

RESEARCH SUBMISSIONS

Network meta-analysis of therapies for cluster headache: Effects of acute therapies for episodic and chronic cluster

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Abstract

Objective: We used network meta-analysis (NMA) to characterize the relative effectiveness and harms of acute treatment options for cluster headache.

Background: There are few evidence-based acute treatments available for cluster headache. As most treatments were compared only against placebos in clinical trials, few head-to-head comparisons of treatments are available.

Methods: An a priori registered scoping review was performed to identify randomized controlled trials evaluating treatments in adult patients (>18 years old) with cluster headache per accepted diagnostic criteria. Bayesian NMAs were performed to compare treatments in terms of headache relief at 15 or 30 min, and also the occurrence of adverse events. We report odds ratios (ORs) of relative treatment effects along with corresponding 95% credible intervals (CrIs), as well as measures of treatment ranking.

Results: A total of 13 randomized controlled trials informed NMAs. We found high flow oxygen to be the most effective therapy for headache response at 15 and 30 min (OR 9.0, 95% CrI 5.3 to 15.9 vs. placebo), with injectable sumatriptan demonstrating the next highest effect (OR 6.4, 95% CrI 3.75 to 11.1 vs. placebo). High flow oxygen was also more effective than low flow oxygen (OR 2.55, 95% CrI 1.13 to 5.8), nasal spray zolmitriptan (OR 3.75, 95% CrI 1.72 to 8.4), octreotide (OR 4.5, 95% CrI 1.64 to 12.5), and non-invasive vagal nerve stimulation (nVNS; OR 5.2, 95% CrI 2.29 to 11.9). Sumatriptan injectable was also effective for headache relief and was found to be better than nasal spray zolmitriptan (OR 2.67, 95% CrI 1.21 to 5.9), octreotide (OR 3.20, 95% CrI 1.17 to 8.8), and nVNS (OR 3.69, 95% CrI 1.63 to 8.4). Octreotide (OR 4.1, 95% CrI 1.71 to 10.5) and sumatriptan (OR 2.40, 95% CrI 1.39 to 4.2) were associated with greater risk of adverse events compared to placebo, while other treatments did not demonstrate increased risk. When focusing on patients with episodic cluster headache, nVNS was significantly better than placebo (OR 4.9, 95% CrI 1.89 to 14.1).

Conclusions: Our findings suggest that high flow oxygen is more efficacious when compared to low flow oxygen for headache relief. When low flow oxygen fails in patients who can tolerate oxygen, increased flow rates should be tried. Additionally,

Abbreviations: AAN, American Academy of Neurology; CH, cluster headaches; CrI, credible intervals; DIC, deviance information criteria; FE, fixed-effects; NMA, network meta-analysis; NS, nasal spray; nVNS, non-invasive vagal nerve stimulation; OR, odds ratios; PMA, pair-wise meta-analysis; RCT, randomized controlled trial; RE, random-effects; ROB, risk of bias; SC, subcutaneous injection; SPG, sphenopalatine ganglion; SUCRA, Surface Under the Cumulative Ranking curve; VNS, vagal nerve stimulation.

high flow oxygen is likely more effective than zolmitriptan nasal spray, nVNS, and octreotide. Sumatriptan injectable is more likely to be effective when compared to zolmitriptan nasal spray, octreotide, and nVNS.

KEYWORDS

acute and preventive treatment, cluster headache, network meta-analysis, trigeminal autonomic cephalalgias

INTRODUCTION

Rationale

There are few acute evidence-based treatments available for cluster headache (CH), and no head-to-head comparisons of therapies are available. This study was undertaken to compare the acute treatment response in CH between the various therapies utilized in terms of efficacy, adverse events, and in subgroups where available. Network meta-analysis was used to synthesize available direct and indirect evidence from the literature. This work was undertaken to provide clinicians with comparative data for the various acute treatments where none were previously available.

Objectives

This is the second of two studies performed to summarize evidence regarding current interventions for CH. In the first manuscript, we presented findings from a scoping review performed to establish a collection of comparative studies of interventions for acute treatment and prevention of CH as well as their key findings.¹ The studies identified in the scoping review were used to develop a listing of the treatment comparisons available, the relevant study population characteristics, the types and frequency of outcomes reported, the study designs, and the sample sizes. Using the data from that review, we sought to provide a high-level synopsis of the effectiveness and safety of interventions for treatment and prevention of CH while assessing the feasibility of network meta-analysis (NMA) to estimate between-treatment comparisons. In that work, we established that while NMAs were feasible for comparing acute treatments for CH, NMAs were not feasible for informing comparisons of preventive therapies due to substantial heterogeneity in trial characteristics that may have been treatment effect modifiers.

In the current review, we build upon findings from our scoping review by using NMA to characterize treatment response to acute therapies in CH patients. We aim to identify and rank effective acute treatments, comparing different administration and dosing strategies. We aim to provide further guidance to clinicians regarding the comparative effects of various treatments based upon available direct and indirect evidence. Where possible, we also present subgroup NMAs evaluating treatment response in episodic

and CH populations separately. The pathogenesis of chronic CH may be such that they are a subgroup of patients with cluster headache who are more treatment refractory.² Instead of remitting on medications, they stay in bout;² some have suggested this may be because there is a subtype that is distinct in pathophysiology that may require different treatments,^{3,4} and specific analyses of medications currently used but not tested in this subgroup would be informative.

PICOS questions

This review addresses the following research question:

In adult patients with episodic and/or chronic cluster, what is the comparative effectiveness and safety of acute therapies, including drugs, procedures, surgeries, and devices, for decreasing CH severity?

While traditional pairwise meta-analysis (i.e., focused on the comparison of two interventions) is informative for combining data from multiple trials in many situations, there are many medical conditions wherein an array of available treatment options exists. For disorders like CH where there exist multiple acute and preventive therapies, comparison of only two therapies is less informative than a comparison of all available therapies in terms of efficacy and safety.

NMA is an extension of pairwise meta-analysis allowing for the comparison of many treatments simultaneously that were not directly compared to each other.⁵⁻⁹ If studies have at least one intervention in common with each other, a network can be formed of these comparisons, and further elaborated upon using statistical methods to compare treatments with no previous head to head data.^{10,11} In brief, NMA is used to create evidence networks, where both “direct” evidence (e.g., data from comparisons between two active treatments) and “indirect” evidence (e.g., data from comparisons with interventions such as placebo and no treatment) are combined.¹⁰ The solid lines in Figure 1 denote where there are comparisons with available trial evidence in the network (A, B, and C each compared to placebo, and A compared to C), whereas the dashed lines represent where we can estimate based on statistical methods the relative effects of interventions compared to each other even though there were no head-to-head trials of these comparisons (Drugs A and B, B and C). In addition, because there can be treatment loops (such as the

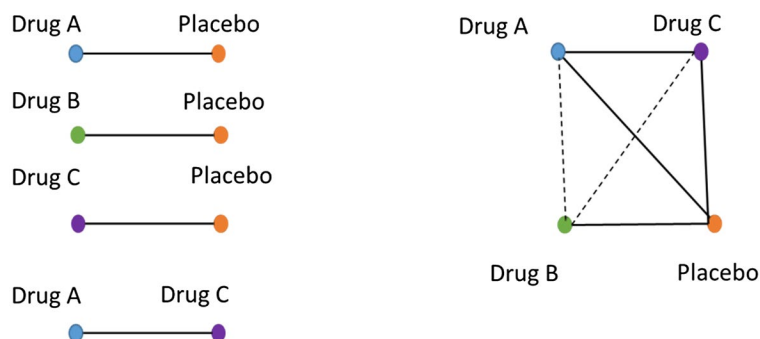


FIGURE 1 Graphical representation of a pairwise meta-analysis versus network meta-analysis. For traditional systematic reviews involving traditional pairwise meta-analysis (see left panel), treatment effects comparing the different drugs in this example are based upon four separate sets of analyses based upon the available direct evidence from randomized controlled trials. For systematic reviews involving network meta-analysis (see right panel), treatment effects comparing the four drugs can be estimated from a unified analysis of all available trial data. This also allows for the estimation of treatment effects with no underlying trial data available using indirect evidence (as denoted by dashed lines) [Color figure can be viewed at wileyonlinelibrary.com]

example of comparisons between drugs A, C, and placebo) in situations where there are head-to-head comparisons (Drugs A and C), direct estimates from head-to-head comparisons can be combined with results of indirect comparisons, thereby considering a broader evidence base, to get more robust estimates of treatment effects.

STUDY METHODOLOGY

The protocol for our scoping review and NMA was registered a priori¹ on the Open Science Framework.¹² In this manuscript, findings have been reported in consideration of guidance from the PRISMA extension statement for network meta-analysis.¹³

Identification of studies for evidence synthesis

The scoping review was used to identify the randomized controlled trials (RCTs) to be included in NMAs. We assessed the availability of outcomes of a priori interest to establish those that were commonly reported within the eligible trials.¹⁴

The population of interest for NMAs aligned with the target population from our scoping review,¹ namely adults with episodic or chronic CH as defined by accepted diagnostic criteria. For each trial, data were gathered regarding patients' demographics and clinical characteristics that could influence treatment response.¹⁴ We compared these characteristics across trials where available to inform assessment of the assumptions of homogeneity and similarity necessary for NMA.¹⁵ The outcomes we selected were headache response at 15 or 30 min as primary endpoints as per guidelines for acute CH trials,¹⁶ and adverse events as secondary endpoints. Headache response, also called headache relief or pain relief, was defined as movement from moderate to severe or very severe to no or mild pain at these time points after treatment.

Data collection and risk of bias appraisal

Study characteristics and outcome information were collected by one reviewer using a pre-defined data extraction form developed in Microsoft Excel. For all trials that were included in NMAs, two authors independently assessed the risk of bias (ROB) using the related scale from the American Academy of Neurology (AAN).¹⁷ The AAN ROB tool was used in prior headache systematic reviews and clinical guidelines, and is well known and accepted by clinicians in the field,^{18–20} and this was the reason for its use in our review. Please see Appendix 2.1 for a sample of the assessment form used. If disagreements were encountered, these were resolved by discussion between reviewers, consulting a third party if needed. All risk of bias assessments are provided in the appendices of this review and have been described narratively. We also used these in further defining sensitivity analyses related to study risk of bias.

Approach to data analysis

We performed NMAs and represented each intervention, dose, and mode of delivery (e.g., "Sumatriptan 20 mg nasal spray") by its own node in the evidence network. In cases where different doses were tested in different trials, these groups were not collapsed into a single node. As an example, for oxygen, the 6 and 12 L/min are represented by separate nodes, as there is no consensus that these treatments are equivalent.^{21,22} We did not collapse nor include all doses of medications, but rather opted for only the clinically appropriate dose where there were multiple doses used. An additional example is that we only looked at sumatriptan 6 mg subcutaneous injection (SC) in our NMA, we opted not to utilize the 12 mg dose as a separate node nor to collapse these two doses together in one node. The decision to avoid combining or collapsing of interventions in this fashion was discussed by clinical experts on the team (I.M., S.C.), and this decision was undertaken to maximize clinical relevance of all analyses.

The network geometry for outcomes of interest was reviewed and discussed by the research team regarding the factors identified above. The team assessed studies in terms of their populations and design to empirically judge the homogeneity across studies and appropriateness of the transitivity assumption.^{23–25} There was a paucity of data in a few of the recommended criteria to identify in the trials; however, there were no especially notable differences noted in the scoping review to preclude inclusion for most trials.

In the first stage of analysis, methodological and clinical suitability for NMAs was assessed amongst the sets of studies forming different edges within treatment networks. This was determined by initially assessing the clinical homogeneity of the trials and the quality of studies by looking at the RoB; where this was felt to be adequate and the degree of statistical heterogeneity between studies (as assessed with standard statistical measures, namely Cochrane Q and I^2) was minimal (<40%),²⁶ we proceeded to the next stage. We used R²⁷ and RStudio²⁸ to conduct pair-wise meta-analyses (PMAs) using the *pma()* function. We report odds ratios (OR; along with 95% confidence intervals) of response comparing treatment with placebo/other for categorical outcomes. Subgroup analyses for episodic and chronic cluster were also performed where data were available.

For the second stage of analyses, Bayesian NMAs were performed in R²⁷ and RStudio²⁸ using the BUGSNet package for NMA.^{29–31} For dichotomous outcomes such as headache response at 15 min, we used a binomial NMA model with a logit link function. The default prior distributions from the BUGSNet package were used.³¹ Summary effect measures were expressed as odds ratios for dichotomous outcomes and reported along with 95% credible intervals (CrI). To ensure that consistency between direct and indirect evidence was present, the ORs from pairwise meta-analyses were compared with those estimated using NMA. Unrelated means models and their corresponding fit measures were also assessed, along with scatterplots of residuals from the consistency and unrelated means models. We displayed forest plots of treatment effects versus placebo with 95% CrI, and league tables were created for all comparisons displaying ORs and CrIs looking at all treatments incorporating direct and indirect comparisons. Potential ordering/hierarchies of therapies were also evaluated with the Surface Under the Cumulative Ranking curve (SUCRA)³² measure, and the ranking of treatments was also evaluated with probability bar plots of likelihood of ranking. The adequacy of fit of individual models was evaluated in consideration of deviance information criteria (DIC), and the best model was selected when there was a difference in DIC of 3 points or more, with lower values being preferred; otherwise we used fixed effects models.^{5,7,15,31} As there was no reason to prefer random effects, and in sparse networks such as those encountered in the current review random effects models can artefactually have large credible intervals (due to limited study data to estimate the between-study variance parameter), in cases where there was no large difference (DIC of 3 or more) we used the fixed effects model.^{5,15,25} Burn-in and sampling iterations of 20,000 and 50,000 were used in all cases. To assess model convergence, we used trace plots and Gelman Rubin plots.^{5,25} As recommended by guidance for the conduct of NMAs, studies with

0 events in all groups were removed from NMAs, as they are unable to contribute to the analysis and can impede model convergence.²⁵

Evaluation of meta-biases

We reviewed trial registries in search of negative trials that were not published to assess for publication bias. While inspection of funnel plots was also planned, this approach was not undertaken due to the limited number of included studies (10 or more studies are typically recommended).³³

RESULTS

Study selection

As described in the accompanying manuscript, we initially reviewed 3257 abstracts. This was followed by full-text assessments of 482 of these reports. Overall, 44 RCTs were evaluated as part of the scoping review. We identified 13 acute treatment trials that we used to perform the NMAs featured in this review. Eleven of these trials enrolled mixed populations, including patients diagnosed with both episodic and chronic CH.^{22,34–44} The two trials that included patients with chronic CH only^{45,46} were used in subgroup analyses. Ten of the 13 acute treatment trials featured a crossover design.

Risk of bias (ROB) assessments

The detailed judgments generated by ROB appraisals are presented in Appendix 1. Findings from these assessments revealed Class II ROB (i.e., moderate risk of bias) in nine of the 12 studies (Tables A1 and A2, Figures A1–A4). Three of the 12 studies, one in which patients were treated with injectable sumatriptan³⁸ and two that featured vagal nerve stimulation (VNS)^{37,43} were identified as Class I (i.e., low risk of bias). Class II studies were downgraded either because they did not present baseline characteristics of treatment order groups or they did not mention how allocation concealment was performed; others were downgraded due to their crossover design. In the subgroup analysis of the patients diagnosed with chronic CH, two studies that featured sphenopalatine ganglion (SPG) stimulation were also scored as Class I.^{45,46}

Findings and comparisons of acute therapies

Headache response data at clinically meaningful time points (i.e., at 15 or 30 min, depending on the timing of the treatment effect) were available for 12 trials. Therapeutic approaches studied in these trials included triptans as injectable and nasal spray (NS) formulations ($n = 6$),^{34,38,39,42,44,47} oxygen at high (≥ 12 L/min) or low flow (>5 and <12 L/min; $n = 3$),^{22,35,40} lidocaine intra-nasal application

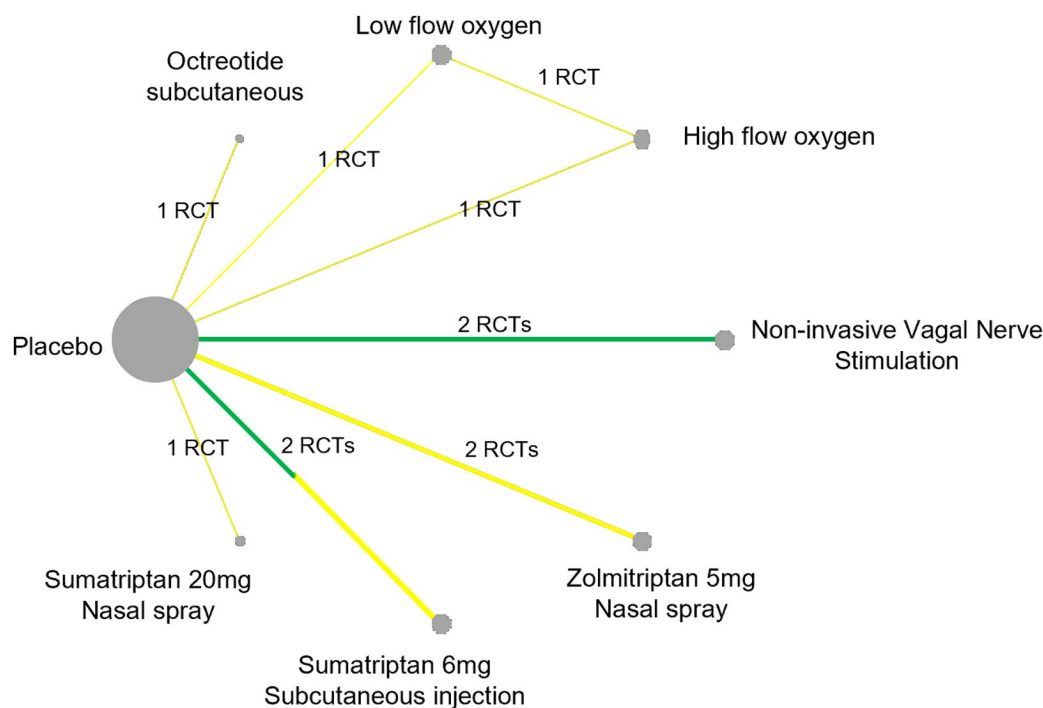


FIGURE 2 Network diagram of responses to acute treatments for cluster headache at 15–30 min. A network diagram for headache responses at 15–30 min is shown. Nodes are sized proportionately to reflect the number of attacks studied with each intervention. The lines connecting the interventions have widths that reflect the number of randomized controlled trials (RCTs) per comparison. The colors of the individual lines reflect the risk of bias assessments of each study as per the American Academy of Neurology, with Class I in green and Class II in yellow. Overall, eight interventions were compared from a total of 11 studies ($n = 1395$ cluster headache events) [Color figure can be viewed at wileyonlinelibrary.com]

($n = 1$),³⁶ octreotide intra-venous ($n = 1$)⁴¹ and non-invasive VNS (nVNS; $n = 2$).^{37,43} One trial was open-label⁴⁷ and included two active treatment arms and a placebo group. This latter study was excluded from primary analysis, as the lack of blinding may have influenced the treatment response. Overall, results from 11 trials involving acute treatment strategies for episodic and chronic CH were found to be suitable for NMA; a network diagram of the evidence is shown in Figure 2. The network included eight interventions studied in 11 trials involving 1395 episodes of CH with a total of 28 possible pairwise comparisons.

Outcome 1: Acute headache response

Characteristics of the studies used to formulate the evidence network were described in the accompanying scoping review. The findings presented in the forest plot in Figure 3 summarize the treatment effects resulting from active interventions versus placebo, while the findings presented in the league table in Figure 4 compare the treatment effects attributed to each of these therapies to one another. Figure 5 presents a bar plot of the SUCRA values associated with each intervention. A fixed-effects (FE) model was used for these analyses, as we observed no significant improvement in fit when a random-effects (RE) model was used (DIC = 37.1 vs. 39.0 for FE vs. RE models, respectively). A comparison of the fits associated with these two models and the results obtained with a random-effects model is provided in Appendix 1.

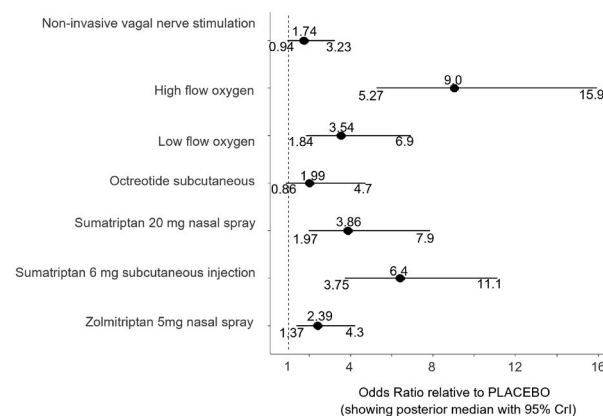


FIGURE 3 Odds ratios of treatment effects leading to headache response at 15 and 30 min versus placebo. Treatment effects based on the network meta-analyses are shown. Values >1 favor active treatment compared to placebo

We considered headache response at 15 min for all comparisons involving oxygen therapy. High flow oxygen was associated with the highest probability ranking and SUCRA value and had the largest treatment effect versus placebo (OR 9.03, 95% CrI 5.27 to 15.93). High flow oxygen was found to be more effective when compared to low flow oxygen (OR 2.55, 95% CrI 1.13 to 5.76), zolmitriptan 5 mg NS (OR 3.78, 95% CrI 1.72 to 8.35), octreotide (OR 4.5, 95% CrI 1.64 to 12.5), and nVNS (OR 5.2, 95% CrI 2.29 to 11.9). Low flow oxygen,

Comparator	Treatment							
	HIGH FLOW OXYGEN	SUMATRIPTAN 6 mg SUBCUTANEOUS	SUMATRIPTAN 20 mg NASAL SPRAY	LOW FLOW OXYGEN	ZOLMITRIPTAN 5 mg NASAL SPRAY	OCTREOTIDE SUBCUTANEOUS	NON-INVASIVE VAGAL NERVE STIMULATION	PLACEBO
	HIGH FLOW OXYGEN	0.71 (0.316, 1.54)	0.43 (0.183, 1.04)	**0.387** (0.173, 0.880)	**0.261** (0.115, 0.58)	**0.223** (0.080, 0.61)	**0.187** (0.083, 0.44)	**0.105** (0.055, 0.188)
	SUMATRIPTAN 6 mg SUBCUTANEOUS	1.41 (0.65, 3.08)	0.60 (0.251, 1.46)	0.55 (0.239, 1.30)	**0.366** (0.171, 0.817)	**0.307** (0.108, 0.863)	**0.273** (0.117, 0.623)	**0.155** (0.093, 0.266)
	SUMATRIPTAN 20 mg NASAL SPRAY	2.34 (0.96, 5.6)	1.66 (0.68, 3.95)	0.92 (0.352, 2.36)	0.62 (0.246, 1.50)	0.52 (0.173, 1.54)	0.45 (0.179, 1.13)	**0.258** (0.130, 0.513)
	LOW FLOW OXYGEN	**2.55** (1.13, 5.8)	1.80 (0.77, 4.2)	1.09 (0.42, 2.84)	0.68 (0.28, 1.61)	0.56 (0.19, 1.66)	0.49 (0.20, 1.20)	**0.283** (0.138, 0.539)
	ZOLMITRIPTAN 5 mg NASAL SPRAY	**3.78** (1.72, 8.4)	**2.67** (1.21, 5.9)	1.62 (0.66, 3.97)	1.48 (0.62, 3.54)	0.83 (0.303, 2.32)	0.72 (0.308, 1.68)	**0.42** (0.235, 0.73)
	OCTREOTIDE SUBCUTANEOUS	**4.5** (1.64, 12.5)	**3.20** (1.17, 8.8)	1.93 (0.65, 5.8)	1.78 (0.60, 5.2)	1.20 (0.43, 3.34)	0.87 (0.323, 2.47)	0.50 (0.200, 1.16)
	NON-INVASIVE VAGAL NERVE STIMULATION	**5.2** (2.29, 11.9)	**3.69** (1.63, 8.4)	2.23 (0.89, 5.7)	2.04 (0.83, 5.0)	1.38 (0.60, 3.19)	1.15 (0.40, 3.29)	0.58 (0.306, 1.06)
	PLACEBO	**9.0** (5.3, 15.9)	**6.4** (3.75, 11.1)	**3.86** (1.97, 7.9)	**3.54** (1.84, 6.9)	**2.39** (1.37, 4.3)	1.99 (0.86, 4.7)	1.74 (0.94, 3.23)

FIGURE 4 Treatment effects and headache response at 15–30 min. Odds ratios (ORs) and 95% credible intervals (in parentheses) for acute headache response are presented. Below the diagonal, OR values >1 favor the treatment in the column header. Above the diagonal, OR values <1 favor the treatment in the row header. The red/orange color represents results where the odds ratio is >1, and the green color represents results where the odds ratio <1. ** $p < 0.05$ [Color figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com/doi/10.1111/head.14283)]

which exhibited the fourth-highest probability ranking and SUCRA value, was better than placebo (OR 3.54, 95% CrI 1.84 to 7.0), but was not better than nVNS, octreotide, sumatriptan injectable, sumatriptan NS, or zolmitriptan NS.

Injectable sumatriptan at doses of 6 mg SC was associated with the second-highest probability ranking and SUCRA value after high flow oxygen based on results from two trials in which it was compared to placebo.^{38,39} Response to sumatriptan (6 mg SC) was better than for nVNS (OR 3.69, 95% CrI 1.63 to 8.4), octreotide (OR 3.20, 95% CrI 1.17 to 8.8), zolmitriptan NS (OR 2.67, 95% CrI 1.21 to 5.9), and placebo (OR 6.4, 95% CrI 3.75 to 11.1).

Sumatriptan (20 mg NS; OR 3.68, 95% CrI 1.97 to 7.9) and zolmitriptan (5 mg NS; OR 2.39, 95% CrI 1.37 to 4.3) were both identified as better than placebo, although no other differences were observed involving these therapeutic regimens. The lowest-ranked intervention was placebo, followed by nVNS and octreotide SC. In Appendix 6 we provide the ORs of headache response to all treatments in the trials evaluated in direct treatment comparisons and pair-wise meta-analyses compared to the ORs based on our NMA (Tables A3 and A4). These were of similar magnitude to ORs from NMAs, aligning with the fact that there was no evidence of violations of the consistency assumption based upon model fit statistics and scatterplots of residuals (see Appendix 6).

Outcome 2: Acute therapies and adverse events

After the elimination of five studies that reported no adverse events in any groups,^{22,34,35,39,40} we included the five remaining studies in

an NMA which compared the frequencies of treatment-associated adverse events. The network diagram presented in Figure 6 includes adverse events associated with the use of octreotide, zolmitriptan NS (5 mg), VNS, sumatriptan (6 mg injectable), and placebo. An FE model was used to analyze this outcome, as the difference in fit between the two models was negligible (DIC = 19.7 for FE vs. 19.9 for RE). There was again no evidence of violations of the consistency based on inspection of measures of model fit (Appendix 6).

The accompanying league table is shown in Figure 7, and the associated probability bar plot is shown in Figure 8. Placebo was least likely to be associated with adverse events, while octreotide and sumatriptan were the only treatments associated with higher probabilities of adverse events. Octreotide had an OR of 4.1 (95% CrI 1.70 to 10.6) for adverse events compared to placebo, while sumatriptan injectable had an OR of 2.40 (95% CrI, 1.39 to 4.2) compared to placebo. Our analysis revealed no differences in adverse events associated with nVNS or zolmitriptan NS compared to placebo. There were no reported deaths. Adverse events were mostly minimal and varied by intervention.

Subgroup analysis: Response of patients diagnosed with episodic or chronic CH to various acute treatments

Episodic CH

We identified three trials that specifically addressed the outcomes of acute treatments, including zolmitriptan 5 mg NS,³⁴ nVNS,^{37,43} and

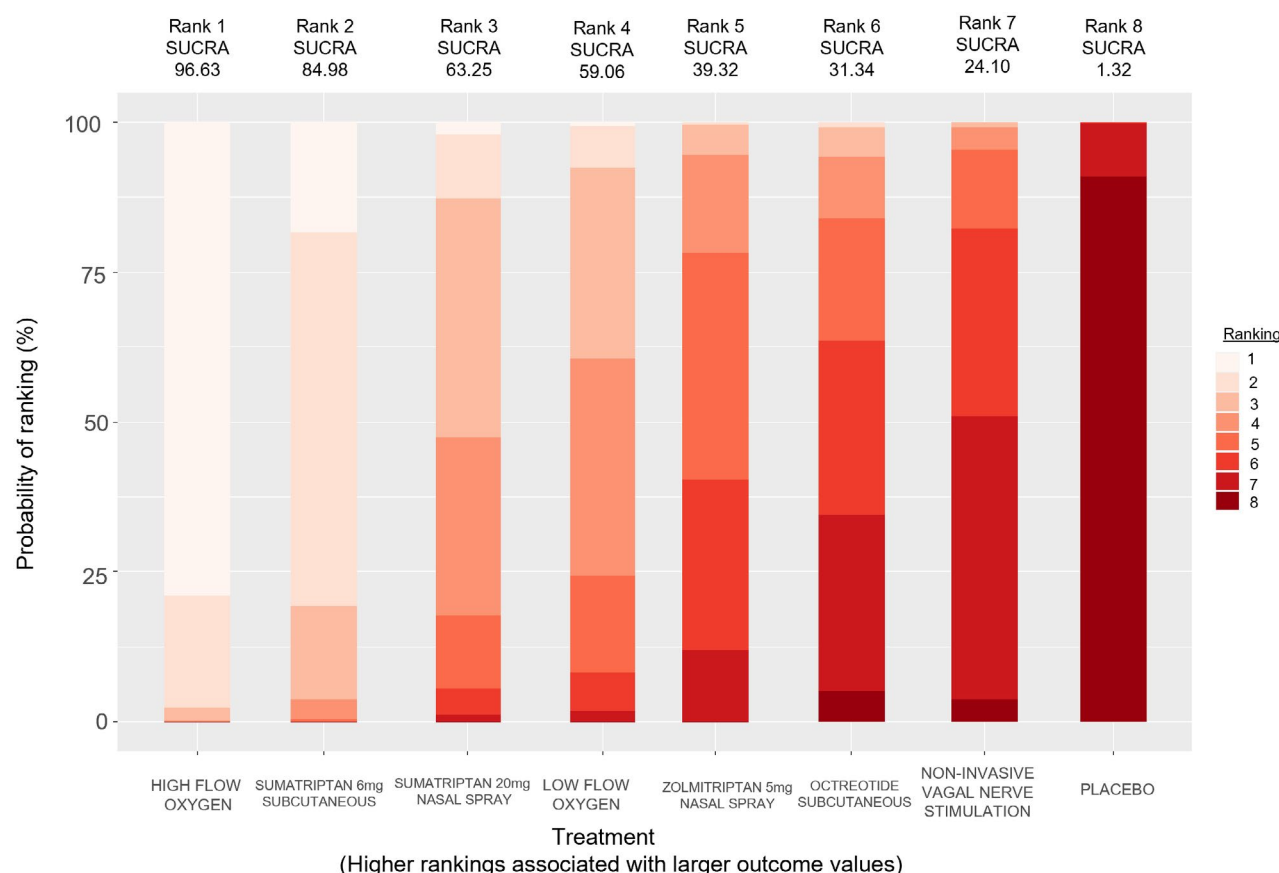


FIGURE 5 Probability rankings of acute therapies and headache response at 15 and 30 min. The probability rankings for each treatment are shown along with their respective Surface Under the Cumulative Ranking curve (SUCRA) values. The individual probabilities per treatment associated with each ranking are shown as a function of 100% within the corresponding bars [Color figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com/doi/10.1111/head.14283)]

placebo for episodic CH with data that could be used to perform an NMA of headache response (see Appendix 4). We used an FE model, as there was no important difference in fit between the two models (DIC = 10.22 vs. 10.87 for FE vs. RE models, respectively). Additional outcome data were obtained from a published meta-analysis⁴⁸ of the two trials featuring nVNS.^{37,43} Our findings suggested that nVNS was better than placebo when evaluating acute responses for patients with episodic CH (OR 4.9, 95% CrI 1.89 to 14.1). Subgroup data for episodic CH were available from one trial featuring treatment with zolmitriptan 5 mg NS.³⁴ Our NMA revealed an OR of 2.10 (95% CrI 0.78 to 5.9) for this subgroup. Overall, nVNS ranked first, with no differences between nVNS and zolmitriptan 5 mg NS; the OR of the treatment effect for episodic CH was 2.36 (95% CrI 0.58 to 10.1) (Figures A5–A9).

Chronic CH

We identified five trials with sufficient data that permitted us to assess treatment effects in patients with chronic CH (see Appendix 5).^{34,37,43,45,46} Therapeutic interventions where subgroup data were available included zolmitriptan nasal spray ($n = 1$),³⁴ nVNS ($n = 2$),^{37,43} and SPG stimulation ($n = 2$).^{45,46} SPG stimulation is a technique that involves having an implantable neurostimulator in the SPG ganglion, however presently this

device is not commercially available. In this case, we reported findings from an RE model, as this resulted in a better fit (DIC = 114.3 for the FE model vs. 20.1 for the RE model) (Figures A10–A13).

Overall, we found that SPG stimulation was associated with the highest probability ranking and highest SUCRA values among the treatments evaluated; however, none of the comparisons were associated with differences in efficacy given wide credible intervals. Two of the trials examined^{45,46} featured SPG stimulation that was only used in patients diagnosed with chronic CH. Compared to placebo, SPG stimulation was associated with an OR of 5.8 (95% CrI, 0.302 to 119.5). Zolmitriptan 5 mg NS had the second-highest probability rank and SUCRA value (OR of 2.44 vs. placebo, 95% CrI 0.029 to 202.8), although no differences were identified. Treatment with nVNS ranked lower than placebo, although this difference was also not clearly established (OR 0.66, 95% CrI 0.025 to 14.4).

Meta-biases

In our companion scoping review, we searched clinical trial registries and identified negative trials for a therapy that has not yet been published to address the issue of potential publication bias. We identified a negative and as yet unpublished trial featuring the synthetic somatostatin analog, pasireotide.⁴⁹ More formal methods,

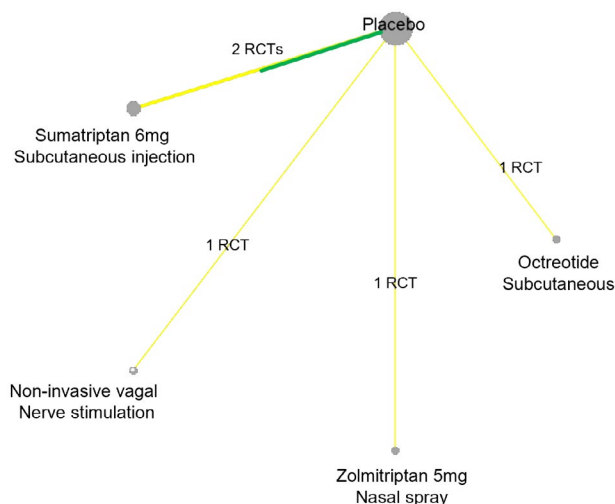


FIGURE 6 Adverse events associated with acute therapies for cluster headache. Shown is a network diagram for adverse events associated with acute treatments for cluster headache. Nodes are sized proportionately to reflect the number of events associated with each intervention. The lines connecting the interventions have widths that reflect the number of randomized controlled trials (RCTs) per comparison. The line colors reflect the risk of bias assessment as per American Academy of Neurology criteria, with RCTs categorized as Class I in green and Class II in yellow. Overall, five interventions were compared in a total of five studies ($n = 251$ events) [Color figure can be viewed at wileyonlinelibrary.com]

including data assessment using funnel plots, were not undertaken due to the limited number of suitable studies that were available.

DISCUSSION

We conducted network meta-analyses to compare interventions for acute treatment of CH. Findings were suggestive that high flow oxygen was as effective as injectable sumatriptan for headache relief at 15 min. Furthermore, while comparisons of adverse events involving high flow oxygen could not be performed, as it could not be incorporated into the network (there were no adverse events in the treatment or placebo groups, and thus these studies were excluded from quantitative analyses). It is generally regarded to have a better adverse event profile, as systemically it creates no issues, and its use via mask is generally straightforward and safe. We also showed for the first time that high flow oxygen at 15 L/min is better than low flow oxygen at 6 or 7 L/min, with both demonstrating more effectiveness for headache relief than placebo. For the subgroup analyses focusing on episodic and chronic patients, we were able to compare only zolmitriptan NS, nVNS and in the case of chronic cluster also SPG stimulation. For acute therapy of episodic cluster, we found that VNS may be as effective as zolmitriptan NS, and nVNS generally has fewer side effects. For chronic CH, we found that SPG stimulation may be

		Treatment				
		PLACEBO	ZOLMITRIPTAN 5 mg NASAL SPRAY	NON-INVASIVE VAGAL NERVE STIMULATION	SUMATRIPTAN 6 mg SUBCUTANEOUS	OCTREOTIDE SUBCUTANEOUS
Comparator	PLACEBO		1.80 (0.67, 5.09)	1.83 (0.79, 4.33)	**2.40** (1.39, 4.23)	**4.1** (1.70, 10.6)
	ZOLMITRIPTAN 5 mg NASAL SPRAY	0.56 (0.197, 1.49)		1.02 (0.273, 3.73)	1.34 (0.41, 4.17)	2.30 (0.59, 8.9)
	NON-INVASIVE VAGAL NERVE STIMULATION	0.55 (0.232, 1.26)	0.98 (0.27, 3.71)		1.32 (0.48, 3.62)	2.26 (0.66, 7.9)
	SUMATRIPTAN 6 mg SUBCUTANEOUS	**0.42** (0.239, 0.72)	0.75 (0.24, 2.44)	0.76 (0.28, 2.10)		1.72 (0.60, 5.1)
	OCTREOTIDE SUBCUTANEOUS	**0.243** (0.089, 0.59)	0.43 (0.114, 1.69)	0.44 (0.125, 1.51)	0.58 (0.197, 1.66)	

FIGURE 7 Treatments, comparators, and adverse events associated with acute treatments for cluster headache. Odds ratios (ORs) and 95% credible intervals (in parentheses) for adverse events associated with acute treatment for cluster headache. Below the diagonal, OR values <1 favor the treatment in the column header. The red/orange color represents results where the OR is >1 , and the green color represents results where the OR is <1 . Green cells represent favorable treatment effect estimates (i.e., fewer adverse effects) for the treatment group in each comparison below the diagonal, with darker shades representing increasing magnitude of effect. Red cells above the diagonal represent the inverse effect estimates from below the diagonal, with darker shades of red representing increasing magnitude of effect (more risk of adverse effects). ****** $p < 0.05$ [Color figure can be viewed at wileyonlinelibrary.com]

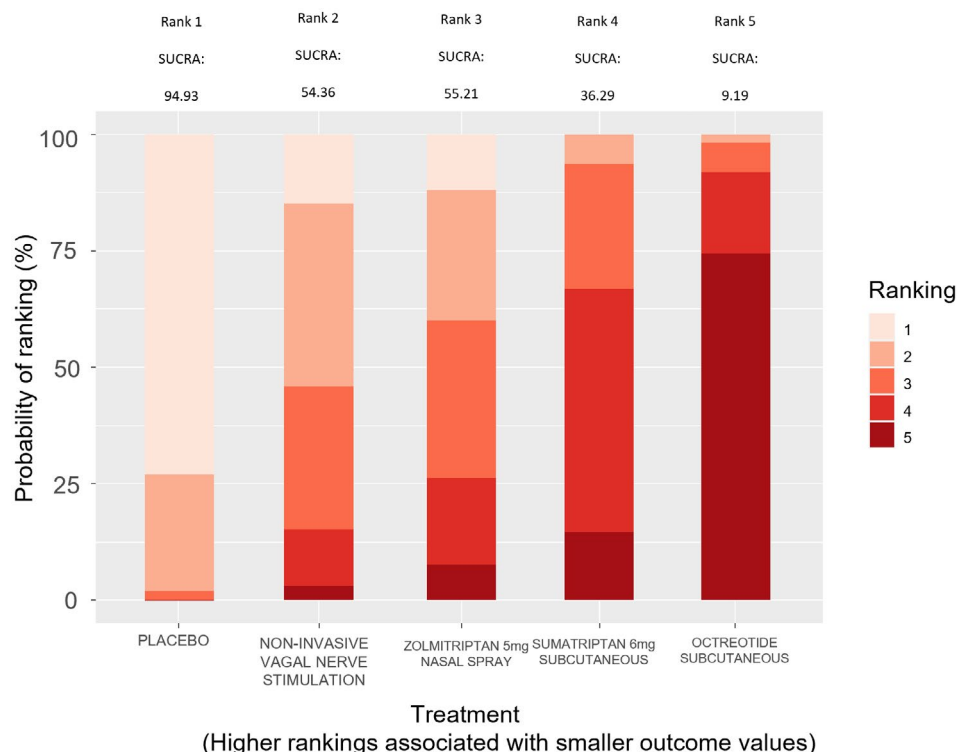


FIGURE 8 Probability rankings of adverse events associated with acute therapies for cluster headache. The highest probability ranking for each treatment is shown along with its respective Surface Under the Cumulative Ranking curve (SUCRA) value. The individual probabilities associated with each treatment and of each ranking are shown as a function of 100% within its corresponding bar [Color figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com/doi/10.1111/head.14283)]

a viable treatment option, comparable or possibly better than zolmitriptan NS. As has been shown by others,^{48,50} nVNS does not appear to be an effective treatment option for chronic CH. Our approach to synthesizing the evidence as well as the inclusion of new trials and interventions represent additions to the literature for clinicians.

To contextualize our findings with the most recent systematic reviews and guidelines for CH,^{19,20} in the current review we also found oxygen to be effective for acute therapy. Additionally, high flow oxygen was found more likely to be efficacious when compared to low flow oxygen. This is the first review to identify this important clinical finding to our knowledge. This has clinical implications, as patients who have a lack of success with low flow oxygen and can tolerate increased flow rates should be tried on high flow oxygen. Additionally, our findings suggest that high flow oxygen may be more effective than zolmitriptan NS, nVNS, and octreotide. Sumatriptan injectable is more likely to be effective when compared to zolmitriptan NS, octreotide, and nVNS. The ability to provide guidance on the relative efficacy of the available therapies compared to each other is also valuable in this field, as there remains a lack of head-to-head clinical trials. Our findings that nVNS may be effective in acute management of episodic cluster and that SPG may be effective for chronic cluster also represent important findings worthy of additional study.

Additionally, we considered the introduction of an open label randomized trial⁴⁷ comparing the effect of sumatriptan injectable to nasal spray, but the response was notably different compared to other trials utilizing the same interventions. There is evidence that the placebo effect is increased if there is expectation introduced to the participant

that the study drug will work,⁵¹ and with open label trials this is more difficult to circumvent. In migraine research, placebo effects for acute treatment are more likely with injection than other means of administration,⁵² and this may also hold true in CH. We did not include this trial in NMAs because its open label design may have impacted the trial results, as the benefit from injection was higher than compared to nasal spray in the blinded trials when we compared them indirectly. Future studies and network meta-analyses should continue to consider expectation of treatment effects if deciding on inclusion of open label and observational data and exploring this in sensitivity analyses.

As it is difficult to enroll patients for acute treatment trials in CH, most of the acute trials were crossover trials. Patients were usually given an active treatment and placebo sequentially, and this merits different considerations.⁵³ We felt it was appropriate to use a binomial model for these data as there were few trials^{35,37} where individuals received multiple treatments with the same intervention, and in those trials, it was not most individuals in the trial.

This current NMA has some limitations that should be noted. Data collection was performed by a single author; while this does not align with best practices, the author is an experienced clinician in the field and has training in the conduct of systematic reviews. Additionally, for most of the treatment comparisons, the linking node that facilitated the conduct of NMAs was placebo. Placebo was variably delivered based on the trial (injection, intravenous solution, nasal spray, electrical device, oxygen mask). There may have been treatment modality modifier effects, especially in the adverse events categories that were quite different between different

placebo interventions. For example there were no placebo adverse events in the oxygen trials,^{35,40} and these were substantially larger for placebo in the injectable placebo formulations.^{38,39} We do show in our companion scoping review that for the treatment efficacy response there was little variability in the placebo response rates between various treatment modalities, and as such we do not think this influenced our results for the treatment efficacy.

NMAs can play a vital role in establishing the relative benefits and risks of treatment modalities for a disease, although the importance of head-to-head RCTs remains high. In NMAs there can be confounders such as differing trial characteristics that modify treatment response, and they cannot be corrected for if unknown. Conversely, RCTs can minimize the effects of such confounders through randomization. Randomized controlled trials are expensive; however, where there are suggestions of a large treatment effect difference from NMAs, it can be worthwhile to consider confirmation by head-to-head trials where possible. The non-inferiority margins and sample sizes necessary can be suggested by data provided from NMAs.

CONCLUSIONS

High flow oxygen is more efficacious when compared to low flow oxygen for headache relief. From a clinical standpoint, patients who have a lack of success with low flow oxygen and can tolerate increased flow rates should be tried on high flow NS. Sumatriptan injectable is more likely to be effective when compared to zolmitriptan NS, octreotide and nVNS. Patients who have a lack of response to nasal spray triptans should be tried with injectable sumatriptan, as our data suggest that with sumatriptan injection patients have more chances of having a decrease in headache than with nasal spray. For episodic CH, nVNS is likely effective in acute treatment. In the chronic CH subgroup, our results suggest that SPG stimulation may be the best treatment amongst those studied.

CONFLICT OF INTEREST

Dr. S. Christie grants for research (no personal compensation): Allergan/Abbvie; Dr. S. Tepper grants for research (no personal compensation): Allergan/Abbvie, Amgen, Eli Lilly, Lundbeck, Neurolief, Novartis, Satsuma, Zosano. Consultant and/or Advisory Boards (honoraria): Aeon, Allergan/Abbvie, Alphasights, Amgen, Aruene, Atheneum, Axsome Therapeutics, Becker Pharmaceutical Consulting, BioDelivery Sciences International, Biohaven, ClearView Healthcare Partners, CoolTech, CRG, Currax, Decision Resources, Defined Health, DRG, Eli Lilly, ExpertConnect, FCB Health, Fenix, GLG, Guidepoint Global, Health Science. Communications, HMP Communications, Impel, InteractiveForums, Keyquest, Krog and Partners, Lundbeck, M3 Global Research, MJH Holdings, Neurolief, Novartis, P Value. Communications, Pain Insights, Inc, Palion Medical, Pulmatrix, Putnam Associates, SAI MedPartners, Satsuma, Spherix Global Insights, Strategy Inc, System Analytic, Taylor and Francis, Teva, Theranica, Trinity Partners, Unity HA, XOC, Zosano. Salary: Dartmouth-Hitchcock Medical Center, American Headache Society,

Thomas; Jefferson University. CME honoraria: American Academy of Neurology, American Headache Society, Annenberg Center for Health Sciences, Catamount Medical Education, Diamond; Headache Clinic, Forefront Collaborative, Haymarket Medical Education, Medical; Education Speakers Network, Medical Learning Institute Peerview, Migraine; Association of Ireland, National Association for Continuing Education, North American; Center for CME, The Ohio State University, Physicians' Education Resource, PlatformQ; Education, Primed, Texas Neurological Society, Vindico Medical Education, WebMD/Medscape. The other authors have no conflicts to declare.

AUTHOR CONTRIBUTIONS

Study concept and design: Ioana Medrea, Brian Hutton, Kednapa Thavorn, Suzanne Christie, Stewart J. Tepper. *Acquisition of data:* Ioana Medrea, Suzanne Christie. *Analysis and interpretation of data:* Ioana Medrea, Brian Hutton, Kednapa Thavorn, Suzanne Christie, Stewart J. Tepper. *Drafting of the manuscript:* Ioana Medrea. *Revising it for intellectual content:* Brian Hutton, Kednapa Thavorn, Suzanne Christie, Stewart J. Tepper. *Final approval of the completed manuscript:* Brian Hutton, Kednapa Thavorn, Suzanne Christie, Stewart J. Tepper.

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APPENDIX 1

RISK OF BIAS APPRAISALS

Study ID#:

Reviewed by:

Final class:

TABLE A1 AAN risk of bias sample table

Bias	Author's judgment		Support for judgment
	Yes	No	
*Design (Is it an RCT?)			
*Masked or objective outcome assessment			
*Similar baseline characteristics between groups and if not adjusted for differences			
Allocation concealment			
No more than 2 primary outcomes specified			
Clear definition of inclusion/exclusion criteria			
Less than 20% dropouts and dropouts appropriately accounted for			
For cross-over trials only: period and carryover effects examined and statistical adjustments performed where necessary			

Final decision on quality

1. Class I Study:
 - ☐ RCT meets all criteria above
2. Class II Study:
 - ☐ RCT meets starred (*) criteria (i.e., first 3 in list) but lacks 1–2 of the other criteria above
 - ☐ Crossover trial that either does not describe period/carryover effects OR does not present baseline characteristics of treatment order groups
3. Class III Study:
 - ☐ RCT lacking more than 2 of the criteria above
 - ☐ Crossover trial that both does not describe period/carryover effects AND does not present baseline characteristics of treatment order groups
4. Class IV Study:
 - ☐ Does not apply to this

TABLE A2 Baseline demographics of trials included in the NMA for acute therapies

Study and Year	Treatment	Comparator	Diagnostic criteria	ECH/CCH	M/F	AAN ROB	Reasons for downgrade
Ekbom 1991	Sumatriptan 6 mg SC	Placebo	IHS	56% ECH	3.88:1	Class II	Drop out at 20%; did not talk about allocation concealment
Ekbom 1993	Sumatriptan 6 mg SC	Placebo	IHS	72% ECH	6.44:1	Class I	No downgrades applied
Cittadini 2006	Zolmitriptan 5 mg NS	Placebo	IHS	64% ECH	6.66:1	Class II	Crossover study, did not present baseline treatment order groups; did not talk about allocation concealment
Rapoport 2007	Zolmitriptan 5 mg NS	Placebo	ICHD-2	71% ECH	2.21:1	Class II	Crossover study, did not present baseline treatment order groups; did not talk about allocation concealment
Fogan 1985	O ₂ Low	Placebo	Ad hoc	na	na	Class II	Crossover study, did not present baseline treatment order groups, and no statistical adjustment; did not talk about allocation concealment
Cohen 2010	O ₂ High	Placebo	IHS	75% ECH	4.45:1	Class II	Crossover study, did not present baseline treatment order groups; did not talk about allocation concealment
Dirxs 2018	O ₂ Low	O ₂ High	ICHD-2	67% ECH	1.57:1	Class II	Crossover, and no treatment order groups baseline presented
van Vliet 2003	Sumatriptan 20 mg NS	Placebo	IHS	75% ECH	4.62:1	Class II	Crossover study, did not present baseline treatment order groups; did not talk about allocation concealment
Costa 2000	Lidocaine, cocaine	Placebo	IHS	40% ECH	6.5:1	Class II	Crossover study, did not present baseline treatment order groups; did not talk about allocation concealment
Matharu 2004	Octreotide	Placebo	IHS	73% ECH	3.25:1	Class II	Crossover study, did not present baseline treatment order groups; did not talk about allocation concealment
Silberstein 2016	nVNS	Placebo	ICHD-2	67% ECH	5.25:1	Class I	No downgrades applied
Goadsby 2019	nVNS	Placebo	ICHD-3B	71% ECH	2.52:1	Class I	No downgrades applied
Goadsby 2019_2	SPG	Placebo	ICHD-3B	CCH	na	Class I	No downgrades applied
Schoenen 2013	SPG	Placebo	ICHD-2	CCH	5:25:1	Class 1	No downgrades applied

Abbreviations: analg, analgesic; CCH, chronic cluster headache; DVO, demand valve oxygen; ECH, episodic cluster headache; IHS, International Headache Society; ICHD, International Classification of Headache Disorders; na, not available; NS, nasal spray; nVNS, non-invasive vagal nerve stimulation; O₂, oxygen; PO, by mouth; SC, subcutaneous; SPG, sphenopalatine ganglion bloc.

APPENDIX 2

FINDINGS FROM RANDOM EFFECTS MODEL FOR HEADACHE RESPONSE AT 15 OR 30 MIN

Comparator	Treatment							
	HIGH FLOW OXYGEN	SUMATRIPTAN 6mg SUBCUTANEOUS	SUMATRIPTAN 20mg NASAL SPRAY	LOW FLOW OXYGEN	ZOLMITRIPTAN 5mg NASAL SPRAY	OCTREOTIDE SUBCUTANEOUS	NON-INVASIVE VAGAL NERVE STIMULATION	PLACEBO
HIGH FLOW OXYGEN		0.71 (0.21, 2.46)	0.42 (0.102, 1.71)	0.377 (0.108, 1.16)	**0.260** (0.069, 0.87)	**0.223** (0.053, 0.969)	**0.187** (0.05, 0.65)	**0.109** (0.036, 0.273)
SUMATRIPTAN 6mg SUBCUTANEOUS	1.42 (0.41, 4.88)		0.60 (0.145, 2.24)	0.54 (0.141, 1.80)	0.368 (0.112, 1.14)	0.308 (0.065, 1.27)	**0.26** (0.08, 0.86)	**0.15** (0.072, 0.338)
SUMATRIPTAN 20mg NASAL SPRAY	2.37 (0.58, 10.27)	1.67 (0.45, 6.9)		0.89 (0.195, 3.77)	0.61 (0.163, 2.40)	0.52 (0.094, 2.60)	0.44 (0.114, 1.80)	**0.26** (0.087, 0.77)
LOW FLOW OXYGEN	2.65 (0.86, 9.35)	1.87 (0.55, 7.3)	1.12 (0.269, 5.0)		0.68 (0.188, 2.56)	0.58 (0.133, 2.84)	0.49 (0.138, 1.88)	**0.288** (0.108, 0.80)
ZOLMITRIPTAN 5mg NASAL SPRAY	**3.88** (1.15, 13.72)	2.74 (0.88, 9.0)	1.64 (0.42, 6.3)	1.46 (0.387, 5.27)		0.85 (0.190, 3.56)	0.72 (0.207, 2.39)	**0.42** (0.178, 0.96)
OCTREOTIDE SUBCUTANEOUS	**4.6** (1.04, 21.4)	3.24 (0.79, 14.4)	1.91 (0.38, 9.8)	1.72 (0.352, 8.0)	1.18 (0.275, 5.1)		0.85 (0.196, 3.80)	0.49 (0.145, 1.65)
NON-INVASIVE VAGAL NERVE STIMULATION	**5.4** (1.55, 19.3)	**3.82** (1.17, 12.7)	2.26 (0.56, 8.9)	2.03 (0.53, 7.4)	1.39 (0.42, 4.5)	1.17 (0.26, 4.98)		0.58 (0.243, 1.37)
PLACEBO	**9.2** (3.75, 24.5)	**6.5** (2.97, 15.4)	**3.89** (1.30, 11.6)	**3.47** (1.26, 9.2)	**2.38** (1.04, 5.4)	2.02 (0.61, 6.67)	1.72 (0.73, 4.12)	

FIGURE A1 League plots of treatment effect in network meta-analysis for each of the acute therapies and headache relief. Odds ratios (ORs) and 95% credible intervals for acute headache response are presented. Below the diagonal, OR values >1 favor the treatment in the column header. The red/orange color represents results where the OR is >1, and the green color represents results where the OR is <1.

****p < 0.05** [Color figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com)]

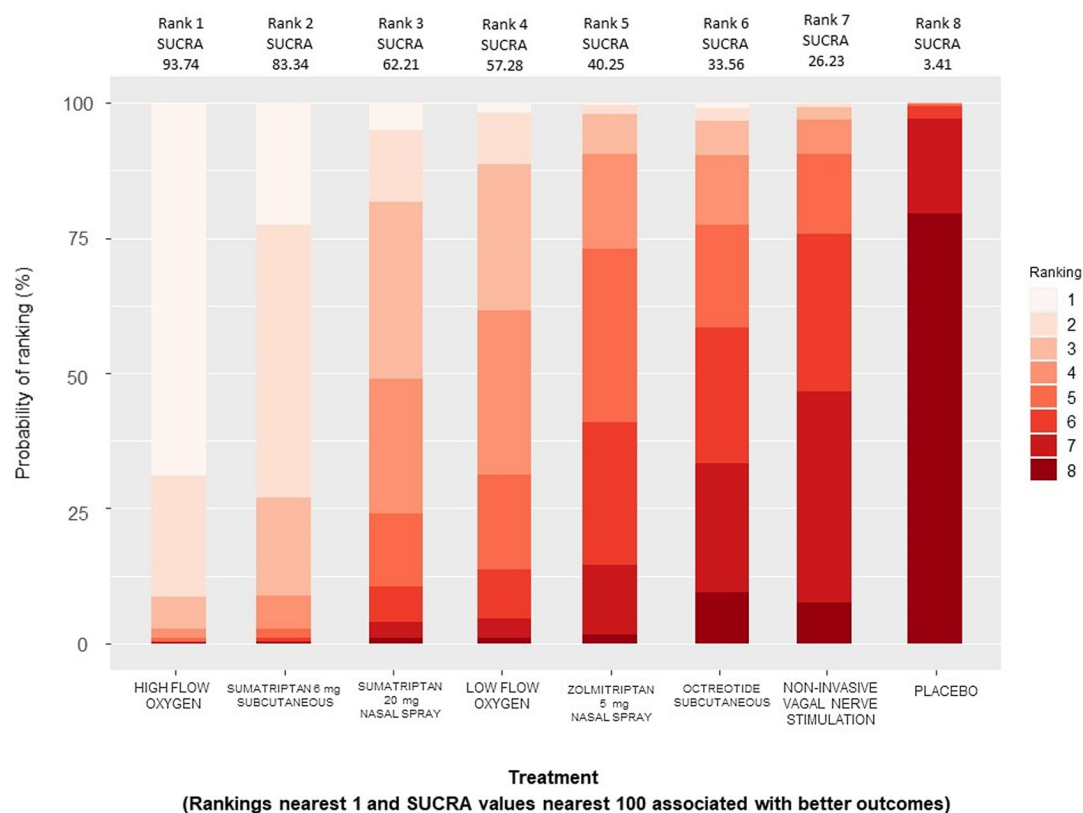


FIGURE A2 Probability bar plot of therapies for acute treatment of cluster headache and headache relief. For each individual treatment, the most probable ranking is shown at the top along with its Surface Under the Cumulative Ranking curve (SUCRA) value. The individual probabilities per treatment of each ranking are shown out of 100% within its corresponding bar [Color figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com/doi/10.1111/head.14283)]

APPENDIX 3

FINDINGS FROM RANDOM EFFECTS MODEL FOR ADVERSE EVENTS

Comparator		PLACEBO	ZOLMITRIPTAN 5 mg NASAL SPRAY	NON-INVASIVE VAGAL NERVE STIMULATION	SUMATRIPTAN 6 mg SUBCUTANEOUS	OCTREOTIDE SUBCUTANEOUS
	PLACEBO		1.79 (0.303, 10.73)	1.83 (0.329, 10.23)	2.32 (0.67, 7.5)	4.2 (0.73, 24.4)
	ZOLMITRIPTAN 5 mg NASAL SPRAY	0.56 (0.087, 3.38)		1.03 (0.088, 12.3)	1.29 (0.152, 11.0)	2.33 (0.185, 28.7)
	NON-INVASIVE VAGAL NERVE STIMULATION	0.55 (0.102, 3.02)	0.97 (0.083, 11.5)		1.26 (0.147, 9.9)	2.28 (0.199, 26.6)
	SUMATRIPTAN 6 mg SUBCUTANEOUS	0.43 (0.133, 1.50)	0.77 (0.000, 6.9)	0.79 (0.098, 6.6)		1.80 (0.222, 15.7)
	OCTREOTIDE SUBCUTANEOUS	0.239 (0.043, 1.37)	0.43 (0.029, 5.2)	0.44 (0.041, 5.1)	0.56 (0.064, 4.5)	

FIGURE A3 League plot of adverse events in acute treatments of cluster headache Odds ratios (ORs) and 95% credible intervals for acute headache response are presented. Below the diagonal, OR values >1 favor the treatment in the column header. The red/orange color represents results where the OR is >1, and the green color represents results where the OR is <1. Green cells represent favorable treatment effect estimates (i.e., fewer adverse effects) for the treatment group in each comparison in below the diagonal, with darker shades representing increasing magnitude of effect. Red cells above the diagonal represent the inverse effect estimates from below the diagonal, with darker shades of red representing increasing magnitude of effect (more risk of adverse effects). ** $p < 0.05$ [Color figure can be viewed at wileyonlinelibrary.com]

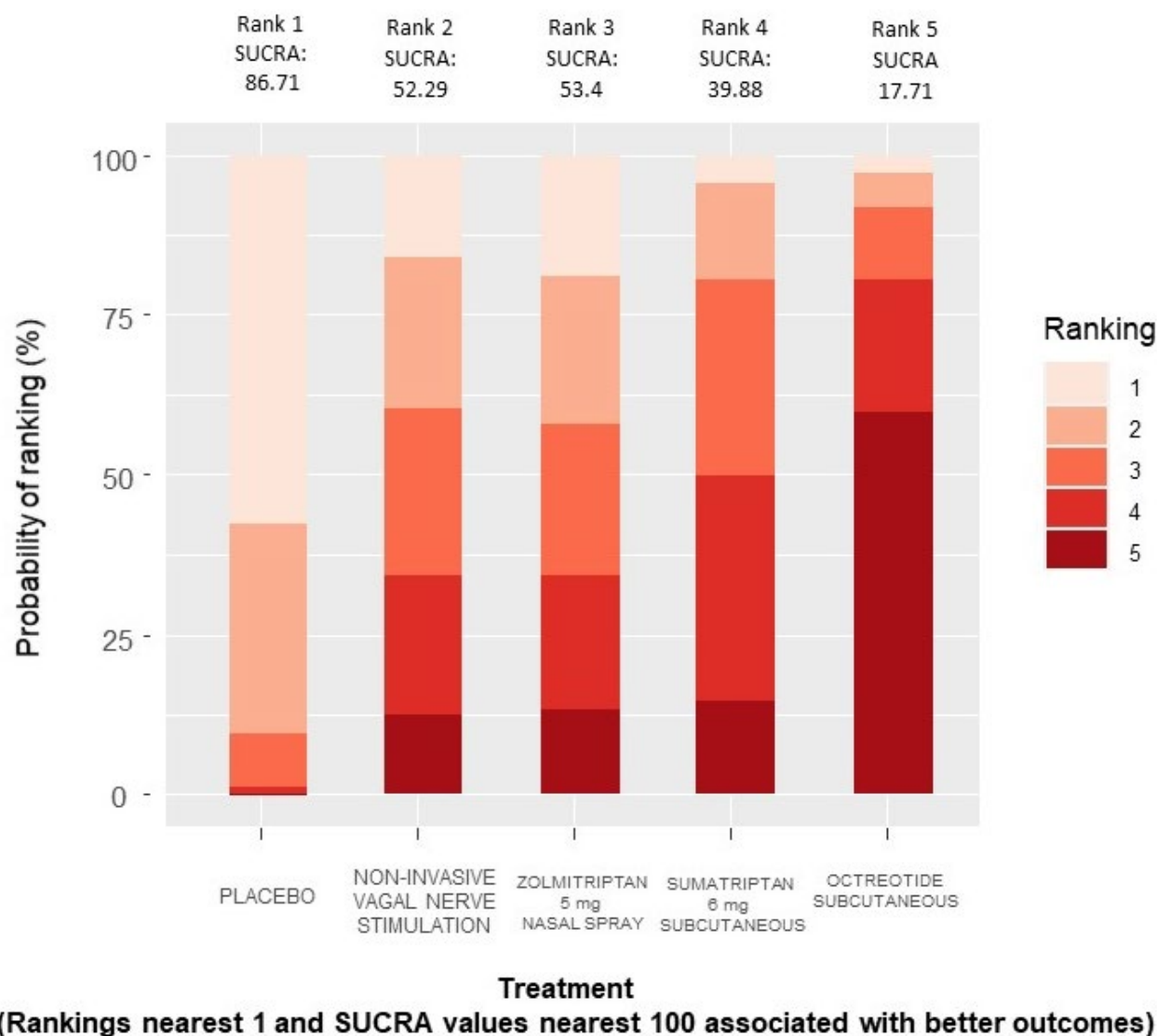


FIGURE A4 Probability bar plot of adverse events in acute treatments of cluster headache—Random effects model. For each individual treatment, the most probable ranking is shown at the top along with its Surface Under the Cumulative Ranking curve (SUCRA) value. The individual probabilities per treatment of each ranking are shown out of 100% within its corresponding bar [Color figure can be viewed at wileyonlinelibrary.com]

APPENDIX 4A

FINDINGS FROM FIXED EFFECTS AND RANDOM EFFECTS MODEL FOR HEADACHE RESPONSE AT 15/30 MIN IN EPISODIC CLUSTER

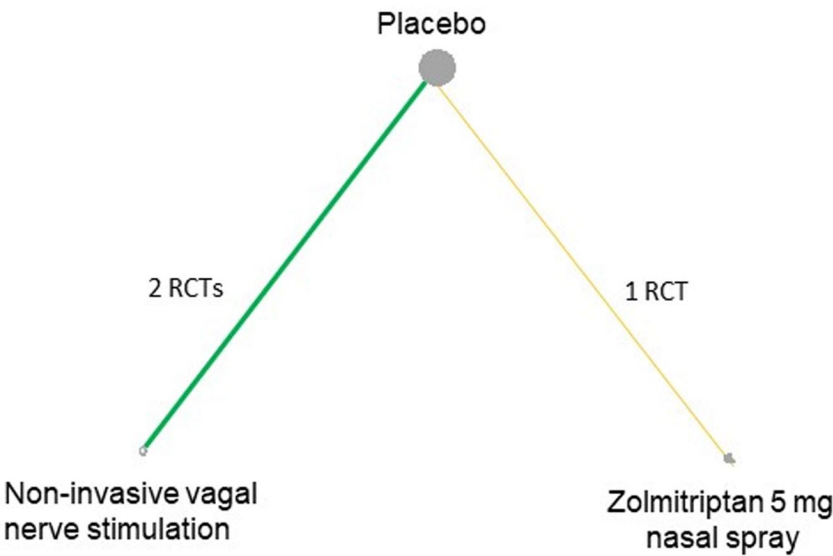


FIGURE A5 Network of treatments with headache response available for acute treatment of cluster headache in episodic cluster patients. The network diagram for headache response at 15/30 min in episodic cluster headache subgroup is shown. Nodes are sized to proportionately reflect the numbers of attacks for each intervention, while edges joining interventions have widths to reflect the numbers of randomized controlled trials (RCTs) per comparison. The color of edges reflects the American Academy of Neurology risk of bias assessment, with Class I shown in green and Class II shown in yellow. Overall, 3 interventions were compared in a total of 3 studies (n = 54 attacks) [Color figure can be viewed at [wileyonlinelibrary.com](#)]

		Treatment		
		NON-INVASIVE VAGAL NERVE STIMULATION	ZOLMITRIPTAN 5 mg NASAL SPRAY	PLACEBO
Comparator	NON-INVASIVE VAGAL NERVE STIMULATION		0.42 (0.096, 1.72)	**0.203** (0.069, 0.53)
	ZOLMITRIPTAN 5 mg NASAL SPRAY	2.36 (0.58, 10.1)		0.48 (0.170, 1.29)
	PLACEBO	**4.9** (1.89, 14.1)	2.10 (0.78, 5.9)	

FIGURE A6 League plot of headache response in episodic cluster patients—fixed effects model. Odds ratios (ORs) and 95% credible intervals for acute headache response are presented. Below the diagonal, OR values >1 favor the treatment in the column header. The red/orange color represents results where the OR is >1, and the green color represents results where the OR is <1. **p < 0.05 [Color figure can be viewed at [wileyonlinelibrary.com](#)]

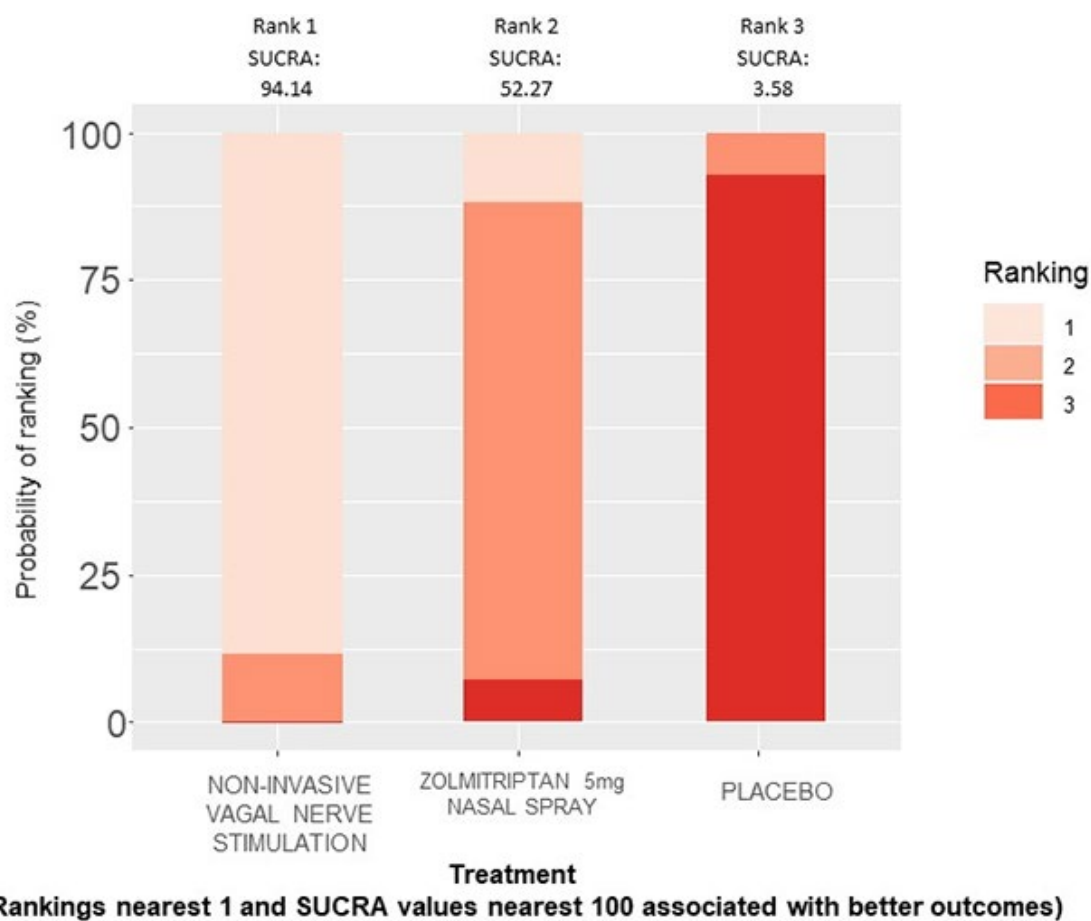


FIGURE A7 Probability bar plot of headache response in episodic cluster patients. For each individual treatment, the most probable ranking is shown at the top along with its Surface Under the Cumulative Ranking curve (SUCRA) value. The individual probabilities per treatment of each ranking are shown out of 100% within its corresponding bar [Color figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com/doi/10.1111/head.14283)]

APPENDIX 4B

EPISODIC CLUSTER HEADACHE RELIEF AT 15 OR 30 MIN: RANDOM EFFECTS MODELS

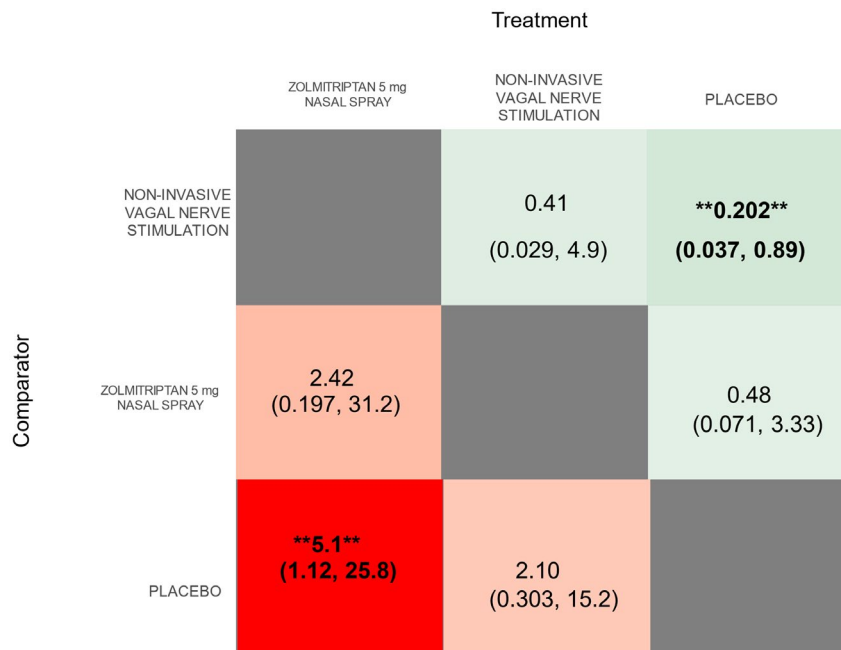


FIGURE A8 League plot of headache response in episodic cluster patients—Random effects. Odds ratios (ORs) and 95% credible intervals for acute headache response are presented. Below the diagonal, OR values >1 favor the treatment in the column header. The red/orange color represents results where the OR is >1, and the green color represents results where the OR is <1. ** $p < 0.05$ [Color figure can be viewed at wileyonlinelibrary.com]

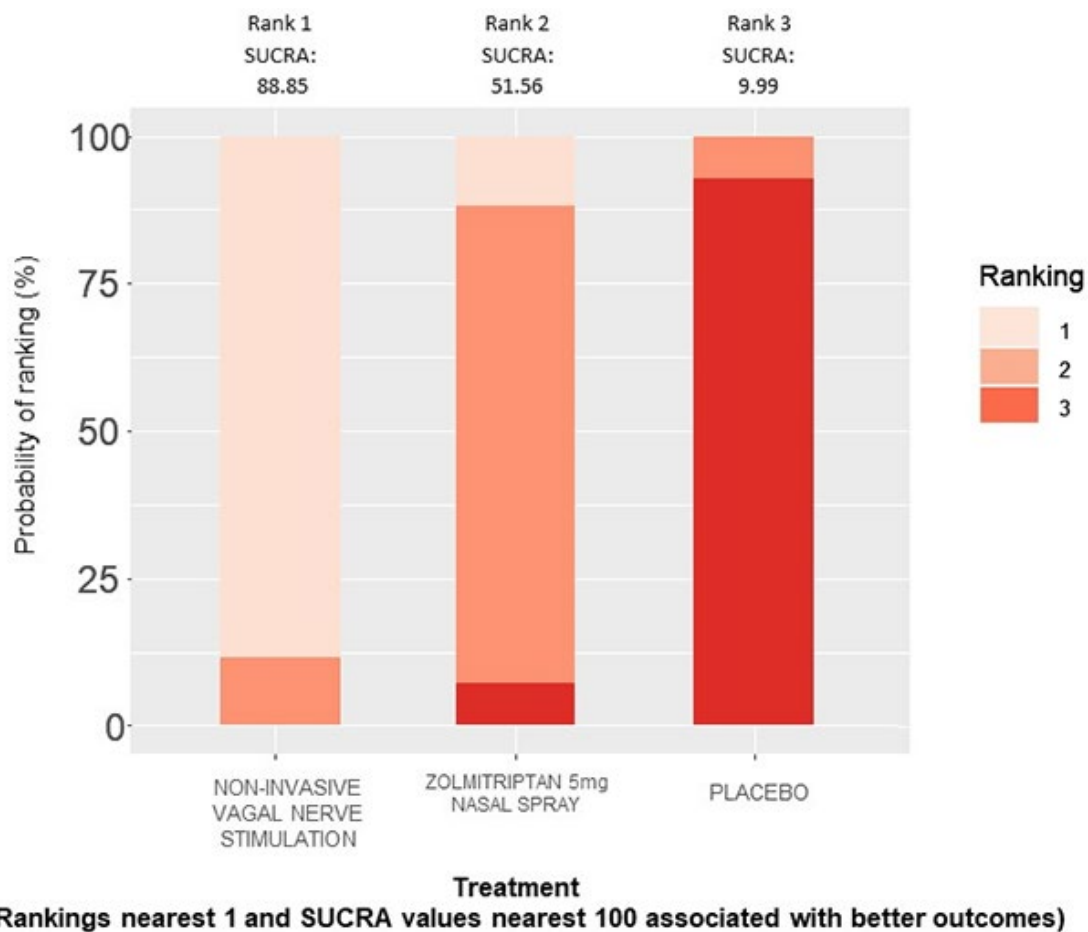


FIGURE A9 Probability bar plot of headache response in patients with episodic cluster [Color figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com)]

APPENDIX 5

CHRONIC CLUSTER HEADACHE RELIEF AT 15 OR 30 MIN RANDOM EFFECTS MODELS

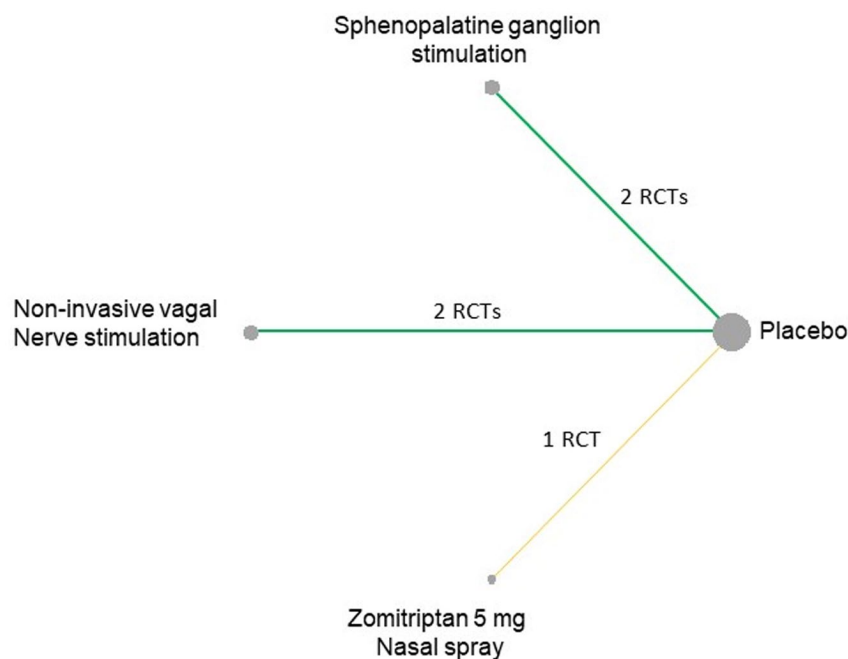


FIGURE A10 Network for acute headache relief in patients with chronic cluster headache. The network diagram for headache response at 15/30 min in chronic cluster is shown. Nodes are sized to proportionately reflect the numbers of attacks for each intervention, while edges joining interventions have widths to reflect the numbers of randomized controlled trials (RCTs) per comparison. The color of edges reflects the American Academy of Neurology risk of bias assessment, with Class I shown in green and Class II shown in yellow. Overall, 4 interventions were compared in a total of 5 studies ($n = 599$ attacks) [Color figure can be viewed at wileyonlinelibrary.com]

		Treatment			
		SPHENOPALATINE GANGLION STIMULATION	ZOLMITRIPTAN 5 mg NASAL SPRAY	PLACEBO	NON-INVASIVE VAGAL NERVE STIMULATION
Comparator	SPHENOPALATINE GANGLION STIMULATION		0.42 (0.000, 85.0)	0.171 (0.013, 3.31)	0.108 (0.000, 8.1)
	ZOLMITRIPTAN 5 mg NASAL SPRAY	2.37 (0.01, 487.0)		0.41 (0.000, 32.44)	0.273 (0.000, 54.8)
	PLACEBO	5.8 (0.302, 119.5)	2.44 (0.029, 202.8)		0.66 (0.025, 14.4)
	NON-INVASIVE VAGAL NERVE STIMULATION	8.8 (0.118, 670.04)	3.7 (0.023, 817.0)	1.51 (0.070, 33.6)	

FIGURE A11 League table for acute headache relief in patients with chronic cluster headache. Odds ratios (ORs) and 95% credible intervals for acute headache response are presented. Below the diagonal, OR values >1 favor the treatment in the column header. The red/orange color represents results where the OR is >1, and the green color represents results where the OR is <1. ** $p < 0.05$ [Color figure can be viewed at wileyonlinelibrary.com]

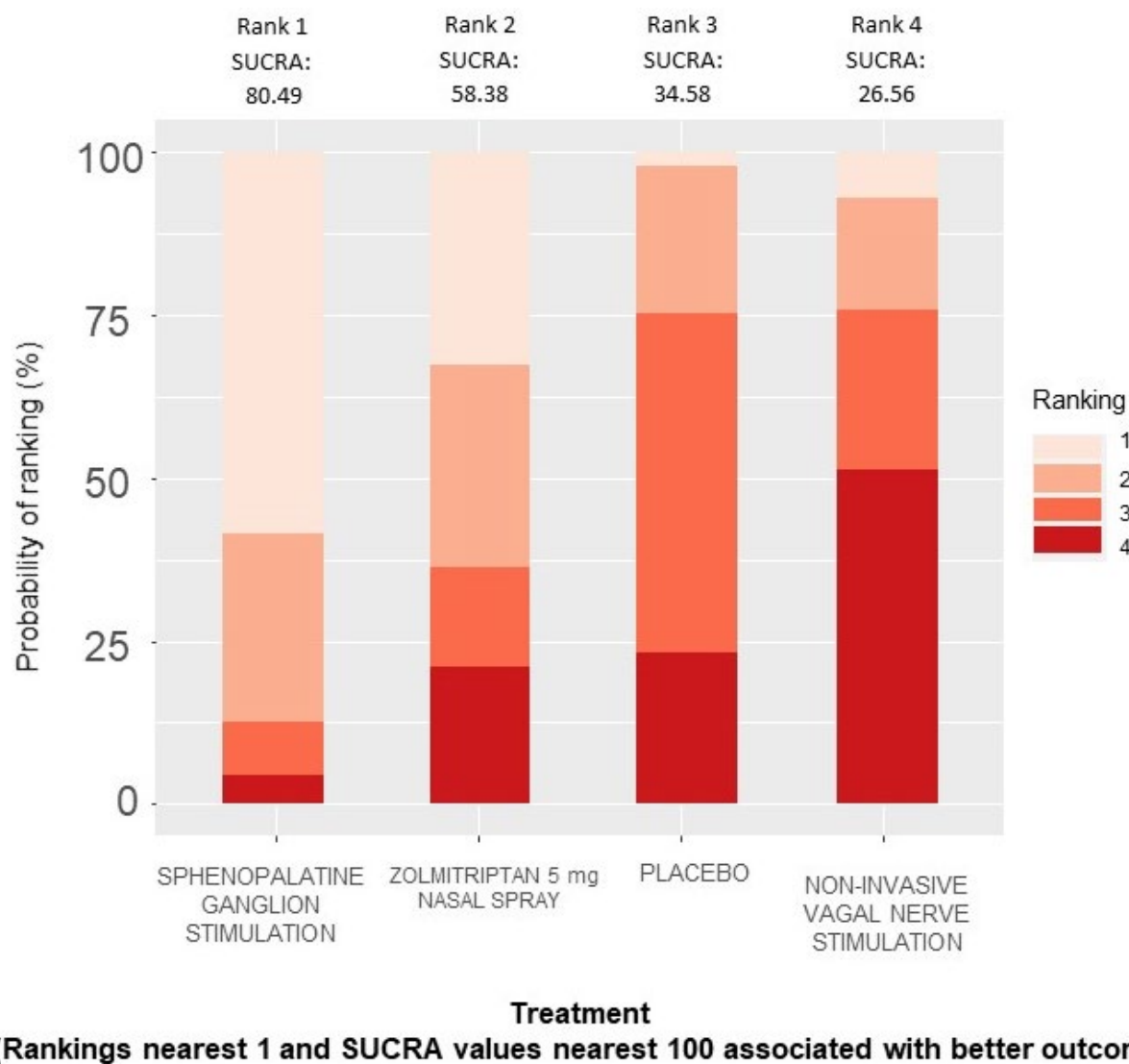


FIGURE A12 Probability bar plot of acute therapies for chronic cluster headache. Abbreviation: SUCRA, Surface Under the Cumulative Ranking curve [Color figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com/doi/10.1111/head.14283)]

APPENDIX 6

NMA MODEL FIT ASSESSMENTS

TABLE A3 Comparison of RCT Treatment Effects versus NMA from best fitting models

Active treatment	Comparison	OR trial or PMA	Confidence interval	I^2 - if PMA	p value	OR NMA	Credible Interval
<i>Acute therapy cluster headache—Headache response</i>							
O ₂ high	Placebo	3.95	2.48 to 6.29	NA	NA	9.03	5.27 to 15.93
O ₂ low	Placebo	1.90	1.04 to 3.47	NA	NA	3.54	1.84 to 6.94
O ₂ high	O ₂ low	2.33	0.39 to 14.04	NA	NA	2.55	1.13 to 5.76
Sumatriptan 6mg SC	Placebo	6.25	3.57 to 11.11	0.00%	0.49	6.39	3.75 to 11.13
Sumatriptan 20mg NS	Placebo	3.80	1.92 to 7.51	NA	NA	3.86	1.97 to 7.85
Zolmitriptan 5mg NS	Placebo	2.38	1.35 to 4.17	0	0.97	2.39	1.37 to 4.25
Octreotide	Placebo	1.47	0.69 to 3.12	NA	NA	1.99	0.86 to 4.72
nVNS	Placebo	1.72	0.93 to 3.13	0	0.57	1.74	0.94 to 3.23
<i>Acute therapy cluster headache—Adverse events</i>							
Octreotide	Placebo	4.02	1.64 to 9.83	NA	NA	4.14	1.70 to 10.60
Sumatriptan 6 mg SC	Placebo	2.33	1.17 to 4.55	30.60%	0.23	2.40	1.39 to 4.23
Zolmitriptan 5 mg NS	Placebo	1.75	0.65 to 4.76	NA	NA	1.80	0.67 to 5.09
nVNS	Placebo	1.27	0.56 to 2.89	86%	<0.01	1.83	0.79 to 4.33
<i>Acute therapy cluster headache—Episodic</i>							
Zolmitriptan 5 mg NS	Placebo	2.06	0.77 to 5.53	NA	NA	2.10	0.78 to 5.85
nVNS	Placebo	4.66	1.77 to 12.3	0%	0.83	4.93	1.89 to 14.11
<i>Acute therapy cluster headache—Chronic</i>							
Zolmitriptan 5 mg NS	Placebo	2.29	0.60 to 8.69	NA	NA	2.44	0.03 to 202.76
SPG-S	Placebo	5.79	0.31 to 107.37	99%	<0.0001	5.82	0.30 to 119.50
nVNS	Placebo	0.74	0.32 to 1.74	0%	0.59	0.66	0.03 to 14.41

Abbreviations: NA, not available; NMA, network meta-analysis; NS, nasal spray; nVNS, non-invasive vagal stimulator; O₂, oxygen; PMA, pair-wise meta-analysis; RCT, randomized controlled trial; SC, subcutaneous; SPG-S, sphenopalatine ganglion stimulation.

TABLE A4 Measures of NMA model fit

Model	# unconstrained data points	Total residual deviance	Tau-2	DIC
Acute—Headache response				
FE Consistency	22	19.06	NA	37.14
RE Consistency	22	19.78	NA	39.03
FE Unrelated Means	22	19.04	NA	37.10
RE Unrelated Means	22	19.88	NA	39.26
Acute treatment—Adverse events				
FE Consistency	10	10.55	NA	19.68
RE Consistency	10	10.11	NA	19.94
FE Unrelated Means	10	10.55	NA	19.68
RE Unrelated Means	10	10.11	NA	19.94
Acute—Headache response episodic				
FE Consistency	6	5.16	NA	10.27
RE Consistency	6	5.47	NA	10.92
FE Unrelated Means	6	5.16	NA	10.27
RE Unrelated Means	6	5.47	NA	10.92
Acute—Headache response chronic				
FE Consistency	10	106.34	NA	114.34
RE Consistency	10	10.06	NA	20.07
FE Unrelated Means	10	106.34	NA	114.34
RE Unrelated Means	10	10.06	NA	20.07

Abbreviations: DIC, deviance information criteria; FE, fixed-effects; NA, not available; NMA, network meta-analysis; RE, random-effects.

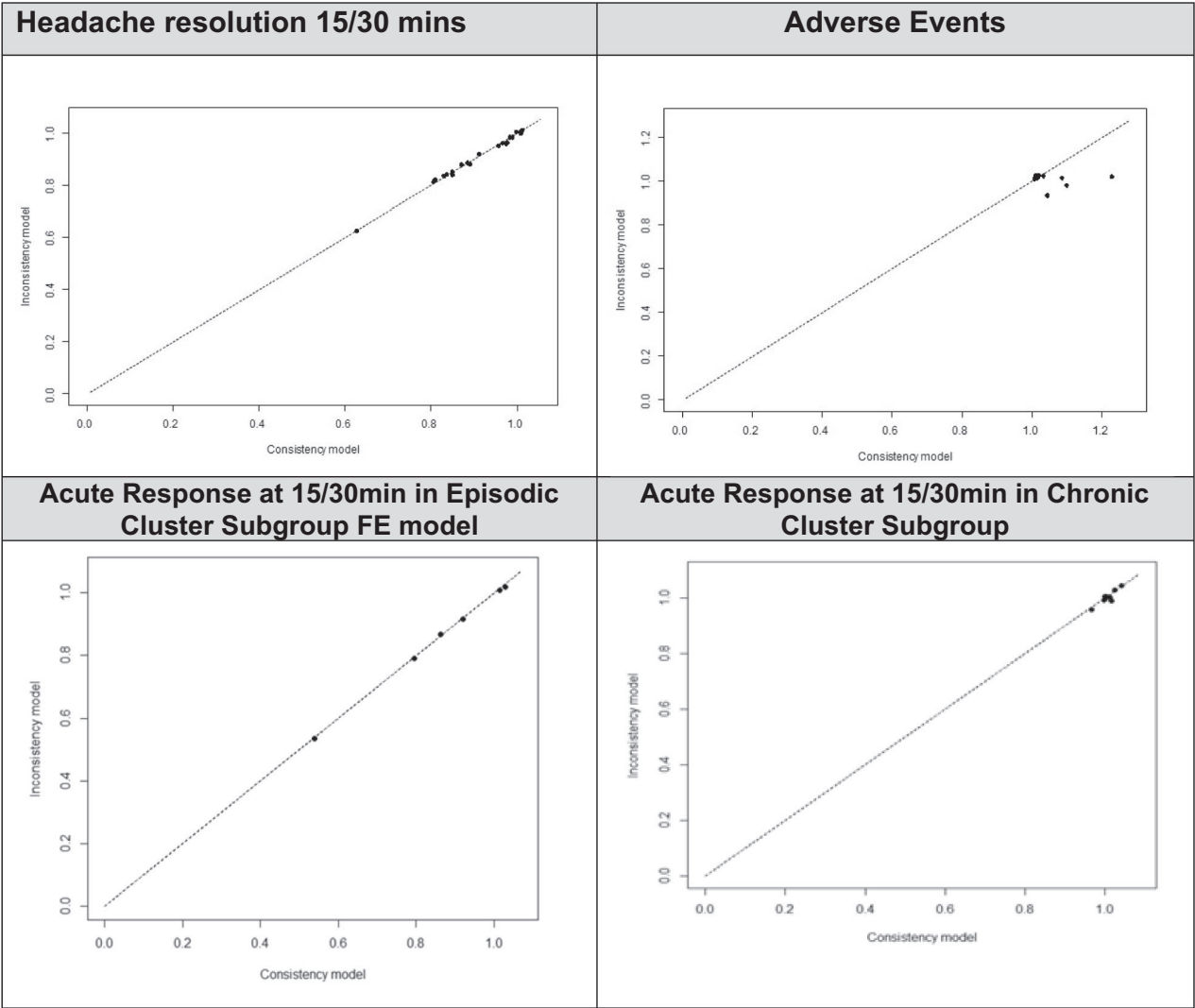


FIGURE A13 Scatterplots of residuals from consistency and unrelated means models from best fitting models per outcome. FE, fixed-effects

APPENDIX 7

PRISMA NMA CHECKLIST OF ITEMS TO INCLUDE WHEN REPORTING A SYSTEMATIC REVIEW INVOLVING A NETWORK META-ANALYSIS

Section/Topic	Item #	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review <i>incorporating a network meta-analysis (or related form of meta-analysis)</i>	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: Background: main objectives Methods: data sources; study eligibility criteria, participants, and interventions; study appraisal; and <i>synthesis methods, such as network meta-analysis</i> Results: number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; <i>treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity</i> Discussion/Conclusions: limitations; conclusions and implications of findings Other: primary source of funding; systematic review registration number with registry name	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known, <i>including mention of why a network meta-analysis has been conducted.</i>	3
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS)	3
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number	Accompanying manuscript
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. <i>Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification)</i>	Accompanying manuscript
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched	Accompanying manuscript
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated	Accompanying manuscript
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Accompanying manuscript
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Accompanying manuscript
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Accompanying manuscript
Geometry of the network	S1	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	9

Section/Topic	Item #	Checklist item	Reported on page #
Risk of bias within individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). <i>Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.</i>	7
Planned methods of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: <ul style="list-style-type: none"> • <i>Handling of multi-arm trials;</i> • <i>Selection of variance structure;</i> • <i>Selection of prior distributions in Bayesian analyses; and</i> • <i>Assessment of model fit.</i> 	5–7
Assessment of Inconsistency	S2	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	7
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6–7, and Appendix 1
Additional analyses	16	Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following: <ul style="list-style-type: none"> • Sensitivity or subgroup analyses; • Meta-regression analyses; • <i>Alternative formulations of the treatment network; and</i> • <i>Use of alternative prior distributions for Bayesian analyses (if applicable).</i> 	6–7
RESULTS^a			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7
Presentation of network structure	S3	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	9
Summary of network geometry	S4	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Accompanying manuscript
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	Appendix 1
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (1) simple summary data for each intervention group, and (2) effect estimates and confidence intervals. <i>Modified approaches may be needed to deal with information from larger networks</i>	10
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. <i>In larger networks, authors may focus on comparisons versus a particular comparator (e.g., placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons.</i> If additional summary measures were explored (such as treatment rankings), these should also be presented.	18
Exploration for inconsistency	S5	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, <i>P</i> values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	Appendix 6

Section/Topic	Item #	Checklist item	Reported on page #
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	Appendix 1
Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses, <i>alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses, and so forth</i>).	Appendix 2–5
DISCUSSION			
Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers).	18–19
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). <i>Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).</i>	18–19
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	20
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	Accompanying manuscript

Note: Text in italics Indicates wording specific to reporting of network meta-analyses that has been added to guidance from the PRISMA statement.

Abbreviations: NMA, network meta-analysis; PICOS, population, intervention, comparators, outcomes, study design.

^aAuthors may wish to plan for use of appendices to present all relevant information in full detail for items in this section.