effects NMA using the Markov chain Monte Carlo method to assess all indirect

comparisons [21]. Comparative odds ratios (ORs) for dichotomous outcomes or weighted mean differences (WMD) change from baseline for continuous outcomes and associated 95% credible intervals (CrIs) across all types of interventions were pooled. A high OR indicates a higher probability of the intervention efficacy but a probably of lower safety of the intervention. For data expressed as mean change from baseline, a lower WMD indicates a stronger beneficial effect of the intervention.

Loop inconsistency that reflects whether discrepancy exists between direct and indirect evidence in NMA was evaluated using the Bucher method [30] in every closed loop. Inconsistency in each network was defined as yielding a 95% confidence interval (CI) excluding zero. When the lower bound and the 95% CIs for the inconsistency factors (IF) is closer to zero, it is regarded as better consistency [31, 32]. The origin of the inconsistency was detected using a node-splitting model [33]. Design inconsistency which reflects whether the treatments of interest in a study are associated with effect sizes for particular contrasts was assessed with a design-by-treatment-interaction model [34] using the χ^2 test when a multi-arm trial was involved. Convergence of the simulations was evaluated using the Brooks-Gelman-Rubin method by calculating the Potential Scale Reduction Factor (PSRF). A PSRF close to one indicates approximate convergence [35].

A sensitivity analysis was performed by removing studies with high risk of bias and studies with primary headache other than chronic migraine. Subgroup analyses were conducted adjusting for different types of pre-existing primary headache and whether or not withdraw of the overused medication occurred before randomization. Therefore, comparisons of results from the migraine with MOH subgroup versus other types of primary headache with MOH and results from acute medication withdraw subgroups versus no acute mediation withdrawal subgroups for the same intervention are provided.

Finally, we ranked each treatment in terms of efficacy and safety (including tolerability) using surface under the cumulative ranking (SUCRA) probabilities, with higher SUCRA scores indicating better efficacy or safety.

The overall quality of the evidence of the pooled analysis was assessed using Grading of Recommendations Assessment, Development and Evaluation (GRADE) guidelines [36]. Evidence was summarized according to GRADE guidance using a partially contextualized framework [37]. Depending on the point estimate, for binary outcomes, an effect size ≤ 1 implies that the intervention is not superior to placebo. Small, moderate and large beneficial effect labels were applied to magnitude of effects > 1, ≥ 2 and ≥ 5 respectively. For continuous outcomes, effect sizes ≥ 0 imply that the intervention is not superior to placebo. Small, moderate and large beneficial effect labels were given to those with threshold of effect of < 0, $\leq$ -3 and $\leq$ -5 respectively.

Analyses were performed with Stata software (version 14.0; Stata Corp, College Station, TX) to depict relevant diagrams for the present NMA. GRADE pro software (Version 3.2.2) was used to transparently grade the certainty of evidence.

Results

Results of study selection

We identified a total of 8,248 studies in the initial search, leaving 5,175 studies after 3,079 duplicates were removed. Of these, 2,096 were excluded by scanning the title and abstract and 57 were excluded through full-text review leaving 28 studies for final analyses. The flow diagram is presented in eFigure 1.

Baseline data of included studies

The eligible studies were conducted from 2001 to 2023 with a total of 5,527 subjects. Sample sizes ranged from 17 to 904. Of the 28 included studies, 13 trials were prospective registration, 6 were open-label design and 2 were single-blind. Eighteen studies were placebo controlled and 7 were a three-arm design. Sixteen studies included patients with migraine, among which 13 were solely patients with CM with medication overuse. Diagnostic criteria for MOH varied over time as it changed from ICHD-1 to ICHD-3β. Two early studies used Silberstein-Lipton criteria (which were published proposed revisions to the 1994 IHS criteria). Medication interventions for MOH included onabotulinum toxin A (BTA) [38–41], topiramate [42–44], amitriptyline [45], methylprednisolone [46], prednisolone [47–50], ibudilast [51], flunarizine [52], nabilone [53], pregabalin [54, 55], sodium valproate [56], naratriptan [48], fremanezumab [57, 58], erenumab [59], galcanezumab [60, 61], eptinezumab [62, 63], celecoxib [64], and amitriptyline + sodium valproate [65]. Baseline information of the enrolled studies is shown in Table 1 and eTable 1.

Risk bias within studies

Most trials were rated as having low or unclear risk of bias, and overall the included studies were found to be of acceptable methodological quality (eFigures 2 and 3). Studies with high or unclear risk in allocation concealment and blinding were largely due to open-label and single-blind study designs.

Summary of network geometry

Effects of direct comparisons for all outcomes and adverse effects are summarized in Table 2. Networks of eligible comparisons for the network meta-analysis

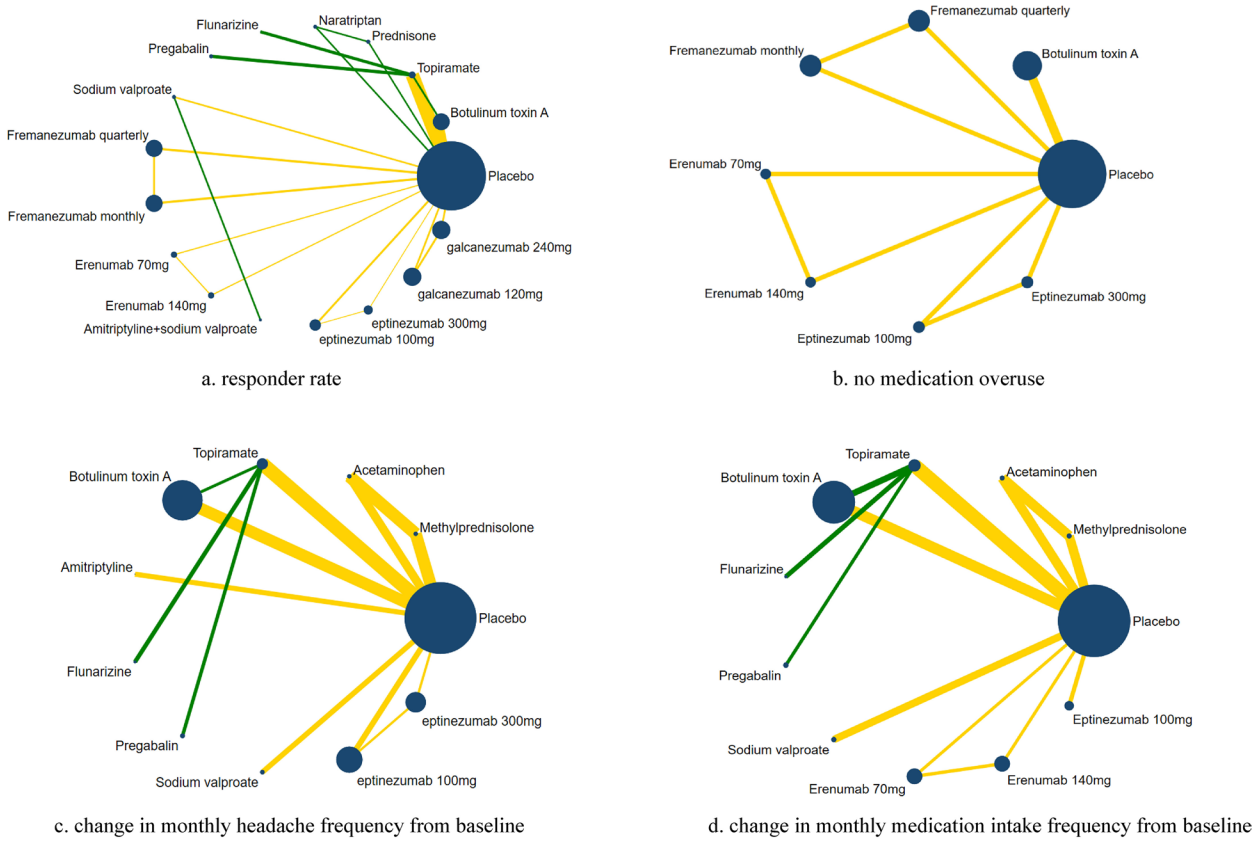


Fig. 1 Network of eligible comparisons for the network meta-analysis for efficacy. The width of the lines for each connection is proportional to the number of randomized controlled trials of each directly compared treatment regimens. The size of the nodes corresponds to the number of randomized participants (sample size). Green line indicates an open-label study design, and yellow line stands for a blinded study design

are shown in Figs. 1 and 2 (for efficacy) and eFigure 3 (for safety/tolerability). Six studies involving 4 different active comparisons (BTA = 2, fremanezumab = 1, erenumab = 1, eptinezumab = 2) and placebo reported outcomes on reversion to no medication overuse without a closed loop.

For the primary outcome, galcanezumab ($I^2 = 57$, OR 2.92; 95% CI 1.86 to 4.58), fremanezumab ($I^2 = 0$, OR 3.39; 95% CI 2.53 to 4.55) and eptinezumab ($I^2 = 50$, OR 2.54; 95% CI 1.89 to 3.43) were superior to placebo in increasing responder rates (eFigure 4a).

Direct comparisons favor onabotulinum toxin A over placebo in decreasing monthly headache day frequency ($I^2 = 0$, SMD −1.92; 95% CI -2.68 to -1.15, eFigure 4c) and acute medication intake frequency from baseline ($I^2 = 0$, SMD −0.83; 95% CI -1.35 to -0.31, eFigure 4d). Topiramate significantly increased responder rates ($I^2 = 0$, OR 9.69; 95% CI 3.13 to 30.01, eFigure 4a) and reduced monthly headache day frequency from baseline ($I^2 = 89$, SMD −10.16; 95% CI -14.98 to -5.35, eFigure 4d).

As for safety/tolerability, a lower risk of AEs was found with pregabalin when compared to topiramate (OR 0.49; 95% CI 0.24 to 0.97, eFigure 5). The other included studies documented similar risk of AEs when compared to placebo.

The comparative effect of included treatment regimens on outcomes and safety/tolerability in the network meta-analysis are shown in Figs. 2a, d and 3 and eFigure 6. All the interventions are equally effective in indirect comparisons when considering the primary outcome and change in headache day and medication intake day frequency. Flunarizine seemed to be superior to the CGRP monoclonal antibodies for the primary outcome (Fig. 3a). Administration of BTA (OR 2.16; 95% CrI 1.05 to 4.44), fremanezumab quarterly (OR 2.19; 95% CrI 1.03 to 4.64) and monthly (OR 2.60; 95% CrI 1.23 to 5.51) were superior to erenumab 70 mg in increasing the probability of reversion to no medication overuse. The safety/tolerability of BTA (OR 0.46; 95% CrI 0.23 to 0.95), fremanezumab quarterly (OR 0.46; 95% CrI 0.22 to 0.97, and monthly (OR 0.38; 95% CrI 0.18 to 0.81) was inferior to erenumab 70 mg (Fig. 3b). Administration of erenumab

Table 1 Baseline information of the enrolled studies

Study ID	Registry number	Participants	Diagnostic criteria on MOH	Sample size	Intervention	Control group	Acute withdraw of overused medication	Rescue therapies	Follow up
Bøe M.G, 2007, Norway		Probable MOH	ICHD-II	100	Prednisolone	Placebo	Yes (4 weeks)	No	6 days
Cevoli S,2017, Italy		MOH	ICHD-IIR	57	Methylprednisolone	Paracetamol, placebo[a]	Yes (5 days)	Metoclopramide 10 mg i.m. and lorazepam 1 mg or 2.5 mg cap	1 and 3 months
Cui,2019, China		CM + MOH	ICHD-3β	60	Botulinum toxin type A	Topiramate	Yes	Yes	6 months
Descombes S, 2001, France		CDH	ICHD-1	17	Amitriptyline	Trihexyphenidyl	Yes (1 week)	Not allowed	4 weeks
Diener H-C, 2007, multicenter		CM + MOH	ICHD-IIR	46	Topiramate	Placebo	Not described	Yes	16 weeks
Diener H-C, 2021, multicenter	NCT02974153	CM + MOH	ICHD-3β	431	Eptinezumab[a]	Placebo	No	Yes	3 and 6 months
Dodick D.W, 2021, multicenter, EVOLVE-1 and – 2	NCT02614183, NCT02614196	EM + MOH	ICHD-3β	334	Galcanezumab[a]	Placebo	No	Yes	Up to 6 months
Dodick D.W, 2021, multicenter, REGAIN	NCT02614261	CM + MOH	ICHD-3β	708	Galcanezumab[a]	Placebo	No	Yes	12 weeks
Imai N, 2023, Japan and Korea	NCT03303079	CM + MOH	ICHD-3β	318	Fremanezumab[a]	Placebo	Not described	Not described	12 weeks
Johnson J.L, 2015, Australia	NCT01317992	Opioid overuse headache	ICHD-IIR,	34	Ibudilast	Placebo	Not described	Not described	8 weeks
Krymchantowski AV, 2003, Brazil		CDH + MOH	Silberstein revised criteria	150	Prednisolone	Blank control, Naratriptan[a]	Yes (5 weeks)	Chlorpromazine i.v. in clinic	6 days and 5 weeks
Lai K.L, 2016, Chinese Taiwan	NCT02639598	CM + MOH	ICHD-IIR	62	Flunarizine	Topiramate	No	Not described	8 weeks
Liao, 2015, China		MOH	ICHD-II	86	Pregabalin	Topiramate	Not described	Not described	3 weeks
Mei D, 2006, Italy		CM + MOH	ICHD-II	35	Topiramate	Placebo	No	Yes	4 and 8 weeks
Pageler L, 2007, Germany		MOH	ICHD-II	18	Prednisone	Placebo	Yes (5 days)	Limited to lysine acetylsalicylic acid i.v.	3 and 5 days
Pijpers J.A, 2019, Netherlands	www.trialregister.nl #3440	CM + MOH	ICHD-3β	179	Botulinum toxin A	Placebo	Yes (12 weeks)	Not allowed	12,24,36 and 48 weeks
Pini LA, 2012, Italy		MOH	ICHD-II	30	Nabilone	Ibuprofen	Yes (1 week)	Yes	8 weeks
Rabe K, 2012, Germany		Migraine or TTH + MOH	ICHD-II	96	Prednisone	Placebo	Yes(0 days)	Yes	3, 5 and 14 days

Table 1 (continued)

Study ID	Registry number	Participants	Diagnostic criteria on MOH	Sample size	Intervention	Control group	Acute withdraw of overused medication	Rescue therapies	Follow up
Rizzato B, 2011, Italy		CH + MOH	ICHD-II	88	Pregabalin	Topiramate	Yes (8 weeks)	Not allowed	12 and 20 weeks
Sandrini G, 2011, Italy		M(A-) + MOH	ICHD-IIR	56	Onabotulinum toxin A	Placebo	Yes (8 ± 2 days)	Not described	4,8,12 and 24 weeks
Sarchielli P, 2014, Italy	EudraCT code 2007-006773-92	M(A-) + MOH	ICHD-IIR	88	Sodium Valproate	Placebo	Yes (6 days)	Yes	12 and 24 weeks
Silberstein SD, 2013, multicenter	NCT00168428	CM + MOH	ICHD-II	904	Onabotulinum toxin A	Placebo	No	Yes	24 weeks
Silberstein SD, 2020, multicenter	NCT02621931	CM + MOH	ICHD-3β	587	Fremanezumab[a]	Placebo	No	Not described	12 weeks
Silvestrini M, 2003, Italy		CM + MOH	Silberstein revised criteria	28	Topiramate	Placebo	No	Not described	9 weeks
Taghdiri F, 2015, Iran	IRCT2013061211560N6	MOH	ICHD-3β	80	Celecoxib + topiramate	Prednisone + topiramate	Yes	Not described	8 weeks
Tepper S.J, 2019, multicenter	NCT02066415	CM + MOH	ICHD-II	667	Erenumab[a]	Placebo	Yes (2 months), preventive drugs	Not described	1,2 and 3 months
Yu S, 2023, multicenter	NCT04772742	CM + MOH	ICHD-3	190	Eptinezumab	Placebo	Not described	Not described	12 weeks
Zhang, 2017, China		MOH	ICHD-3	78	Amitriptyline + sodium valproate	Sodium valproate	Yes	Not described	3 months

CDH Chronic drug-induced headache, *CH* Chronic headache, *EM* Migraine episodic, *M(A-)* migraine without aura, *MO* Medication overuse, *MOH* Medication overuse headache, *i.m* Intramuscular, *i.v*. Intravenous, *TTH* Tension-type headache

[a] 3-arms study

70 mg was less efficacious than erenumab 140 mg (OR 0.41; 95% CrI 0.20 to 0.82), eptinezumab 100 mg (OR 0.26; 95% CrI 0.11 to 0.65) and eptinezumab 300 mg (OR 0.27; 95% CrI 0.11 to 0.67), but had better safety/tolerability (Fig. 3b).

We assessed the proportion of contribution of each comparison in the network using contribution plots (eFigure 7a to 7d). The comparison of placebo versus BTA (14.29%) or topiramate (14.29%) showed that they contributed equally to responder rates. The comparison of placebo versus BTA contributed 25% to the variable of no medication overuse. The comparison of placebo versus prednisolone or naratriptan had the largest contribution for monthly headache day frequency (21.43%) and medication use frequency change from baseline (21.43%).

Inconsistency checks for all closed loops in the network (eTable 2), and effect estimates between direct and indirect comparisons within loops (eTable 3) did not detect any significant difference for outcomes or safety. Global inconsistency in the network was not determined with closed loops in the 'design-by-treatment' model (eTable 4).

Slight asymmetry in the funnel plots for outcomes on change in monthly headache frequency and medication intake frequency was found on visual inspection, which may attribute to the comparison of topiramate vs. placebo (eFigure 8d).

The cumulative ranking probabilities for efficacy and safety of each treatment regimen are shown in Table 3. Flunarizine (96.7%), amitriptyline + sodium valproate (87.8%), and topiramate (69%) were ranked first, second and third for improving responder rates. Administration of eptinezumab 100 mg (88.4%), 300 mg (85.8%), and fremanezumab monthly (64.6%) were among the most efficacious treatments for reverting MO to no medication overuse. Flunarizine (84.7%) and topiramate (69.4%) were superior to the other remaining treatment regimens in decreasing monthly headache day frequency. Topiramate (73.5%) had the highest probability of all treatment regimens to reduce monthly acute medication intake frequency. The treatment regimens with the cumulative probabilities of having the worse outcomes for safety/tolerability were ibudilast (11.3%), topiramate (16.4%) and amitriptyline (18.4%) (eTable 5).

Quality of evidence

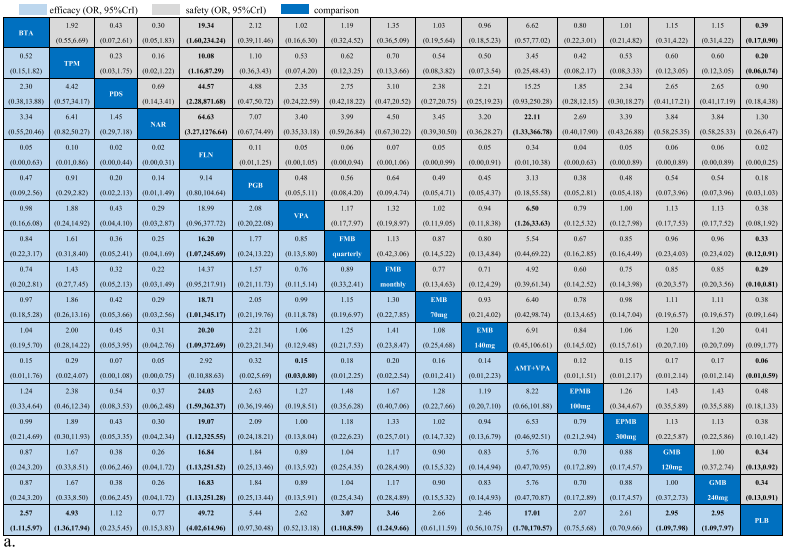
Using the GRADE application, the certainty of evidence was rated as very low and low for all comparisons of most traditional oral preventive medications (Table 3 and eTable 6). Topiramate was rated with moderate certainty of evidence for improving responder rates and decreasing monthly headache frequency. However, fremanezumab, erenumab, eptinezumab and galcanezumab were rated with high certainty for improving all the pooled outcomes. BTA was effective with high certainty only in decreasing monthly headache frequency and medication intake frequency from baseline. Due to several methodological deficits and imprecisions as indicated by 95%CrIs (eTable 6a), certainty of evidence on flunarizine was rated as very low, which means the positive results on flunarizine are inconvincible.

Summary of evidence certainty

Using a partially contextualized framework from GRADE guidance, high certainty of evidence was found for fremanezumab, galcanezumab, eptinezumab, and erenumab on improving responder rates and reversion to no medication overuse. A downgraded moderate certainty of

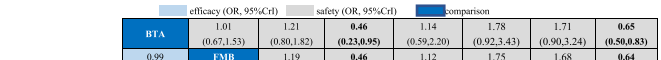
(See figure on next page.)

Fig. 2 **a** Efficacy and safety of the treatment regimens on responder rate. The estimation was calculated as the column-defining treatment compared with the row-defining treatment. For efficacy, ORs higher than 1 favor the column-defining treatment. For safety, ORs lower than 1 indicate the column-defining treatment is safer than the row-defining treatment. Significant results are in bold. BTA: botulinum toxin A; TPM: topiramate; PDS: prednisone; NAR: naratriptan; FLN: flunarizine; PGB: pregabalin; VPA: sodium valproate; FMB: fremanezumab; EMB: erenumab; EPMB: eptinezumab; GMB: galcanezumab; AMT: amitriptyline; PLB: placebo; NA: not applicable due to data unavailable from the refereed study. **b** Efficacy and safety of the treatment regimens on no medication overuse. The estimation was calculated as the column-defining treatment compared with the row-defining treatment. For efficacy, ORs higher than 1 favor the column-defining treatment. For safety, ORs lower than 1 indicate the column-defining treatment is safer than the row-defining treatment. Significant results are in bold. BTA: botulinum toxin A; FMB: fremanezumab; EMB: erenumab; EPMB: eptinezumab; PLB: placebo. **c** Efficacy and safety of the treatment regimens on change in monthly headache frequency from baseline. The estimation was calculated as the column-defining treatment compared with the row-defining treatment. For efficacy, WMDs lower than 0 favor the column-defining treatment. For safety, ORs lower than 1 indicate the column-defining treatment is safer than the row-defining treatment. Significant results are in bold. MP: methylprednisolone; APAP: acetaminophen; TPM: topiramate; BTA: botulinum toxin A; AMT: amitriptyline; FLN: flunarizine; PGB: pregabalin; VPA: sodium valproate; EPMB: eptinezumab; PLB: placebo. **d** Efficacy and safety of the treatment regimens on change in monthly medication intake frequency from baseline. The estimation was calculated as the column-defining treatment compared with the row-defining treatment. For efficacy, WMDs lower than 0 favor the column-defining treatment. For safety, ORs lower than 1 indicate the column-defining treatment is safer than the row-defining treatment. Significant results are in bold. MP: methylprednisolone; APAP: acetaminophen; TPM: topiramate; BTA: botulinum toxin A; FLN: flunarizine; PGB: pregabalin; VPA: sodium valproate; EMB: erenumab; EPMB: eptinezumab; PLB: placebo



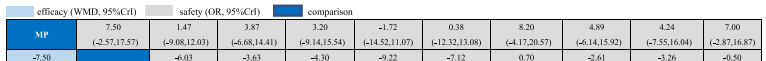
BTA	1.92 (0.55,6.69)	0.43 (0.07,2.61)	0.30 (0.05,1.83)	**19.34 (1.60,234.24)**	2.12 (0.39,11.46)	1.02 (0.16,6.30)	1.19 (0.32,4.52)	1.35 (0.36,5.09)	1.03 (0.19,5.64)	0.96 (0.18,5.23)	6.62 (0.57,77.02)	0.80 (0.22,3.01)	1.01 (0.21,4.82)	1.15 (0.31,4.22)	1.15 (0.31,4.22)	**0.39 (0.17,0.90)**
0.52 (0.15,1.82)	**TPM**	0.23 (0.03,1.75)	0.16 (0.02,1.22)	**10.08 (1.16,87.29)**	1.10 (0.36,3.43)	0.53 (0.07,4.20)	0.62 (0.12,3.25)	0.70 (0.13,3.66)	0.54 (0.08,3.82)	0.50 (0.07,3.54)	3.45 (0.25,48.43)	0.42 (0.08,2.17)	0.53 (0.08,3.33)	0.60 (0.12,3.05)	0.60 (0.12,3.05)	**0.20 (0.06,0.74)**
2.30 (0.38,13.88)	4.42 (0.57,34.17)	**PDS**	0.69 (0.14,3.41)	**44.57 (2.28,871.68)**	4.88 (0.47,50.72)	2.35 (0.24,22.59)	2.75 (0.42,18.22)	3.10 (0.47,20.52)	2.38 (0.27,20.75)	2.21 (0.25,19.23)	15.25 (0.93,250.28)	1.85 (0.28,12.15)	2.34 (0.30,18.27)	2.65 (0.41,17.21)	2.65 (0.41,17.19)	0.90 (0.18,4.38)
3.34 (0.55,20.46)	6.41 (0.82,50.27)	1.45 (0.29,7.18)	**NAR**	**64.63 (3.27,1278.64)**	7.07 (0.67,74.49)	3.40 (0.35,33.18)	3.99 (0.59,26.84)	4.50 (0.67,30.22)	3.45 (0.39,30.50)	3.20 (0.36,28.27)	**22.11 (1.33,366.78)**	2.69 (0.40,17.90)	3.39 (0.43,26.88)	3.84 (0.58,25.35)	3.84 (0.58,25.33)	1.30 (0.26,6.47)
0.05 (0.00,0.63)	0.10 (0.01,0.86)	0.02 (0.00,0.44)	0.02 (0.00,0.31)	**FLN**	0.11 (0.01,1.25)	0.05 (0.00,1.05)	0.06 (0.00,0.94)	0.07 (0.00,1.06)	0.05 (0.00,0.99)	0.05 (0.00,0.91)	0.34 (0.01,10.38)	0.04 (0.00,0.63)	0.05 (0.00,0.89)	0.06 (0.00,0.89)	0.06 (0.00,0.89)	0.02 (0.00,0.25)
0.47 (0.09,2.56)	0.91 (0.29,2.82)	0.20 (0.02,2.13)	0.14 (0.01,1.49)	9.14 (0.80,104.64)	**PGB**	0.48 (0.05,5.11)	0.56 (0.08,4.20)	0.64 (0.09,4.74)	0.49 (0.05,4.71)	0.45 (0.05,4.37)	3.13 (0.18,55.58)	0.38 (0.05,2.81)	0.48 (0.05,4.18)	0.54 (0.07,3.96)	0.54 (0.07,3.96)	0.18 (0.01,1.03)
0.98 (0.16,6.08)	1.88 (0.24,14.92)	0.43 (0.04,4.10)	0.29 (0.03,2.87)	18.99 (0.96,377.72)	2.08 (0.20,22.08)	**VPA**	1.17 (0.17,7.97)	1.32 (0.19,8.97)	1.02 (0.11,9.05)	0.94 (0.11,8.38)	**6.50 (1.26,33.63)**	0.79 (0.12,5.32)	1.00 (0.12,7.98)	1.13 (0.17,7.53)	1.13 (0.17,7.52)	0.38 (0.08,1.92)
0.84 (0.22,3.17)	1.61 (0.31,8.40)	0.36 (0.05,2.41)	0.25 (0.04,1.69)	**16.20 (1.07,245.69)**	1.77 (0.24,13.22)	0.85 (0.13,5.80)	**FMB quarterly**	1.13 (0.42,3.06)	0.87 (0.14,5.22)	0.80 (0.13,4.84)	5.54 (0.44,69.22)	0.67 (0.16,2.85)	0.85 (0.16,4.49)	0.96 (0.23,4.03)	0.96 (0.23,4.02)	**0.33 (0.12,0.91)**
0.74 (0.20,2.81)	1.43 (0.27,7.45)	0.32 (0.05,2.13)	0.22 (0.03,1.49)	14.37 (0.95,217.91)	1.57 (0.21,11.73)	0.76 (0.11,5.14)	0.89 (0.13,5.41)	**FMB monthly**	0.77 (0.13,4.63)	0.71 (0.12,4.29)	4.92 (0.39,61.34)	0.60 (0.14,2.52)	0.75 (0.14,3.98)	0.85 (0.20,3.57)	0.85 (0.20,3.56)	**0.29 (0.10,0.81)**
0.97 (0.18,5.28)	1.86 (0.26,13.16)	0.42 (0.05,3.66)	0.29 (0.03,2.56)	**18.71 (1.01,345.17)**	2.05 (0.21,19.76)	0.99 (0.11,8.78)	1.15 (0.19,6.97)	1.30 (0.22,7.85)	**EMB 70mg**	0.93 (0.21,4.02)	6.40 (0.42,98.74)	0.78 (0.13,4.65)	0.98 (0.14,7.04)	1.11 (0.19,6.57)	1.11 (0.19,6.57)	0.38 (0.09,1.64)
1.04 (0.19,5.70)	2.00 (0.28,14.22)	0.45 (0.05,3.95)	0.31 (0.04,2.76)	**20.20 (1.09,372.69)**	2.21 (0.23,21.34)	1.06 (0.12,9.48)	1.25 (0.21,7.53)	1.41 (0.23,8.47)	1.08 (0.25,4.68)	**EMB 140mg**	6.91 (0.45,106.61)	0.84 (0.14,5.02)	1.06 (0.15,7.61)	1.20 (0.20,7.10)	1.20 (0.20,7.09)	0.41 (0.09,1.77)
0.15 (0.01,1.76)	0.29 (0.02,4.07)	0.07 (0.00,1.08)	0.05 (0.00,0.75)	2.92 (0.10,88.63)	0.32 (0.02,5.69)	**0.15 (0.03,0.80)**	0.18 (0.01,2.25)	0.20 (0.02,2.54)	0.16 (0.01,2.41)	0.14 (0.01,2.23)	**AMT+VPA**	0.12 (0.01,1.51)	0.15 (0.01,2.17)	0.17 (0.01,2.14)	0.17 (0.01,2.14)	**0.06 (0.01,0.59)**
1.24 (0.33,4.64)	2.38 (0.46,12.34)	0.54 (0.08,3.53)	0.37 (0.06,2.48)	**24.03 (1.59,362.37)**	2.63 (0.36,19.46)	1.27 (0.19,8.51)	1.48 (0.35,6.28)	1.67 (0.40,7.06)	1.28 (0.22,7.66)	1.19 (0.20,7.10)	8.22 (0.66,101.88)	**EPMB 100mg**	1.26 (0.34,4.67)	1.43 (0.35,5.89)	1.43 (0.35,5.88)	0.48 (0.18,1.33)
0.99 (0.21,4.69)	1.89 (0.30,11.93)	0.43 (0.05,3.35)	0.30 (0.04,2.34)	**19.07 (1.12,325.55)**	2.09 (0.24,18.21)	1.00 (0.13,8.04)	1.18 (0.22,6.23)	1.33 (0.25,7.01)	1.02 (0.14,7.32)	0.94 (0.13,6.79)	6.53 (0.46,92.51)	0.79 (0.21,2.94)	**EPMB 300mg**	1.13 (0.22,5.87)	1.13 (0.22,5.86)	0.38 (0.10,1.42)
0.87 (0.24,3.20)	1.67 (0.33,8.51)	0.38 (0.06,2.46)	0.26 (0.04,1.72)	**16.84 (1.13,251.52)**	1.84 (0.25,13.46)	0.89 (0.13,5.92)	1.04 (0.25,4.35)	1.17 (0.28,4.90)	0.90 (0.15,5.32)	0.83 (0.14,4.94)	5.76 (0.47,70.95)	0.70 (0.17,2.89)	0.88 (0.17,4.57)	**GMB 120mg**	1.00 (0.37,2.74)	**0.34 (0.13,0.92)**
0.87 (0.24,3.20)	1.67 (0.33,8.50)	0.38 (0.06,2.45)	0.26 (0.04,1.72)	**16.83 (1.13,251.28)**	1.84 (0.25,13.44)	0.89 (0.13,5.91)	1.04 (0.25,4.34)	1.17 (0.28,4.89)	0.90 (0.15,5.32)	0.83 (0.14,4.93)	5.76 (0.47,70.87)	0.70 (0.17,2.89)	0.88 (0.17,4.57)	1.00 (0.37,2.73)	**GMB 240mg**	**0.34 (0.13,0.91)**
2.57 (1.11,5.97)	**4.93 (1.36,17.94)**	1.12 (0.23,5.45)	0.77 (0.15,3.83)	**49.72 (4.02,614.96)**	5.44 (0.97,30.48)	2.62 (0.52,13.18)	**3.07 (1.10,8.59)**	**3.46 (1.24,9.66)**	2.66 (0.61,11.59)	2.46 (0.56,10.75)	**17.01 (1.70,170.57)**	2.07 (0.75,5.68)	2.61 (0.70,9.66)	**2.95 (1.09,7.98)**	**2.95 (1.09,7.97)**	**PLB**

a.



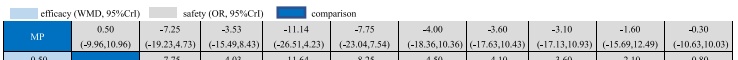
BTA	1.01 (0.67,1.53)	1.21 (0.80,1.82)	**0.46 (0.23,0.95)**	1.14 (0.59,2.20)	1.78 (0.92,3.43)	1.71 (0.90,3.24)	**0.65 (0.50,0.83)**
0.99 (0.65,1.49)	**FMB quarterly**	1.19 (0.86,1.64)	**0.46 (0.22,0.97)**	1.12 (0.56,2.24)	1.75 (0.88,3.49)	1.68 (0.86,3.30)	**0.64 (0.46,0.88)**
0.83 (0.55,1.25)	0.84 (0.61,1.16)	**FMB monthly**	**0.38 (0.18,0.81)**	0.94 (0.47,1.88)	1.47 (0.74,2.94)	1.42 (0.72,2.78)	**0.54 (0.39,0.74)**
2.16 (1.05,4.44)	**2.19 (1.03,4.64)**	**2.60 (1.23,5.51)**	**EMB 70mg**	**2.46 (1.22,4.96)**	**3.84 (1.55,9.51)**	**3.68 (1.50,9.03)**	1.39 (0.71,2.74)
0.88 (0.45,1.70)	0.89 (0.45,1.78)	1.06 (0.53,2.11)	**0.41 (0.20,0.82)**	**EMB 140mg**	1.56 (0.66,3.69)	1.50 (0.64,3.50)	0.57 (0.31,1.04)
0.56 (0.29,1.09)	0.57 (0.29,1.14)	0.68 (0.34,1.35)	**0.26 (0.11,0.65)**	0.64 (0.27,1.51)	**EPMB 100mg**	0.96 (0.55,1.67)	0.36 (0.20,0.67)
0.59 (0.31,1.11)	0.59 (0.30,1.16)	0.71 (0.36,1.38)	**0.27 (0.11,0.67)**	0.67 (0.29,1.55)	1.04 (0.60,1.81)	**EPMB 300mg**	0.38 (0.21,0.68)
1.55 (1.20,1.99)	**1.57 (1.13,2.18)**	**1.87 (1.35,2.59)**	0.72 (0.36,1.41)	1.76 (0.96,3.24)	**2.75 (1.50,5.05)**	**2.64 (1.47,4.76)**	**PLB**

b.



MP	7.50 (-2.57,17.57)	1.47 (-9.08,12.03)	3.87 (-6.68,14.41)	3.20 (-9.14,15.54)	-1.72 (-14.52,11.07)	0.38 (-12.32,13.08)	8.20 (-4.17,20.57)	4.89 (-6.14,15.92)	4.24 (-7.55,16.04)	7.00 (-2.87,16.87)
-7.50 (-17.57,2.57)	**APAP**	-6.03 (-15.31,3.26)	-3.63 (-12.91,5.64)	-4.30 (-15.57,6.97)	-9.22 (-20.99,2.54)	-7.12 (-18.79,4.54)	0.70 (-10.61,12.01)	-2.61 (-12.43,7.20)	-3.26 (-13.92,7.41)	-0.50 (-9.00,8.00)
-1.47 (-12.03,9.08)	6.03 (-3.26,15.31)	**TPM**	2.39 (-2.12,6.90)	1.73 (-6.56,10.02)	-3.20 (-10.43,4.03)	-1.10 (-8.16,5.97)	6.73 (-1.62,15.07)	3.41 (-2.76,9.59)	2.77 (-4.68,10.22)	**5.53 (1.79,9.27)**
-3.87 (-14.41,6.68)	3.63 (-5.64,12.91)	-2.39 (-6.90,2.12)	**BTA**	-0.67 (-8.94,7.61)	-5.59 (-14.11,2.93)	-3.49 (-11.87,4.89)	4.33 (-3.99,12.66)	1.02 (-5.14,7.18)	0.38 (-7.06,7.82)	3.13 (-0.57,6.84)
-3.20 (-15.54,9.14)	4.30 (-6.97,15.57)	-1.73 (-10.02,6.56)	0.67 (-7.61,8.94)	**AMT**	-4.92 (-15.92,6.07)	-2.82 (-13.71,8.07)	5.00 (-5.50,15.50)	1.69 (-7.19,10.57)	1.04 (-8.77,10.86)	3.80 (-3.60,11.20)
1.72 (-11.07,14.52)	9.22 (-2.54,20.99)	3.20 (-4.03,10.43)	5.59 (-2.93,14.11)	4.92 (-6.07,15.92)	**FLN**	2.10 (-8.01,12.21)	9.92 (-1.12,20.96)	6.61 (-2.90,16.12)	5.97 (-4.41,16.35)	8.72 (0.59,16.86)
-0.38 (-13.08,12.32)	7.12 (-4.54,18.79)	1.10 (-5.97,8.16)	3.49 (-4.89,11.87)	2.82 (-8.07,13.71)	-2.10 (-12.21,8.01)	**PGB**	7.82 (-3.11,18.75)	4.51 (-4.87,13.89)	3.87 (-6.40,14.14)	6.62 (-1.37,14.61)
-8.20 (-20.57,4.17)	-0.70 (-12.01,10.61)	-6.73 (-15.07,1.62)	-4.33 (-12.66,3.99)	-5.00 (-15.50,5.50)	-9.92 (-20.96,1.12)	-7.82 (-18.75,3.11)	**VPA**	-3.31 (-12.25,5.62)	-3.96 (-13.81,5.90)	-1.20 (-8.66,6.26)
-4.89 (-15.92,6.14)	2.61 (-7.20,12.43)	-3.41 (-9.59,2.76)	-1.02 (-7.18,5.14)	-1.69 (-10.57,7.19)	-6.61 (-16.12,2.90)	-4.51 (-13.89,4.87)	3.31 (-5.62,12.25)	**EPMB 100mg**	-0.64 (-7.09,5.80)	2.11 (-2.80,7.03)
-4.24 (-16.04,7.55)	3.26 (-7.41,13.92)	-2.77 (-10.22,4.68)	-0.38 (-7.82,7.06)	-1.04 (-10.86,8.77)	-5.97 (-16.35,4.41)	-3.87 (-14.14,6.40)	3.96 (-5.90,13.81)	0.64 (-5.80,7.09)	**EPMB 300mg**	2.76 (-3.69,9.20)
-7.00 (-16.87,2.87)	0.50 (-8.00,9.00)	**-5.53 (-9.27,-1.79)**	-3.13 (-6.84,0.57)	-3.80 (-11.20,3.60)	**-8.72 (-16.86,-0.59)**	-6.62 (-14.61,1.37)	1.20 (-6.26,8.66)	-2.11 (-7.03,2.80)	-2.76 (-9.20,3.69)	**PLB**

c.



MP	0.50 (-9.96,10.96)	-7.25 (-19.23,4.73)	-3.53 (-15.49,8.43)	-11.14 (-26.51,4.23)	-7.75 (-23.04,7.54)	-4.00 (-18.36,10.36)	-3.60 (-17.63,10.43)	-3.10 (-17.13,10.93)	-1.60 (-15.69,12.49)	-0.30 (-10.63,10.03)
-0.50 (-10.96,9.96)	APAP	-7.75 (-19.73,4.22)	-4.03 (-15.99,7.93)	-11.64 (-27.00,3.72)	-8.25 (-23.53,7.04)	-4.50 (-18.86,9.86)	-4.10 (-18.12,9.92)	-3.60 (-17.62,10.42)	-2.10 (-16.19,11.99)	-0.80 (-11.12,9.52)
7.25 (-4.73,19.23)	7.75 (-4.22,19.73)	TPM	3.72 (-3.24,10.69)	-3.89 (-13.52,5.74)	-0.49 (-10.00,9.01)	3.25 (-8.42,14.93)	3.65 (-7.61,14.91)	4.15 (-7.11,15.42)	5.65 (-5.69,17.00)	6.95 (0.89,13.02)
3.53 (-8.43,15.49)	4.03 (-7.93,15.99)	-3.72 (-10.69,3.24)	BTA	-7.61 (-19.50,4.27)	-4.22 (-16.00,7.57)	-0.47 (-12.13,11.19)	-0.07 (-11.31,11.17)	0.43 (-10.82,11.68)	1.93 (-9.40,13.26)	3.23 (-2.80,9.26)
11.14 (-4.23,26.51)	11.64 (-3.72,27.00)	3.89 (-5.74,13.52)	7.61 (-4.27,19.50)	FLN	3.39 (-10.14,16.93)	7.14 (-7.99,22.27)	7.54 (-7.27,22.35)	8.04 (-6.77,22.86)	9.54 (-5.34,24.42)	10.84 (-0.53,22.22)
7.75 (-7.54,23.04)	8.25 (-7.04,23.53)	0.49 (-9.01,10.00)	4.22 (-7.57,16.00)	-3.39 (-16.93,10.14)	PGB	3.75 (-11.31,18.80)	4.15 (-10.59,18.88)	4.65 (-10.09,19.38)	6.15 (-8.65,20.95)	7.45 (-3.83,18.72)
4.00 (-10.36,18.36)	4.50 (-9.86,18.86)	-3.25 (-14.93,8.42)	0.47 (-11.19,12.13)	-7.14 (-22.27,7.99)	-3.75 (-18.80,11.31)	VPA	0.40 (-13.37,14.17)	0.90 (-12.87,14.67)	2.40 (-11.44,16.24)	3.70 (-6.28,13.68)
3.60 (-10.43,17.63)	4.10 (-9.92,18.12)	-3.65 (-14.91,7.61)	0.07 (-11.17,11.31)	-7.54 (-22.35,7.27)	-4.15 (-18.88,10.59)	-0.40 (-14.17,13.37)	EMB 70mg	0.50 (-9.01,10.01)	2.00 (-11.49,15.49)	3.30 (-6.19,12.79)
3.10 (-10.93,17.13)	3.60 (-10.42,17.62)	-4.15 (-15.42,7.11)	-0.43 (-11.68,10.82)	-8.04 (-22.86,6.77)	-4.65 (-19.38,10.09)	-0.90 (-14.67,12.87)	-0.50 (-10.01,9.01)	EMB 140mg	1.50 (-11.99,14.99)	2.80 (-6.69,12.29)
1.60 (-12.49,15.69)	2.10 (-11.99,16.19)	-5.65 (-17.00,5.69)	-1.93 (-13.26,9.40)	-9.54 (-24.42,5.34)	-6.15 (-20.95,8.65)	-2.40 (-16.24,11.44)	-2.00 (-15.49,11.49)	-1.50 (-14.99,11.99)	EPMB 100mg	1.30 (-8.29,10.89)
0.30 (-10.03,10.63)	0.80 (-9.52,11.12)	**-6.95 (-13.02,-0.89)**	-3.23 (-9.26,2.80)	-10.84 (-22.22,0.53)	-7.45 (-18.72,3.83)	-3.70 (-13.68,6.28)	-3.30 (-12.79,6.19)	-2.80 (-12.29,6.69)	-1.30 (-10.89,8.29)	PLB

d.

Fig. 2 (See legend on previous page.)

Table 2 Effects of direct comparisons on outcomes and adverse events

	Outcomes				Adverse events		
	Responder rate (events/ total)	No medication overuse (events/ total)	Change in monthly headache frequency from baseline (WMD,95%CI)	Change in monthly medication frequency from baseline (WMD,95%CI)	Events/ total	OR (95%CI)	
vs. Placebo							
Naratriptan	20/35 vs. 26/41	NA	NA	NA	1/50 vs. 0/50		NA
Fremanezumab monthly	98/309 vs. 38/299	161/201 vs. 87/120	NA	NA	141/309 vs. 120/299		1.25 (0.90, 1.72)
Fremanezumab quarterly	103/297 vs. 38/299	164/198 vs. 87/120	NA	NA	141/297 vs. 120/299		1.34 (0.97, 1.86)
Erenumab 70 mg	28/77 vs. 20/113	17/77 vs. 32/113	NA	**-2.80 (-4.23**, **-1.37)**	36/77 vs. 39/113		1.66 (0.92, 3.01)
Erenumab 140 mg	27/78 vs. 20/113	32/78 vs. 32/113	NA	**-3.30 (-4.70**, **-1.90)**	38/78 vs. 39/113		1.86 (0.99, 3.25)
Eptinezumab 100 mg	112/229 vs. 74/245	11/229 vs. 13/245	**-2.67 (-3.58**, **-1.75)**	NA	92/229 vs. 113/245		0.78 (0.54, 1.12)
Eptinezumab 300 mg	91/147 vs. 50/145	3/147 vs. 13/145	**-3.20 (-4.63**, **-1.77)**	NA	83/147 vs. 75/145		1.21 (0.76, 1.92)
Galcanezumab 120 mg	94/255 vs. 97/526	NA	NA	NA	NA		NA
Galcanezumab 240 mg	98/261 vs. 96/526	NA	NA	NA	NA		NA
Topiramate	35/58 vs. 3/51	NA	**-10.16 (-14.98**, **-5.35)**	-8.65 (-19.14, 1.85)	38/46 vs. 17/55		**10.61 (4.09**,**27.53)**
Prednisone	29/44 vs. 26/41	NA	NA	NA	2/159 vs. 1/159		2.01 (0.18, 22.43)
Valproate	18/40 vs. 10/42	NA	1.20 (-1.88, 4.28)	**-3.70 (-7.09**, **-0.31)**	25/44 vs. 25/44		1.00 (0.43, 2.32)
Botulinum toxin A	239/559 vs. 173/576	315/532 vs. 270/547	**-1.91 (-2.68**, **-1.14)**	**-0.83 (-1.35**, **-0.30)**	303/561 vs. 257/575		**1.45 (1.15**, **1.83)**
Methyl prednisone	NA	NA	**/**	0.04 (-0.58, 0.67)	0/19 vs. 0/19		NA
Acetaminophen	NA	NA	0.06 (-0.56, 0.68)	0.12 (-0.51, 0.74)	0/19 vs. 0/19		NA
Amitriptyline	NA	NA	**-3.80 (-6.85**, **-0.75)**	NA	NA		NA
vs. Topiramate							
Pregabalin	46/89 vs. 43/85	NA	-1.10 (-2.99, 0.79)	-0.50 (-2.05, 1.05)	46/89 vs. 54/93		0.77 (0.43, 1.38)
Botulinum toxin A	20/30 vs. 8/30	NA	-1.10 (-3.45, 1.25)	0.60 (-2.27, 3.47)	12/30 vs. 26/30		0.10 (0.02, 0.36)
Flunarizine	11/15 vs. 3/14	NA	**-3.20 (-5.82**, **-0.58)**	**-3.90 (-6.08**, **-1.72)**	11/29 vs. 14/27		0.56 (0.19, 1.64)
vs. Valproate							
Amitriptyline + valproate	26/38 vs. 10/40	NA	NA	NA	4/38 vs. 3/40		1.45 (0.30, 6.95)
vs. Prednisone							
Naratriptan	20/35 vs. 29/44	NA	NA	NA	1/50 vs. 1/50		1.00 (0.06, 16.44)
Celecoxib	NA	NA	**-9.24 (-9.84**, **-8.64)**	NA	3/42 vs. 12/38		0.16 (0.04, 0.65)
vs. Methyl prednisone							
Acetaminophen	NA	NA	**-7.50 (-14.99**, **-0.01)**	0.50 (-4.13, 5.13)	NA		NA

CI confidence intervals, *OR* odds ratio, *WMD* weighted mean difference, *NA* not applicable due to data unavailable from the referred study

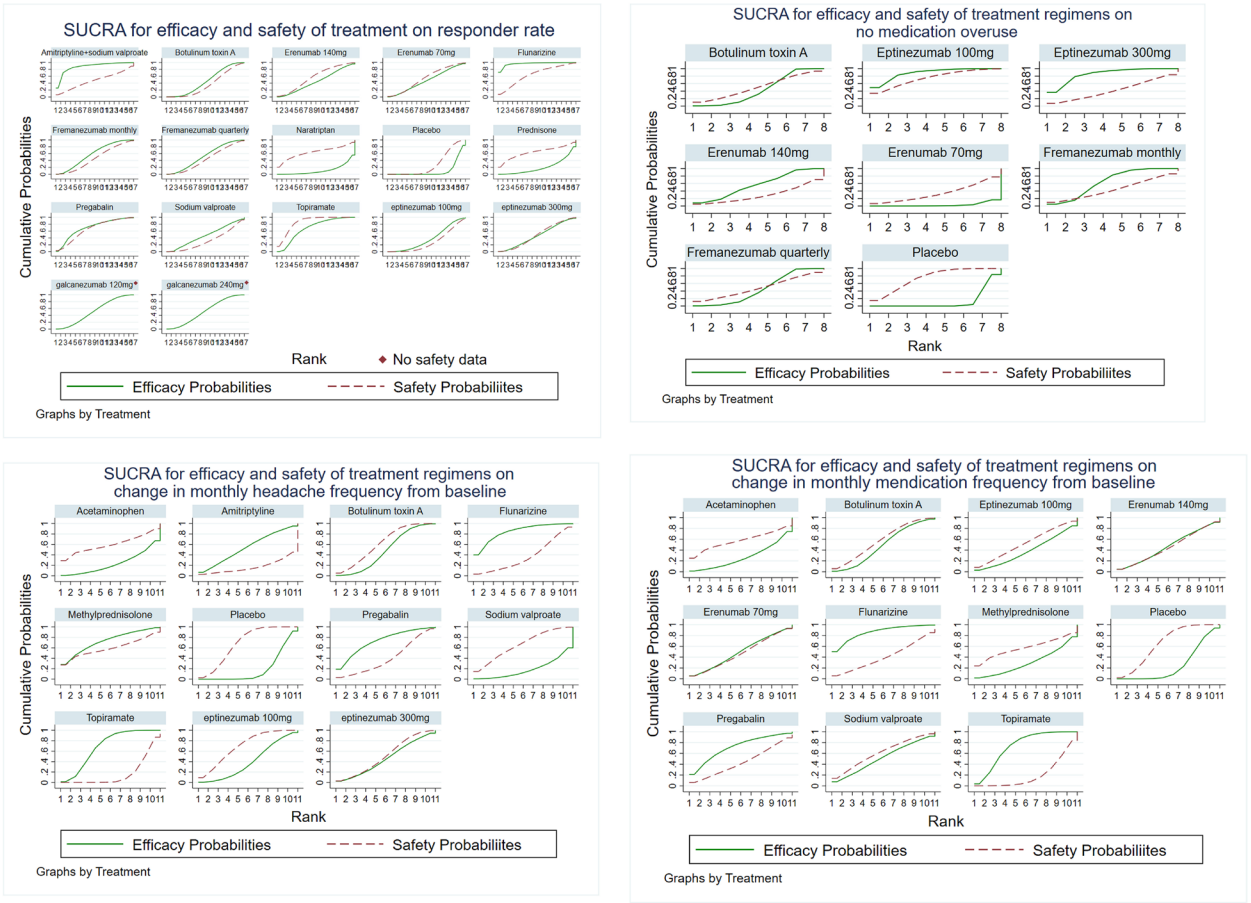


Fig. 3 Plots of cumulative ranking probability for efficacy and safety. Rank indicates the probability to be the best treatment, the second best, the third best, and so on, among the included treatment regimens on different outcomes. SUCRA: surface under the cumulative ranking curve

evidence was found for eptinezumab with large beneficial effect (OR 3.84 for 100 mg and OR 3.70 for 300 mg), fremanezumab (OR 2.60 for quarterly and OR 2.49 for monthly) and BTA (OR 2.16) with moderate beneficial effect, when compared to erenumab 70 mg because of indirect comparisons. We also observed a moderate certainty of evidence for topiramate in improving responder rates (OR 4.93) and reducing monthly headache frequency (WMD −5.53) with a large beneficial effect. There was a low certainty of evidence for topiramate in reducing monthly acute medication intake frequency (WMD −6.95). For BTA, low certainty of evidence was detected on responder rates with moderated beneficial effect (OR 2.57). Moderate certainty of evidence was detected on reversion to no medication overuse with a small beneficial effect (OR 1.55). A partially contextualized framework summary of evidence is provided in Table 4.

Sensitivity analyses and subgroup analyses

As mentioned above, publication bias was detected in the outcomes of change in monthly headache frequency and medication intake frequency from baseline in one study which compared topiramate versus placebo (eFigure 8c and 8d). By excluding the study suspected of publication bias, positive beneficial effects were detected from several interventions including flunarizine, sodium valproate, erenumab, and BTA with narrower CrI boundaries (eTable 7). Nevertheless, results of another sensitivity analysis by examining studies with pre-existing headache of CM were in agreement with those previously produced in NMA (eTable 8a and 8b).

Sensitivity analysis reveal that the Mei D 2006 study [43] is the source of the statistical heterogeneity in the pairwise meta-analysis for the endpoint of change in monthly medication intake frequency from baseline. When this outlier study was removed, no heterogeneity

Table 3 Efficacy rank and quality of evidence of all included treatment regimens

Outcomes	Treatment regimen	Effect size	SUCRA	Certainty of evidence[a]
Responder rate (OR, 95% CrI)	FLN	**49.72 (4.02 to 614.96)**	96.7	Very low
	AMT + VPA	**17.01 (1.70 to 170.57)**	87.8	Very low
	PGB	5.44 (0.97 to 30.48)	69.7	Very low
	TPM	**4.93 (1.36 to 17.94)**	69	Moderate
	FMB monthly	**3.46 (1.24 to 9.66)**	58.1	High
	FMB quarterly	**3.07 (1.10 to 8.59)**	52.7	High
	GMB 240 mg	**2.95 (1.09 to 7.97)**	51.9	High
	GMB 120 mg	**2.95 (1.09 to 7.98)**	51.5	High
	EMB 70 mg	2.66 (0.61 to 11.59)	47.5	High
	EPMB 300 mg	2.61 (0.70 to 9.66)	47.1	High
	VPA	2.62 (0.52 to 13.18)	46.6	Low
	BTA	**2.57 (1.11 to 5.97)**	45.8	Low
	EMB 140 mg	2.46 (0.56 to 10.75)	44.7	High
	EPMB 100 mg	2.07 (0.75 to 5.68)	37.4	High
	PDS	1.12 (0.23 to 5.45)	21	Low
	NAR	0.77 (0.15 to 3.83)	11.8	Low
Reversion to nMO (OR, 95% CrI)	EPMB 100 mg	**2.75 (1.50 to 5.05)**	88.4	High
	EPMB 300 mg	**2.64 (1.47 to 4.76)**	85.5	High
	FMB monthly	**1.87 (1.35 to 2.59)**	64.6	High
	EMB 140 mg	1.76 (0.96 to 3.24)	56.8	High
	FMB quarterly	**1.57 (1.13 to 2.18)**	45.1	High
	BTA	**1.55 (1.20 to 1.99)**	44	Low
	EMB 70 mg	0.72 (0.36 to 1.41)	3.1	High
Mean change of monthly headache frequency (SMD, 95% CrI)	FLN	**-8.72 (-16.86 to -0.59)**	84.7	Very low
	MP	-7.00 (-16.87 to 2.87)	73.1	Very low
	PGB	-6.62 (-14.61 to 1.37)	72	Very low
	TPM	**-5.53 (-9.27 to -1.79)**	69.4	Moderate
	AMT	-3.80 (-11.20 to 3.60)	53.8	Very low
	BTA	-3.13 (-6.84 to 0.57)	48.9	High
	EPMB 300 mg	-2.76 (-9.20 to 3.69)	46.4	High
	EPMB 100 mg	-2.11 (-7.03 to 2.80)	39.9	High
	APAP	0.50 (-8.00 to 9.00)	23.8	Low
	VPA	1.20 (-6.26 to 8.66)	18.8	Low
Mean change of monthly medication intake frequency (SMD, 95% CrI)	FLN	-10.84 (-22.22 to 0.53)	86.3	Very low
	PGB	-7.45 (-18.72 to 3.83)	71.4	Very low
	TPM	**-6.95 (-13.02 to -0.89)**	73.5	Low
	VPA	-3.70 (-13.68 to 6.28)	51.4	Low
	EMB 140 mg	-2.80 (-12.29 to 6.69)	47.1	High
	BTA	-3.23 (-9.26 to 2.80)	49.5	High
	EMB 70 mg	-3.30 (-12.79 to 6.19)	50.2	High
	EPMB 100 mg	-1.30 (-10.89 to 8.29)	37.9	High
	MP	0.30 (-10.03 to 10.63)	30	Low
	APAP	0.80 (-9.52 to 11.12)	27	Low

OR odds ratio, *CrI* credible intervals, *WMD* weighted mean difference, *nMO* no medication overuse, *SUCRA* surface under the cumulative ranking, *BTA* botulinum toxin A, *TPM* topiramate, *PDS* prednisone, *NAR* naratriptan, *FLN* flunarizine, *PGB* pregabalin, *VPA* sodium valproate, *FMB* fremanezumab, *EMB* erenumab, *EPMB* eptinezumab, *GMB* galcanezumab, *AMT* amitriptyline, *PLB* placebo

[a] evidence in direct comparison

Table 4 Summary of the evidence of including treatment regimens on MOH

Outcomes	Comparison	NMA estimate	Certainty of evidence[c]	Classification of effect size
Responder rate (OR, 95% CrI)	FLN vs. PLB	49.72 (4.02 to 614.96)	Very Low[a]	Large beneficial effect
	FLN vs. EPMB 100 mg	24.03 (1.59 to 362.37)	Very Low[a]	
	FLN vs. EMB 140 mg	20.20 (1.09 to 372.69)	Very Low[a]	
	FLN vs. EPMB 300 mg	19.07 (1.12 to 325.55)	Very Low[a]	
	FLN vs. EMB70mg	18.71 (1.01 to 345.17)	Very Low[a]	
	AMT + VPA vs. PLB	17.01 (1.70 to 170.57)	Very Low[a]	
	FLN vs. GMB 120 mg	16.84 (1.13 to 251.52)	Very Low[a]	
	FLN vs. GMB 240 mg	16.83 (1.13 to 251.28)	Very Low[a]	
	FLN vs. FMB quarterly	16.20 (1.07 to 245.69)	Very Low[a]	
	AMT + VPA vs. VPA	6.67 (1.25 to 33.33)	Very Low[a]	
	TPM vs. PLB	4.93 (1.36 to 17.94)	Moderate	
	FMB monthly vs. PLB	3.46 (1.24 to 9.66)	High	
	FMB quarterly vs. PLB	3.07 (1.10 to 8.59)	High	
	GMB 120 mg vs. PLB	2.95 (1.09 to 7.98)	High	Moderate beneficial effect
	GMB 240 mg vs. PLB	2.95 (1.09 to 7.97)	High	
	BTA vs. PLB	2.57 (1.11 to 5.97)	Low	
Reversion to nMO (OR, 95% CrI)	EPMB 100 mg vs. EMB70mg	3.84 (1.53 to 9.09)	Moderate[b]	Large beneficial effect
	EPMB 300 mg vs. EMB70mg	3.70 (1.49 to 9.09)	Moderate[b]	
	EPMB 100 mg vs. PLB	2.75 (1.50 to 5.05)	High	Moderate beneficial effect
	EPMB 300 mg vs. PLB	2.64 (1.47 to 4.76)	High	
	FMB quarterly vs. EMB70mg	2.60 (1.23 to 5.51)	Moderate[b]	
	FMB monthly vs. EMB70mg	2.49 (1.13 to 5.48)	Moderate[b]	
	EMB 140 mg vs. EMB70mg	2.44 (1.22 to 5.00)	High	
	BTA vs. EMB70mg	2.16 (1.05 to 4.44)	Moderate[b]	
	FMB monthly vs. PLB	1.87 (1.35 to 2.59)	High	Small beneficial effect
	FMB quarterly vs. PLB	1.57 (1.13 to 2.18)	High	
	BTA vs. PLB	1.55 (1.20 to 1.99)	Moderate	
Mean change of monthly headache frequency (WMD, 95% CrI)	TPM vs. PLB	-5.53 (-9.27 to -1.79)	Moderate	Large beneficial effect
Mean change of monthly medication intake frequency (WMD, 95% CrI)	TPM vs. PLB	-6.95 (-13.02 to -0.89)	Low	Large beneficial effect

OR odds ratio, *CrI* credible intervals, *WMD* weighted mean difference, *nMO* no medication overuse, *NMA* network meta-analysis, *FLN* flunarizine, *EPMB* eptinezumab, *BTA* botulinum toxin A, *FMB* fremanezumab, *EMB* erenumab, *EPMB* eptinezumab, *TPM* topiramate, *VPA* sodium valproate, *GMB* galcanezumab, *AMT* amitriptyline, *PLB* placebo

[a] Downgrade due to indirectness and imprecision

[b] Downgrade due to indirectness

[c] evidence in NMA estimate

existed within the four remaining studies. This heterogeneity may be attributed to a methodological deficit in the study of interest including unclear allocation concealment, unclear blinding and selective reporting of outcomes (eFigure 2b).

Due to the limited number of studies, subgroup analyses were only available for comparisons for topiramate versus placebo and BTA versus placebo. The beneficial effects in increasing responder rates by topiramate and BTA were more evident in the subgroup of non-withdrawal of overused medication before randomization (eTable 9).

Discussion

Optimal treatment of MOH or CM with MO has long been debated and in fact, the Medication Overuse Treatment Strategy (MOTS) study was designed to evaluate the optimal treatment approach for patients with chronic migraine and medication overuse (CMMO) by comparing the efficacy of migraine preventive pharmacotherapy with or without switching from the overused medication

to an alternative, restricted to ≤2 days per week [14]. This open-label, pragmatic clinical trial randomized 720 adults with CMMO to either continue using their overused medication without a frequency limit or switch to a new medication restricted to ≤2 days per week, alongside preventive treatment. Participants were recruited from 34 clinics across the United States. The primary outcome was the frequency of moderate to severe headache days during weeks 9 to 12 post-randomization, as well as during weeks 1 to 2. After 12 weeks, the frequency of moderate to severe headache days was similar between the two treatment groups, with those who switched medications averaging 9.3 headache days compared to 9.1 days in the group that continued overusing their medication ($p=0.75$, 95% CI -1.0 to 1.3). The first two weeks also showed no significant difference between groups (6.6 vs. 6.4 days; $p=0.57$, 95% CI -0.4 to 0.7). These findings indicate that migraine preventive therapy without switching or limiting the overused medication is not inferior to preventive therapy with switching for reducing moderate to severe headache days in patients with CMMO. However, this important study did not provide data on the relative efficacy and tolerability of the range of pharmacologic preventive medications available. Our network meta-analysis provides data on the many options in treating MOH. Results of this meta-analysis shed light on the most effective and tolerable preventive therapies for treatment of MOH. Topiramate is the only currently available oral medication which might have a large beneficial effect on MOH in increasing the chance of ≥50% reduction in monthly headache days and reducing monthly headache frequency. Intravenous infusion of eptinezumab, subcutaneous administration of fremanezumab or erenumab, and intramuscular injection of BTA are ranked as the four most effective agents for MOH in withdrawal of overused acute headache medication and supported by acceptable levels of evidence. In terms of safety and tolerability, more adverse events were reported with topiramate than BTA.

These findings may help guide clinical choices when balancing both benefits of efficacy and tolerability. Non-pharmacologic therapies also play an important role in the treatment of MOH and may be involved in withdrawal of the offending acute medication [66, 67], effective education [68], and combination of pharmacologic and behavioral treatments which may include cognitive behavioral therapy or mindfulness based therapies among other validated approaches [69]. Research shows that behavioral therapies are associated with sustained remission and benefits following successful treatment of MO [69, 70]. Findings from the ongoing EASTERN study are anticipated, as it is the first 2-arm placebo controlled trial which will investigate the efficacy of Gastrodin (a main bioactive constituent of *Rhizoma Gastrodiae*) in treating MOH together with withdrawal therapy [71].

The findings of the present network meta-analysis are meaningful because decreasing headache days and acute medication intake frequency are fundamental goals in the treatment of MOH. Although evidence from randomized controlled trials [66, 67, 72] confirms that the abrupt withdrawal of the overused acute therapy (or therapies) is first choice for MOH treatment, withdrawal symptoms as well as uncontrolled headache may lead to a higher probability of treatment failure. After discontinuation of overused acute medications, patients may experience worsening of headache (termed withdraw headache or rebound headache), as well as a range of symptoms including but not limited to nausea, vomiting, arterial hypotension, tachycardia, sleep disturbances, restlessness, anxiety, and nervousness which may last for 2 to 10 days [73]. These symptoms make MOH treatment difficult and can lower the chances of adherence to not using acute medications and successful outcomes. Hence the utility in bridging therapy using a preventive drug during the withdrawn phase needs to be determined. However, two previous systematic reviews failed to reach a positive conclusion [16, 18] due to methodological deficits in the direct comparison meta-analysis. The present study is the first network meta-analysis to comprehensively analyze which pharmacological agents are most effective and tolerable for use in bridging therapy of MOH during the withdrawal of overused acute medications.

Strengths of the present network meta-analysis are the selected outcomes are highly practical for clinicians in treatment planning. Despite the fact that they are somewhat different from IHS guideline outcomes for controlled trials of preventive treatment of chronic migraine in adults [25], we believe in the utility of these findings in both clinical research and practice as outcomes were selected based on extensive review of clinical trials for MOH and following experts' recommendations [24]. Furthermore, key to interpreting the results in such a network analysis is the consideration of the range of tools used to assess certainty, quality, risk of bias and in grading level of evidence. Beside the well-established GRADE approach in assessing certainty of evidence, we adopted the newly published partially contextualized framework by GRADE guidance for drawing conclusions from an NMA. This framework allows review authors to classify interventions through the thresholds of small, moderate, and large effects and other decision criteria according to clinical demands considering the magnitude of effect balancing between health benefits and harms. For example, topiramate was studied in five trials within the network, with a large beneficial effect size and acceptable width of credible

interval. But the certainty of the evidence was moderate due to serious inconsistencies and unclear reporting of allocation concealment and the blinding methods, which are key issues that downgrade the evidence level for topiramate. The majority of the studies included in the analysis were of a limited sample size, and only about a third involved more than 100 patients. The limitation could be best exemplified by the finding of the present study that topiramate was the most effective preventive medication for MOH, which was derived from relatively small studies ($n = 25–46$) and could be misleading. In fact, in a post hoc analysis of the pivotal trials of topiramate in chronic migraine, it was found that topiramate was more effective than placebo in the number of monthly migraine days in the European trial, but the difference was not significant in the US trial [42, 74, 75]. Therefore, such a conclusion could be associated with great uncertainty. On the contrary, the ranking for fremanezumab was of high certainty despite a small beneficial effect size based on fewer comparisons than topiramate. Given the low number of studies published, a larger beneficial effect of fremanezumab, as well as of BTA are expected in the future following further clinical trials. Indeed, before publication of CGRP antagonist clinical trials, BTA injections and oral topiramate had been listed with Class A level of evidence in recommendations for the treatment of chronic migraine by consensus of the Brazilian Headache Society [76], and BTA was suggested as effective in treating chronic migraine with or without MO by the German Migraine and Headache Society and the German Society of Neurology in 2019 [77]. None of the included treatment regimens were intended for or tested with pediatric and adolescent populations.

These analyses have many clinical implications. Clinical professionals should be vigilant for risk factors for MOH, and make personalized treatment plans based on patient preferences, history, tolerability, and comorbidities and contraindications by choosing pharmacological and combining non-pharmacological strategies tailored to the needs of each patient [76, 78]. For instance, topiramate should be avoided during pregnancy and lactation. But perhaps another patient had anxiety and high interictal burden and would benefit from CBT in addition to a preventive pharmacologic approach. Several risk factors have been identified for medication overuse in migraine including higher Migraine Symptom Severity Scale scores and Migraine Disability Assessment score, pain intensity, rates of cutaneous allodynia, monthly headache days ≥ 15, interictal burden and anxiety, use of preventive medication, and emergency department / urgent care visits for headache within the previous 6 months [5, 6]. Although there are not serum biomarkers for MOH [79], neurophysiological and neuroimaging abnormalities [80], as well as polymorphisms of the serotonin5HT2A receptor gene (C516T) [81] are related to MOH.

There were limited data for conducting subgroup analyses in the present review. The MOST study determined that for patients with CM and MOH, therapeutic strategies of preventive medication with or without switching/limiting the overused medication were equally effective [14]. Therefore, it is unlikely that the baseline treatment before intervention would induce bias to the present findings.

Sensitivity analysis found a lower certainty of topiramate in reducing monthly medication intake frequency when assessed with the GRADE approach. This trend may be attributed to the low methodological quality of design of the trial of interest, which could be supported by the great heterogeneity detected in direct comparison (supplemental 6d). Yet it does not seem appropriate to exclude the study as no publication bias was detected in the other remaining outcomes. Furthermore, additional sensitivity analyses were conducted by removing studies with other types of primary headache. Estimated effects and SUCRA for all outcomes were consistently significant, which indicated the robustness of our findings.

Follow-up in studies of prednisolone [47–50] were too short to estimate change in monthly headache frequency and monthly acute medication intake frequency. However, it is not likely that longer studies would reach a positive result as none of the available guidelines or consensus statements report efficacy of corticosteroids in treating MOH. Contrarily, the long-term benefit in efficacy and tolerability of CGRP antagonists and BTA on MOH was established by 24 weeks of follow-up (up to 48 weeks on BTA), supporting its use in treating MOH.

Several limitations of this work should be noted. First, data from several controlled trials were obtained from post-hoc or subgroups analysis [40, 42, 57, 59, 60, 62], which may result in false positive results due to the broken randomization. It may also contribute to the risk of bias in the Mei D, 2006 study [43] that finally led to instability of the model in the sensitivity analysis. Similarly, the false negative result of CGRP antagonists and BTA in indirect comparisons may also be largely attributed to post-hoc analysis as lack of sufficient pre-estimation on statistical power for subgroups. Second, nearly all the included single center trials in our analysis did not provide sufficient information on allocation concealment, which might weaken the certainty of overall findings. Third, outcomes with continuous variables expressed by least-squares means in some studies were unable to be merged with mean values in direct or indirect comparisons. This may lead to underestimating the validity and effect size of the interventions. Finally, heterogeneity

among the included studies is worthy of concern and can increase the risk of bias. Care should be taken in the interpretation of the results in light of this limitation. The included studies varied in study population, blinding, sample sizes, baseline treatment before study intervention (i.e., with or without concomitant preventive medications, with or without acute withdrawal of overused medications) and follow-up durations (3 days to 48 weeks). Variation in overused medication types may also result in differences in risk of MOH and patients' response to treatment regimens, as well as outcomes. A 35% and 65% relative risk reduction for developing MOH was noted in favor of triptans as the overused acute medications when compared to nonopioid analgesics and opioid analgesics, respectively [82]. Therefore, such a conclusion could be associated with great uncertainty and findings from the present NMA cannot be generalized to all people with MOH, as data on migraine with MOH contributed primarily in direct comparisons within the network.

Conclusions

Healthcare professionals have a wide range of pharmacologic treatment options available for treating MOH and managing MO. In terms of pharmacologic treatments, despite a higher risk of adverse events and issues with tolerability, topiramate *probably* has large beneficial effects on increasing responder rates and reducing monthly headache frequency and monthly acute medication intake frequency for patients with MOH. It *might* also have a large beneficial effect on reducing monthly acute medication intake frequency. When considering improving the outcome of reversion to no medication overuse, with a large beneficial effect, eptinezumab is *probably* superior to erenumab 70 mg. With a moderate beneficial effect, eptinezumab is superior to placebo, and erenumab 140 mg is superior to erenumab 70 mg. Both fremanezumab administration and BTA are *probably* superior to erenumab 70 mg. With a small beneficial effect, fremanezumab administration is superior to placebo and BTA is *probably* superior to placebo. Treatment of MOH must balance the efficacy, tolerability and accessibility, while at the same time considering patient preferences, history, comorbidities and goals.

Supplementary Information

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Supplementary Material 1.

Authors' contributions

Fanyi Kong: Data curation, Formal analysis, Investigation, Methodology, Project administration, and Writing – original draft. Dawn C. Buse: Data curation, Resources, Supervision, Validation, Writing – review & editing. Guoliang Zhu: Software and Visualization.Jingjing Xu: Conceptualization, Data curation, Formal analysis, Software and Visualization.

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Availability of data and materials

The datasets generated and/or analyzed during the current study are available from Supplementary material, further inquiries can be directed to the corresponding author or the first author upon reasonable request.

Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Competing interests

KF, JX and GZ declare that there are no conflicts of interest.
DCB has grants from Amgen, the National Headache Foundation and the FDA. She has been a consultant for Amgen/Novartis, Allergan/Abbvie, Biohaven, Lilly, Lundbeck, Pfizer, Theranica and Teva. She is on the editorial board of Current Pain and Headache Reports.

Author details

[1]Department of Neurology, The Affiliated Hospital of Yunnan University, Yunnan Province, PR, China. [2]Department of Neurology, Albert Einstein College of Medicine, Bronx, NY, USA. [3]Department of Neurology, Sichuan Academy of Medical Sciences & Sichuan Provincial People's Hospital, University of Electronic Science and Technology of China, Sichuan Province, PR, China. [4]Department of Neurology, Xiangya Changde Hospital, No. 1688, Yueliang Road, Changde 415000, Hunan Province, P R China.

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