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Network meta-analysis comparing efficacy of different strategies on medication-overuse headache

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Abstract

Background Medication-overuse headache (MOH) is the most common secondary headache disorder, resulting from or leading to the frequent use of acute headache medications. Despite the availability of various treatment strategies, the optimal approach remains uncertain.

Objective This network meta-analysis (NMA) aimed to evaluate the comparative efficacy of different strategies for managing MOH, focusing on reducing monthly headache days.

Methods We systematically reviewed randomized controlled trials (RCTs) comparing withdrawal strategies, including bridging therapies, the use of concurrent migraine prevention drugs, and additional education, in adult patients diagnosed with MOH. The primary outcome was the reduction in monthly headache days. Eligible studies were analyzed using a random-effects NMA model, integrating both direct and indirect evidence. Treatments were ranked using p-scores, and risk of bias was assessed using the Cochrane risk of bias tool 2.0.

Results Sixteen RCTs involving 3,000 participants were included. Compared to control, combination therapies, such as abrupt withdrawal with oral prevention and greater occipital nerve block and restriction of overused acute medication with oral prevention and Calcitonin gene-related peptide (CGRP) therapies, demonstrated the greatest efficacy, with reductions in monthly headache days of -10.6 (95% CI: [-15.03; -6.16]) and -8.47 (95% CI: [-12.78; -4.15]), respectively. Headache prevention strategies, including oral prevention (P), anti-calcitonin gene-related peptide (receptor) (CGRP(R)) therapies (A), and botulinum toxin (B) showed significant in reduction of monthly headache days, but no single initial prevention strategy demonstrates superior efficacy over the others. In contrast, abrupt withdrawal alone (W) showed no significant efficacy, with a mean difference of -2.77 (95% CI: [-5.74; 0.20]).

Conclusion Combination therapies, including anti-CGRP(R) therapies and nerve blocks, appear to be the most effective strategies for MOH management, highlighting their potential as initial treatment options. While headache prevention strategies demonstrated similar efficacy, abrupt withdrawal alone was insufficient. The observed reduction in headache frequency after treatment suggests that strategies with greater efficacy may help lower the likelihood of MOH relapse.

Trial registration PROSPERO, CRD 42024620487.

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Keywords Medication-overuse headache, Medication overuse, Chronic migraine, Calcitonin gene-related peptide therapy

Background

Medication-overuse headache (MOH), formerly also called rebound headache, is now recognized as the most common cause of secondary headache. It develops as a consequence of the excessive and frequent use of analgesics for the acute treatment of primary headache disorders. MOH can be diagnosed in patients with a pre-existing primary headache who experience headaches on 15 or more days per month and regularly overuse acute treatments for more than 10 or 15 days per month over a period of three consecutive months [1].

MOH is most common among individuals aged 30–50 years old and affects women three-to-four times more often than men [2]. The prevalence of MOH headache in adults ranges between 0.5 and 2.6%, with higher rates, of up to 7.6%, reported in Russia [3]. Between 11 and 70% of people with chronic headache, particularly migraine, also have MOH [3]. Chronic migraine (CM) combined with MOH, was the third leading cause of disability worldwide, as measured by years of life lost to disability [4].

Many MOH treatment strategies have been proposed including (i) restriction or complete withdrawal of overused drug, (ii) headache prevention, (iii) adding educational sessions or psycho-behavioral therapy, (iv) non-pharmacological strategies, (v) rescue or bridging therapy, and (vi) outpatient versus inpatient treatment. A previous systematic review and meta-analysis showed no benefit of rescue therapy and no difference between inpatient or outpatient treatment on the number of headache days [5]. The treatment strategies for MOH patients still are a debated topic without clear guidance [6]. A randomized controlled trial (RCT) comparing 3 strategies: withdrawal group (W); preventive group (P); and withdrawal plus preventive group (WP), demonstrated no difference in reduction of monthly headache days [7]. Over the past few decades, migraine prevention with oral preventions, botulinum toxin, and monoclonal antibodies targeting calcitonin gene-related peptide (CGRP) or its receptor have proven effective in patients with CM [8], but the efficacy for MOH patients remain unclear. MOH is also described as a biobehavioral disorder [9, 10]. Several RCTs studied the potential benefits of additional behavioral or educational interventions during withdrawal, and their effects on motivation and reduction of overused medication [11–13]. Non-pharmacological or neurostimulation treatment such as transcranial direct current stimulation, occipital nerve stimulation, and transcranial magnetic stimulation can be adopted in case of failure of any recommended drugs [14–16].

Therefore, we conducted a network meta-analysis to evaluate the comparative efficacy of current treatment strategies for patients with MOH, focusing on (i) withdrawal strategies, (ii) headache prevention, (iii) additional education sessions, and (iv) bridging with neurostimulation. These strategies were ranked based on the reduction in the number of monthly headache days.

Methods

We followed the Preferred Reporting Items for Systematic reviews and Meta Analyses (PRISMA) guidelines for reporting systematic reviews and NMA [17]. The review protocol has been registered with the international prospective register of systematic reviews (PROSPERO, CRD 42024620487).

Eligibility criteria

Inclusion criteria followed the PICOS (patients, intervention, comparison, outcome, and study design) framework. We included adult patients (≥ 18 years old) that fulfilled The International Classification of Headache Disorders (ICHD) diagnostic criteria for MOH (ICHD-2 or ICHD-3 or ICHD-3 beta) or had a primary headache disorder and medication overuse as defined by the frequency of acute medication intake according to ICHD criteria [1, 18, 19]. Included studies were required to be randomized controlled trials comparing different strategies including (i) withdrawal strategies, (ii) headache prevention, (iii) additional education sessions, and (iv) bridging with neurostimulation, which could be applied independently or in combination. The primary outcome was the reduction in monthly headache or migraine frequency, assessed either within 2–6 months after starting the intervention or 6 months after completing the education sessions. Studies were excluded if they did not control for each component of strategies outlined in the protocol. For instance, studies comparing abrupt withdrawal plus education to abrupt withdrawal alone without controlling for headache prevention were excluded.

Information source, search strategy, and selection process

We systematically searched in PubMed, MEDLINE and Cochrane through December 2024 for randomized controlled trials published in English. We used keywords relating to (i) overused drug withdrawal (e.g., acute

withdrawal, restriction), (ii) headache prevention (e.g., oral prevention, anti-CGRP(R) therapies, botulinum toxin), (iii) additional education (e.g., education, behavioral therapy), and (iv) neurostimulation (e.g., transcranial direct current stimulation, transcranial magnetic stimulation, occipital nerve stimulation). Titles and abstracts of the retrieved reports were screened using Rayyan [20] by two independent reviewers (PK and SY) to identify potentially eligible studies. The full-text articles of these studies were then independently assessed for inclusion and exclusion criteria by PK and SY. Any disagreements between the reviewers were resolved by a third reviewer (SS). The complete, detailed search syntax for each database can be found in Supplementary Material 1.

Data collection process

Two authors (PK and SY) extracted data independently including the author names, publication date, study design, study setting, study centers, population information (age, sex, primary headache disorders, sample size), intervention (withdrawal strategies, prevention strategies, additional education sessions, neurostimulations), outcome (mean difference of monthly headache/migraine day, standard deviation (SD), follow-up time). Disagreements between the authors were resolved by the third reviewer (SS).

We anticipated variability of outcome measurement across study periods, such as differences in assessing headache or migraine days over 8 to 24 weeks. To address this, we aimed to standardize the time points for reporting headache or migraine frequency to 12 weeks wherever possible.

The outcome, defined as the reduction in the number of monthly headache or migraine days, was measured on a continuous scale and was reported in various formats, including mean change in headache days, or means at baseline and follow-up, or percentage change in headache days. For missing data, we either calculated the necessary values from available information, such as deriving SD from the standard error (SE) and sample size (N), or contacted the primary authors for clarification.

Risk of bias and publication bias assessment

We assessed study risk of bias in the included studies using the Cochrane risk of bias tool 2.0 [21]. For each numerical data item collected, we evaluated the risk of bias across the following domains: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, and bias in selection of the reported result. The results of the risk of bias assessment are categorized as low risk, some concerns, and high risk. The risk of bias plots were generated using the robvis tool [22]. A funnel plot is used to assess publication bias in R program [23].

Geometry of the network

The geometry of the network characterizes the relationships and precision of direct comparisons between treatments. This was assessed by generating network graphs in RStudio using the netmeta package [23]. Each node represents a treatment strategy. The size of the node reflects the number of participants that include those strategies in the network. Larger nodes indicate that more participants evaluated a specific strategy. Edges between nodes represent direct comparisons between treatments in the included studies. The thickness of the edge reflects the number of studies that directly compare the two strategies.

Statistical analysis

We used mean difference (MD) and SD as our effect size in these analyses. Initially, we evaluated a standard pairwise meta-analysis with a random effect model for comparisons of each strategy. We employed a random-effects model due to the anticipated clinical and methodological heterogeneity among studies (e.g., variability in patient populations, intervention types, and follow-up durations). Subsequently we performed network meta-analysis to compare the effect of all strategies on the reduction of monthly headache/migraine days. Studies that could not connect in the network were excluded. For data expressed as the mean change from baseline comparing each strategy to control and all indirect comparisons, a lower mean difference (MD) indicates a stronger beneficial effect of the strategy. We used p-scores to rank treatments. p-scores range from 0 (treatment least likely to be effective) to 1 (treatment most likely to be effective). For transparency, we also provide a league table of pairwise comparisons.These analyses were conducted in RStudio using the netmeta package [23].Statistical heterogeneity in these analyses was assessed with calculation of an I^2 and τ^2 value. An I^2 value of $\geq 50\%$ or a τ^2 test > 0.1 indicated significant heterogeneity [24].

Results

Results of study selection

We identified a total of 1546 studies in the initial search. After removing duplicates, 728 records remained for title and abstract screening. After the initial screening, 52 studies were identified for full-text screening. Thirty-six were excluded through full text review leaving 16 RCT for final analyses. The flow diagram is presented in Fig. 1.

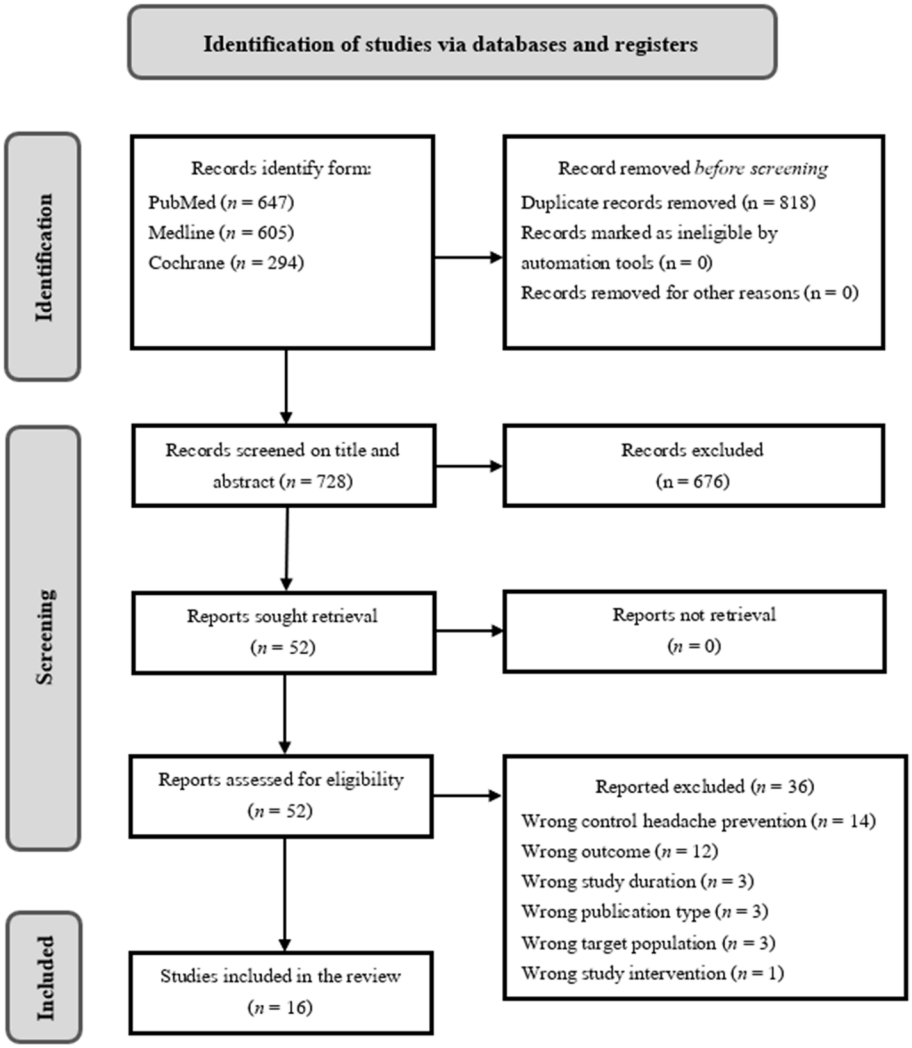

Fig. 1 Flow diagram of study selection process

Baseline data and included studies

The eligible studies were conducted from 2006 to 2023 with a total of 3,000 subjects. Sample sizes ranged from 46 to 904. Of the 16 included studies, four studies were placebo controlled and two were a three-arm design. Diagnostic criteria for MOH varied over time as it transitioned from ICHD-2 to ICHD-3. Two studies were included participants diagnosed with a primary headache disorder who also had medication overuse. Strategies for MOH management included abrupt withdrawal (W) [7, 25–31], oral prevention(s) (P) [7, 25, 32, 33], botulinum toxin injection (B) [34], anti-CGRP(R) therapies (A) [35], abrupt withdrawal plus oral prevention (W + P) [7, 28, 29, 31, 36, 37], abrupt withdrawal plus botulinum toxin injection (W + B) [27, 30], abrupt withdrawal plus greater occipital nerve blocks (W + Nb) [26], abrupt withdrawal plus additional education (W + E) [38], overused drug restriction plus oral prevention(s) (R + P) [33, 39], overused drug restriction plus additional education (R + E) [38], abrupt withdrawal with oral prevention with greater occipital nerve blocks (W + P + Nb) [36], abrupt withdrawal with oral prevention with additional education (W + P + E) [37], overused drug restriction plus oral prevention(s) plus anti-CGRP(R) therapies (R + P + A) [39]. Most studies (81.25%) reported follow-up outcomes at 8–16 weeks, while three extended follow-up to 24 weeks. Detailed baseline characteristics of the included studies are summarized in Table 1.

Summary of geometry of the network

The network meta-analysis includes networks of eligible comparisons, as depicted in Fig. 2. The network includes 15 studies and 12 strategies, with control (C) as the reference treatment. Two closed loops are present: one among

Table 1 Baseline information of the enrolled studies

Study	Country	Participants	Age	Female Size	Sample Size	Intervention(s) vs Control	Withdrawal	Prevention or Intervention	Additional Education	Outcome	F/U
Arab 2022 [36]	Iran	MOH3, CM, EM, TTH	38	62%	54 (27,27)	W+P+Nb vs W+P	Abrupt	GONB with 2% lidocaine and TA Oral prevention BB (12.9%), TPM (9%), AMT (29.6%), MTZ (22.8%), Others (25.7%)	No	MHDs	12 weeks
Carlsen 2018 [38]	Denmark	MOH3β, CM, EM, TTH	47	75%	53 (27, 26)	W+E vs R+E	Abrupt vs restriction	No	8 lectures by nurses	MHDs	8 weeks
Carlsen 2020 [7]	Denmark	MOH3β, CM, EM, TTH	44	79%	102 (31,35, 36)	W+P vs P vs W	Abrupt	Oral prevention CDT (51.5%), AMT (19.6%), MT (13.6%), Others (28.8%)	No	MHDs	8 weeks
Diener 2007 [32]	Multicenter	MOH2, CM	46	75%	46 (23, 23)	P vs C	No	Oral prevention TPM (100%)	No	MMDs	16 weeks
Dodick 2020	Multicenter	MO, EM, CM	44	84%	250 (77,173)	A vs C	No	Galcanezumab 120 mg SC monthly (100%)	No	MMDs	24 weeks
Hagen 2009	Norway	MOH2, CM TTH	41	60%	56 (20, 17, 19)	W vs P vs C	Abrupt	Oral prevention CDT, BB, VPA, AMT, GBP (not mention %)	No	MHDs	12 weeks
Karadaş 2017	Turkey	MOH3β	37	75%	70 (35, 35)	W+Nb vs W	Abrupt	GONB with 1%lidocaine	No	MHDs	8 weeks
Krymchantowski 2023	Brazil	MOH3, CM	44	73%	172 (114, 58)	R+P+A vs R+P	Restriction	Oral prevention(s) TPM +NT (50%), VPA (29.7%), AT +NT (14.5%), AT +NT+FLN (5.8%)	No	MHDS	12 weeks
Mose 2020	Denmark	MOH3β, CM, TTH, Cluster	44	68%	79 (40, 39)	W+P+E vs W+P	Abrupt	Oral prevention VPA (72%), TPM (8%), BB (8%), VP (6%),	12 weeks education with 6 sessions	MHDs	24 weeks after education
Pijpers 2019	Netherlands	MOH3β, CM	45	76%	179 (90,89)	W+B vs W	Abrupt	Botulinum toxin 155U (100%)	No	MHDs	12 weeks
Rossi 2006	Italy	MOH2, CM	44	85%	79 (39,40)	W+P vs W	Abrupt	Oral prevention VPA (35.8%), AT (30.7%), AMT (25.6%), TPM (7.6%)	No	MHDs	8 weeks

Table 1 (continued)

Study	Country	Participants	Age	Female Size	Sample Size	Intervention(s) vs Control	Withdrawal	Prevention or Intervention	Additional Education	Outcome	F/U
Rossi 2013	Italy	MOH2, CM	46	80%	92 (46,46)	W+P vs W	Abrupt	Oral prevention VPA (34.7), MT (23.9%), TPM (21.7%), AMT (19.5%)	No	MHDs	10 weeks
Sandrini 2011	Italy	MOH2, CM	49	80%	56 (27,29)	W+B vs W	Abrupt	Botulinum toxin 100U (100%)	No	MHDs	12 weeks
Sarchielli 2014	Italy	MOH2, EM	NA	78%	88 (44,44)	W+P vs W	Abrupt	Oral prevention VPA (100%)	No	MHDs	12 weeks
Schwedt 2022	US	MOH3β, CM	44	88%	720 (361,359)	R+P vs P	Restriction	Headache prevention(s) TPM 25%, Botulinum toxin 14%, AMT 8.1%, Others (each less than 10%)	No	MHDs	12 weeks
Silberstein 2013	Multicenter	MO, CM	43	86%	904 (445,459)	B vs C	No	Botulinum toxin 155-195U (100%)	No	MHDs	24 weeks

MOH Medication-overuse headache, *CM* Chronic migraine, *EM* Episodic migraine, *TTH* Tension-type headache, *C* Control, *B* Botox, *W* Abrupt withdrawal, *A* Anti-CGRP, *P* Oral prevention(s), *E* Additional education, *Nb* Nerve block, *R* Restriction of overused medication <=2days/week, *GONB* Greater occipital nerve blocks, *TA* Triamcinolone acetonide, *BB* Beta-blocker, *TPM* Topiramate, *AMT* Amitriptyline, *MTZ* Mirtazapine, *CDT* Candesartan, *MT* Metoprolol, *VPA* Valproic acid, *GBP* Gabapentin, *NT* Nortriptyline, *AT* Atenolol, *FLN* Flunarizine, *MHDs* Monthly headache days, *MMDs* Monthly migraine days

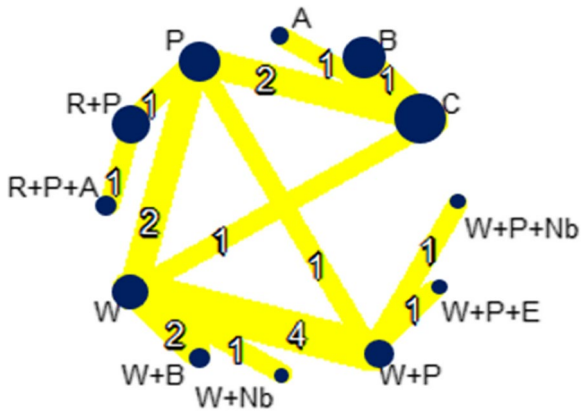

Fig. 2 Network of eligible comparisons for the network meta-analysis for efficacy. The width of the lines for each connection is proportional to the number of randomized controlled trials of each directly compared treatment regimens. The size of the nodes corresponds to the number of randomized participants (sample size). *C* control, *B* botox, *W* abrupt withdrawal, *A* anti-CGRP, *P* oral prevention(s), *E* additional education, *Nb* Nerve block, *R* restriction of overused medication < = 2 days/week. The treatment nodes include C (*N* = 674), B (*N* = 445), A (*N* = 77), P (*N* = 434), R + P (*N* = 419), R + P + A (*N* = 114), W (*N* = 339), W + B (*N* = 117), W + Nb (N = 35), W + P (*N* = 226), W + P + E (*N* = 40), and W + P + Nb (*N* = 27)

control (C), abrupt withdrawal (W), and oral preventions (P), and another among abrupt withdrawal (W), oral preventions (P), and abrupt withdrawal plus oral prevention (W + P). These loops enable consistency checks between direct and indirect evidence. Eight strategies exhibit limited direct evidence and depend more on indirect comparisons. Notably, one study evaluating W + E versus R + E [38] was excluded because it could not connect with the network. The network structure remains well-suited for conducting a robust network meta-analysis, allowing for the estimation of treatment effects by integrating both direct and indirect evidence. The networks of eligible comparisons included in the analysis are detailed in Fig. 2.

The network meta-analysis was conducted using a random effects model, comparing 12 treatment strategies to control (C), as shown in Fig. 3. W + P + Nb achieved the largest reduction in monthly headache days, decreasing by 10.6 days (95% CI: [−15.03; −6.16]). This was followed by R + P + A (MD = −8.47, 95%-CI = [−12.78; −4.15]). Other significant reductions were noted for R + P (MD = −5.87, 95%-CI = [−8.97; −2.76]), W + Nb (MD = −4.77, 95%-CI = [−8.23; −1.31]), WP (MD = −4.55, 95%-CI = [−7.86; −1.23]), P (MD = −4.37, 95%-CI = [−7.09; −1.64]), and W + B (MD = −4.14, 95%-CI = [−7.69; −0.59]). Smaller reductions were observed for A (MD = −3.60, 95%-CI = [−5.12; −2.08]), and B (MD = −2.00, 95%-CI = [−2.49; −1.51]). Two treatments, W (MD = −2.77, 95%-CI = [−5.74; 0.20], p = 0.0673) and W + P + E (MD = −4.55, 95%-CI = [−9.28; 0.19], p = 0.0600), did not show statistically significant reductions compared to the control.

Regarding abrupt withdrawal (W), additional treatment with single oral prevention (W + P), and GONB (W + Nb) demonstrated significant benefits in reducing

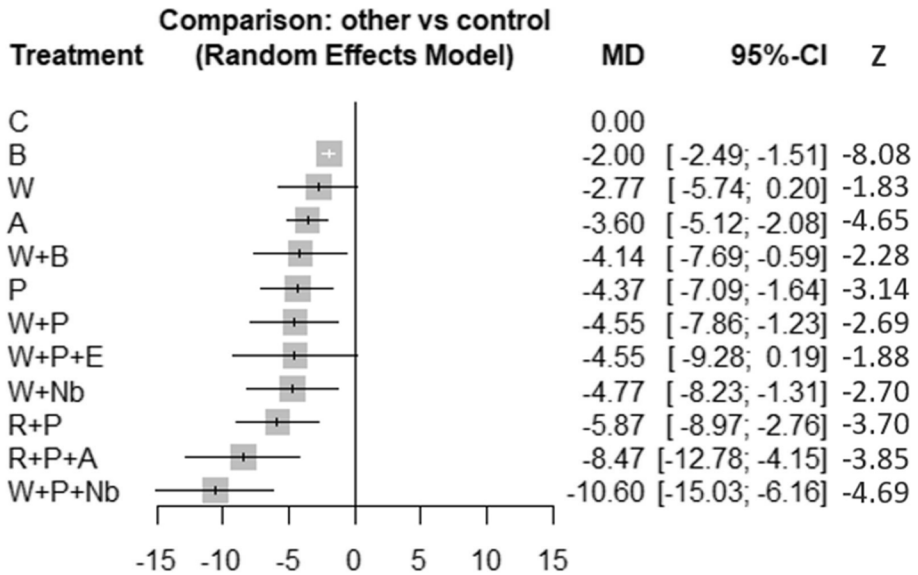

Fig. 3 Forest plot of comparison between different strategies versus control. Change in monthly headache days from baseline among patients with medication overuse headache. *C* control, *B* botox, *W* abrupt withdrawal, *A* anti-CGRP, *P* oral prevention(s), *E* additional education, *Nb* Nerve block, *R* restriction of overused medication < = 2 days/week, *MD* Mean difference, *CI* Confidential interval, *Z* Z-score

monthly headache days. Compared with W, W + P reduced monthly headache days by 1.8 (95% CI: [−3.3; −0.2]), while W + Nb achieved a reduction of 2 days per month (95% CI: [−3.7; −0.2]). However, adding botulinum toxin (W + B) did not result in a significant reduction in headache frequency, with a mean difference (MD) of −1.4 (95% CI: [−3.3; 0.6]). There was no head-to-head comparison between abrupt withdrawal (W) and restriction (R) strategies in this study. However, the outcome of W + P and R + P did not have significant difference, suggesting comparable efficacy between these two approaches, as detailed in Table 2.

In terms of headache prevention, there was no significant difference in the outcome among treatments initiated with oral prevention(s) (P), botulinum toxin (B), or anti-CGRP(R) therapies (A). Specifically, the comparisons showed the following mean differences (MDs): P vs. B, MD = −2.4 (95% CI: [−5.1; 1.4]); P vs. A, MD = −0.8 (95% CI: [−3.9; 2.4]); and A vs. B, MD = −1.6 (95% CI: [−3.2; 0.0]). The results indicate that no single initial prevention strategy demonstrates superior efficacy over the others. Combination therapies demonstrated significant benefits in reducing headache frequency. This included R + P + A compared with each single headache prevention strategy, with mean differences (MD) as follows: R + P + A vs. B, MD = −6.5 (95% CI: [−10.8; 2.1]); R + P + A vs. A, MD = −4.9 (95% CI: [−9.4; 0.3]); and R + P + A vs. P, MD = −4.1 (95% CI: [−7.4; 0.8]). Similarly, W + P + Nb compared with other interventions (excluding R + P + A) also showed significant reductions of monthly headache days, as detailed in Table 2.

Only one trial evaluated the effect of education. The results showed that W + P + E did not reduce headache frequency compared to W + P, with a MD of 0 (95% CI: [−3.4; 3.4]). Additionally, no statistically significant differences were observed between W + P + E and other strategies, as detailed in Table 2.

The ranking of the different strategies was compared with control (C) using p-scores, as presented in Table 3 (supplementary material 1). The highest-ranked treatment was W + P + Nb with a P-score of 0.98, indicating it is the most effective intervention. This was followed by R + P + A and R + P, with P-scores of 0.90 and 0.72, respectively. Moderately effective treatments included W + Nb, W + P, W + P + E, P, W + P, and A, with P-score ranging from 0.58 to 0.40. The least effective treatments were W and B, with P score = 0.22 and 0.16.

Quantifying heterogeneity revealed that the estimated between-study variance was 0, with $\tau^2 = 0$; tau = 0; $I^2 = 0\%$ [0.0%; 70.8%], suggesting low to no heterogeneity across the network. Tests of heterogeneity and inconsistency further supported these findings, with no significant heterogeneity observed across the network (Q = 4.99, d.f. = 6, p = 0.5454) or within designs (Q = 4.45, d.f. = 3, p = 0.2171), and no evidence of inconsistency between designs (Q = 0.54, d.f. = 3, p = 0.9099).

Risk of bias and publication bias

Among 15 trials that are included in the network, we judged 6 (40%) to be at high risk of bias, 5 (33.3%) to be low risk of bias, and 4 (26.7%) to be some concerns. The most common reasons for trials being rated as having some concerns or high risk of bias were missing outcome

Table 2 Efficacy of the treatment regimens on change in monthly headache frequency from baseline

C											
-2.0 (-2.5, -1.5)	B										
-2.8 (-5.7, 0.2)	-0.8 (-3.8, 2.2)	W									
-3.6 (-5.1, -2.1)	-1.6 (-3.2, 0.0)	-0.8 (-4.1, 2.5)	A								
-4.1 (-7.7, -0.6)	-2.1 (-5.7, 2.2)	-1.4 (-3.3, 0.6)	-0.5 (-4.4, 3.3)	W+B							
-4.4 (-7.1, -1.6)	-2.4 (-5.1, 1.4)	-1.6 (-4.1, 1.0)	-0.8 (-3.9, 2.4)	-0.2 (-3.5, 3.0)	P						
-4.5 (-7.9, -1.2)	-2.5 (-5.9, 0.4)	**-1.8** (-3.3, -0.2)	-0.9 (-4.6, 2.7)	-0.4 (-2.9, 2.1)	-0.2 (-3.1, 2.8)	W+P					
-4.5 (-9.2, 0.2)	-2.5 (-7.3, 0.8)	-1.8 (-5.5, 2.0)	-0.9 (-5.9, 4.0)	-0.4 (-4.6, 3.8)	-0.2 (-4.7, 4.3)	0.0 (-3.4, 3.4)	W+P+E				
-4.8 (-8.2, -1.3)	-2.8 (-6.2, 2.2)	**-2.0** (-3.7, -0.2)	-1.2 (-4.9, 2.6)	-0.6 (-3.2, 2.0)	-0.4 (-3.5, 2.7)	-0.2 (-2.6, 2.2)	-0.2 (-4.4, 3.9)	W+Nb			
-5.9 (-9.0, -2.8)	**-3.9** (-7.0, -0.7)	**-3.1** (-6.1, -0.1)	-2.3 (-5.7, 1.2)	-1.7 (-5.3, 1.8)	-1.5 (-3.0, 0.0)	-1.3 (-4.6, 2.0)	-1.3 (-6.0, 3.4)	-1.1 (-4.6, 2.4)	R+P		
-8.5 (-12.8, -4.2)	**-6.5** (-10.8, -2.1)	**-5.7** (-9.9, -1.4)	**-4.9** (-9.4, -0.3)	-4.3 (-9.0, 0.3)	**-4.1** (-7.4, -0.8)	-3.9 (-8.4, 0.5)	-3.9 (-9.5, 1.7)	-3.7 (-8.3, 0.9)	-2.6 (-5.6, 0.4)	R+P+A	
-10.6 (-15.0, -6.2)	**-8.6** (-13.1, -4.1)	**-7.8** (-11.2, -4.4)	**-7.0** (-11.7, -2.3)	**-6.5** (-10.3, -2.6)	**-6.2** (-10.4, -2.0)	**-6.1** (-9.0, -3.1)	**-6.1** (-10.5, -1.6)	**-5.8** (-9.6, -2.0)	**-4.7** (-9.1, -0.31)	-2.2 (-7.5, 3.2)	W+P+Nb

The estimation was calculated as the column-defining treatment compared with the row-defining treatment. MDs lower than 0 favor the row-defining treatment. Significant results are in bold. *C* control, *B* botox, *W* abrupt withdrawal, *A* anti-CGRP, *P* oral prevention(s), *E* additional education, *Nb* Nerve block, *R* restriction of overused medication <=2days/week

data and deviations from intended interventions. Notably, most studies with a low risk of bias were those evaluating headache prevention alone strategies (Table 4 in supplementary material 1).

The funnel plot suggests minimal risk of small-study effects or publication bias in this network meta-analysis, as shown in Fig. 4 of supplementary material 1. The plot appears symmetrical around the vertical line at zero. The triangular region represents the 95% confidence limits, with most data points falling within this boundary. The statistical tests show a p-value of 0.90 for Egger's test, 0.38 for the Begg-Mazumdar test, and 0.95 for the Thompson-Sharp test. All p-values are greater than 0.05, indicating no significant evidence of funnel plot asymmetry or rank correlation between effect sizes and variances.

Discussion

Many strategies have been proposed for the treatment of MOH and the optimal approach remains a long-debated topic. Our network meta-analysis provided a deeper understanding of which strategies are more effective in reducing monthly headache days. It offers a comprehensive perspective on the effect sizes of each strategy and enables comparisons of both direct and indirect evidence from multiple studies.

Withdrawal strategies

Our results suggest that an abrupt withdrawal strategy alone may not be an effective treatment for MOH. For improved outcomes, it should be combined with other strategies. Abrupt withdrawal alone reduced the mean number of monthly headache days by 2.7. However, when abrupt withdrawal combined with other treatments, the reduction in monthly headache days ranged between 0.2 and 2.1 days (W + P vs. P, MD = −0.2 (95% CI: [−3.1; 2.8]); W + B vs. B, MD = −2.1 (95% CI: [−5.7; 2.2])).

The restriction of overused drugs to no more than two days per week has been proposed as a strategy for managing MOH due to its feasibility and alignment with patient preferences [38]. However, the relative efficacy of this approach compared to abrupt withdrawal remains unresolved, as no indirect comparisons between these two strategies are available. However, our analysis found no significant difference in the reduction of monthly headache days between withdrawal plus oral prevention (W + P) and restriction plus oral prevention(s) (R + P), with a mean difference (MD) of −1.3 (95% CI: [−4.6; 2]). While R + P appeared to offer slightly greater benefit in this study, this may not represent the true effect of the restriction strategy. Notably, the R + P studies included in this analysis involved 1–2 oral preventions [33, 39], whereas all W + P studies utilized only one oral prevention [7, 28, 29, 31, 36, 37]. This imbalance in the number of oral preventions could have influenced the observed outcomes. A previous RCT reported that complete detoxification was more effective than restriction treatment [38]. But that study included eight extra-educational sessions delivered by nurses in both groups, which could have introduced potential confounding factors.

Headache preventions and interventions

Our findings indicate that all headache prevention strategies, including oral prevention(s) (P), botulinum toxin (B), and anti-CGRP(R) therapies (A), significantly reduce monthly headache days. However, no single initial prevention strategy demonstrates superior efficacy over the others. While P showed a slightly greater benefit compared to A and B, this difference might be explained by variations in placebo effects among the control groups [40]. Participants who received normal saline injections at the scalp as a placebo might experience a greater reduction in monthly headache days compared to those who took an oral placebo. This enhanced placebo response, driven by the expectancy mechanism [40] associated with injection-based interventions, may have led to an underestimation of the true efficacy of botulinum toxin and anti-CGRP therapies. Given the lack of significant differences in efficacy among these strategies, the choice of headache prevention should be considered by patient preferences, tolerability, comorbidities, contraindications, and costs to ensure suitability for individual patients [41].

Greater Occipital Nerve Blocks (Nb) demonstrate high efficacy in managing MOH. When added to the abrupt withdrawal strategy (W), Nb significantly reduce the mean number of monthly headache days by 2 days (W + Nb vs. W, MD = −2, 95% CI: [−3.7; −0.2]). Furthermore, combining Nb with abrupt withdrawal plus oral prevention yields an even greater reduction, with a mean difference of −6.1 days (W + P + Nb vs. W + P, MD = −6.1, 95% CI: [−9.0; −3.1]). These findings highlight the substantial benefit of incorporating Nb into MOH management. Nb is particularly suitable for initial MOH management, as it provides rapid relief within days to a week, with effects lasting from days to weeks [42]. It resulted in a reduction in headache frequency, intensity, and analgesic consumption [42].

However, the efficacy of Nb should be interpreted with caution. Unlike B and A, which were directly compared to C—potentially underestimating their true efficacy—Nb was assessed through indirect comparisons to C via non-injected strategies (W and W + P). As a result, Nb efficacy may have no effect as B and A or even show an exaggerated benefit, potentially influenced by expectancy mechanism [40]. Additionally, the number of studies and sample sizes evaluating Nb

remain limited (W + Nb N = 35, W + P + Nb N = 27) [26, 36], necessitating further research to confirm its effectiveness.

Combination therapies

Our results suggest the potential of combination therapies, such as W + P + Nb and R + P + A, to deliver superior outcomes for patients with MOH. These strategies demonstrated the greatest efficacy in reducing monthly headache days, highlighting their role as promising initial treatment options. While Nb provide rapid relief and temporary duration of effect, anti-CGRP(R) therapies exhibit an accumulative effect, delivering increasing efficacy over a period of 3–6 months [41, 43–45]. Future studies are needed to investigate optimal combinations and long-term outcomes, including the number of acute medication days, reversion of MOH, and sustained reduction in monthly headache days (MHDs). These insights would help refine treatment strategies and ensure better management of MOH over time.

Education

In our study, there is only one study [37] that evaluated the impact of education on the reduction of monthly headache days, and it did not demonstrate significant benefit. Several RCTs have examined the addition of behavioral or educational interventions during withdrawal, suggesting potential effects on motivation and the reduction of overused medication [11–13, 46]. Unfortunately, these studies did not control for the component of headache prevention, making them ineligible for inclusion in our analysis.

The educational effect observed in these RCTs was generally positive, with one study showing no significant effect [11], while three studies reporting benefits in reducing monthly headache days when education was combined with withdrawal treatment, with or without pharmacological therapies [12, 13, 46]. These findings suggested that the efficacy of MOH treatments could improve when education is integrated with overused drug withdrawal and/or pharmacological therapies. Future studies should explore ways to incorporate non-pharmacological and pharmacological therapies. However, in countries where opioids are commonly overused [47], education and other conservative strategies may not be adequately evaluated or properly considered in real-world clinical practice. The heavy reliance on pharmacological treatments often leads to the undervaluation of non-pharmacological interventions. Additionally, with reimbursement policies favoring medications, discourage the adoption of these approaches.

Strengths and limitations

There are numerous strategies for managing MOH, and no single RCT can definitively determine the best approach. Our network meta-analysis addresses this gap by providing a deeper understanding of the relative efficacy of various strategies in reducing monthly headache days. It offers a comprehensive perspective on the effect sizes of each strategy and enables comparisons of both direct and indirect evidence across multiple studies, enhancing the robustness and generalizability of the findings. Although many studies were excluded because they did not adequately control for the component of headache prevention [11–14, 16, 43, 45, 46, 48–52], this allowed us to more accurately evaluate the effect size of each component within the included strategies. These insights provide a clearer understanding of the contribution of individual components to the overall efficacy of MOH management.

There are several limitations to our analysis. First, we categorized different types of control under the same node (C), including no intervention, oral placebo-controlled, and injected placebo-controlled groups. A key closed loop in our network is C vs. W vs. P from the Hagen study [25], meaning that the C node in our network represents no intervention. In the Botox study, the exact reduction in mean monthly headache days was 8.2 days for Botox compared to 6.2 days for the injected placebo control [34]. Meanwhile, in our study, Botox demonstrated efficacy by reducing monthly headache days by just 2 days compared to the control. The difference in control conditions may contribute to injection-based interventions, such as Botox and anti-CGRP(R), appearing less effective when directly compared to the control due to the expectancy mechanism associated with injected placebos [40]. Conversely, injection interventions indirectly compared to the control via non-injected strategies, such as Nb, may show no effect or even an exaggerated benefit. In contrast, W and P are less affected by differences in control conditions. While this categorization was necessary for the network meta-analysis, it may reduce the precision of the findings.

Similarly, in headache prevention strategies, we grouped different oral preventions and anti-CGRP(R) therapies into the same nodes (P and A), assuming that these interventions produce similar effects. However, this simplification may overlook variations in efficacy among specific treatments. For instance, a previous systematic review and meta-analysis comparing the effectiveness of migraine preventive drugs found high-certainty evidence supporting all anti-CGRP therapies in reducing monthly migraine days compared to placebo [53]. Nonetheless, slight differences in the certainty of evidence were observed among various oral prevention strategies [53].

Although this categorization was essential for the network meta-analysis, they may slightly compromise the accuracy of the findings.

With regard to the oral prevention strategies, most studies included single oral prevention, but two studies included 1–2 oral preventions [33, 39]. Furthermore, the MOTS trial used botulinum toxin as a headache prevention option in 14% of cases, while the remainder involved oral prevention(s) [33]. We believe that this proportion of botulinum toxin use is relatively small, and the efficacy of botulinum toxin and oral prevention does not differ significantly [54]. These variations in oral prevention strategies may limit the precision of the analysis and should be considered when interpreting the results.

Additionally, we acknowledge the limited number of studies per strategy and the small sample sizes, particularly for Nb and educational studies (W + P + Nb: N = 27; W + Nb: N = 35; and W + P + E: N = 40) [26, 36, 37], which may be insufficient to draw definitive conclusions about these strategies. This limitation underscores the need for more studies with standardized designs to strengthen the evidence base for MOH management strategies.

For studies with a moderate to high risk of bias, most included in the meta-analysis fell into this category. Unfortunately, we were unable to conduct a sensitivity analysis using only studies with the lowest risk of bias due to the limited number of studies per strategy. Excluding certain studies would have disrupted the network, making the analysis unfeasible.

Lastly, our research focuses solely on headache frequency outcomes over a 2–6 month period, without addressing long-term efficacy or evaluating relapse rates in MOH patients—a primary concern for this population. Predictors of MOH relapse include headache frequency both before and after treatment [55, 56], the numbers of analgesic used prior to withdrawal [55], types of over used medication [57], and duration and types of primary headaches [56, 57]. The observed reduction in headache frequency after treatment suggests that strategies with greater efficacy may help lower the likelihood of MOH relapse.

Conclusion

This network meta-analysis highlights the efficacy of combination therapies, such as W + P + Nb and R + P + A, in significantly reducing monthly headache days, making them promising initial treatments for MOH. Headache prevention strategies, including oral prevention, botulinum toxin, and anti-CGRP(R) therapies, demonstrated comparable efficacy in initial treatment. Abrupt withdrawal alone is insufficient and should be combined with other strategies, while the role of educational interventions remains inconclusive and requires further investigation. The reduction in headache frequency observed after treatment suggests that implementing more effective strategies may further decrease the likelihood of MOH relapse. However, MOH management decisions should consider not only efficacy but also patient preferences, tolerability, comorbidities, contraindications, and costs. Despite limitations in study categorization and representation, this analysis offers a valuable foundation for guiding clinical practice and advancing future research on optimal treatment combinations and long-term outcomes.

Abbreviations

A	Anti-CGRP
AMT	Amitriptyline
AT	Atenolol
W	Abrupt withdrawal
B	Botox
BB	Beta-blocker
C	Control
CDT	Candesartan
CGRP	Calcitonin gene-related peptide
CI	Confidence interval
CM	Chronic migraine
E	Additional education
EM	Episodic migraine
FLN	Flunarizine
GBP	Gabapentin
GONB	Greater occipital nerve blocks
ICHD	International Classification of Headache Disorders
MD	Mean difference
MHDs	Monthly headache days
MMDs	Monthly migraine days
MT	Metoprolol
MTZ	Mirtazapine
N	Sample size
Nb	Nerve block
NT	Nortriptyline
P	Oral prevention(s)
R	Restriction of overused medication ≤ 2 days/week
SE	Standard error
TA	Triamcinolone acetonide
TTH	Tension-type headache
TPM	Topiramate
VPA	Valproic acid
Z	Z-score

Supplementary Information

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Supplementary Material 1.

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Authors' contributions

PK served as the first reviewer, contributing to the conception and design of the study and drafting the initial manuscript. SY acted as the second reviewer and edited the manuscript. SS participated as the third reviewer. TT supervised the systematic review and meta-analysis while also editing the manuscript. PC provided supervision for the network meta-analysis. BW oversaw the aspects related to MOH, edited, and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
PK, SY, SS, TT, and PC declare that there are no conflicts of interest. BRW is the founder of Ceftronics limited and the CEFREF migraine mobile application. He has done consultancy for Invex Therapeutics and received honoraria from AbbVie.

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