SCOPING REVIEW OF ACUTE AND PREVENTIVE THERAPIES IN CLUSTER HEADACHE AND NETWORK META-ANALYSIS OF ACUTE THERAPIES, SUBGROUP ANALYSIS BY HEADACHE SUBTYPE (EPISODIC AND CHRONIC)

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ABSTRACT

Cluster headache is a primary headache disorder that can be highly disabling. In this thesis we look at the treatment landscape of cluster headache with a scoping review of preventive and acute therapies for cluster headache as identified in randomized controlled trials and two-arm observational studies. We subsequently compare these therapies where data are available using network meta-analysis of randomized trials, and we attempt subgroup analyses again where data are available for acute treatments of episodic and chronic cluster. We identify the ranking of treatments for acute cluster headache, and certain acute therapies that may be beneficial in episodic and chronic cluster headache. Based on our findings, we also identify future directions for cluster headache trials.

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CHAPTER 1
Introduction

INTRODUCTION

Cluster headache is a rare primary headache disorder that is associated with significant impact in terms of pain and disability and reduced quality of life in individuals with this disorder. While the benefits of various treatments for this condition have been studied in randomized trials and observational studies, there is a pressing need for knowledge synthesis research in this area to compare the benefits and harms of available therapies to guide clinical practice. This chapter introduces key background information regarding cluster headache disorder, and introduces evidence known for treatments to delineate how the research from this thesis project will add to the literature. The first objective of this thesis was to identify and catalogue the available randomized and observational studies to create a repository of studies evaluating interventions for cluster headache. Based on the available data, our second objective was to compare efficacy and tolerability of the available treatments for cluster headache using network meta-analysis.

OVERVIEW OF CLUSTER HEADACHE AS A PRIMARY HEADACHE DISORDER

Headache is one of the most common afflictions we experience in daily life. For some, it is a normal physiological reaction to insults such as trauma or inflammation to the pain sensitive structures in the head (1), such as skin, connective tissue, muscles, bone, vasculature, dura, globe structures, sinus mucosa and teeth and nerves located in the head (1). However, with primary headache disorders, there is no ongoing insult or injury to these structures. Instead, they are thought to be due to an increased propensity of pain generation by neurovascular inflammation in the meningeal structures, cranial and parasympathetic nerves and the brain, such as has been shown for migraine and cluster headaches (1–3).

In the past, **cluster headache**, like migraine, was thought to be due to vascular phenomena, but more recently this explanation has been discounted by published data (1, 3, 4). Cluster headache, as a primary headache disorder, is thought to result from

increased propensity of pain generation in certain brain circuitry including the posterior hypothalamus, brainstem pain-processing structures, trigeminal vascular complex and parasympathetic nerves (3–5). Changes in the central nervous system, in the hypothalamus are thought to be driving the process, and the peripheral changes are thought to have a secondary role. However, the mechanisms are still incompletely understood, and research is ongoing (3, 4).

A genetic change may predispose individuals to cluster headaches, as we know that first degree relatives of individuals with cluster headache have a rate 18 times higher than the rate of cluster headache in the general population (4). Genetic studies have yet to pinpoint high yield loci (3, 4), although involvement of circadian cycle genes and some neurovascular inflammatory (PACAP) genes has been identified (3, 4).

Cluster is the most common primary headache amongst the trigeminal autonomic cephalalgias (TACs), with a yearly prevalence of 1 per 1,000 (3, 6). The TACs are identified by their unilateral pain location, and ipsilateral autonomic features such as lacrimation, conjunctival injection, rhinorrhea, miosis, ptosis, hyperhidrosis, eyelid edema and flushing. Alternatively, if no autonomic features are present, then agitation can fulfill the criteria (7). The autonomic features are likely mediated by secondary changes in the parasympathetic nerves in the head, which are thought to be involved in cluster and the other TACs (3, 4).

Among the TACs, cluster is characterized by its relatively short duration, severe intensity and gender predisposition with a 3:1 male to female ratio (3). Each individual headache lasts between 15 minutes to three hours, and there are typically eight or fewer episodes of severe headache in a day (7). The headaches often occur with clock-like regularity during the day, and can often be nocturnal, thereby disturbing sleep (3, 6). The regularity of the headache is thought to be linked to hypothalamic involvement (3). This area of the brain is also responsible for circadian rhythm establishment, and thus may drive the circadian rhythmicity seen in this disorder. There are two types of cluster, *episodic* and *chronic*. In episodic cluster headache, there are periods where patients are headache

free for longer than 1 month (7). For chronic cluster headache, there are no remissions of duration of 1 month of greater, and headaches occur continuously for at least 1 year (7). About 10-20% of cluster headache patients experience the chronic variant (4, 6). There is evidence that chronic cluster headache may, in some patients, arise with treatment resistance from the episodic variant (8–10). In other patients, it may represent a different pathology, as these headaches occur continuously rather than seasonally and are chronic (i.e. without any remission periods, from onset) (9, 10). Features that may influence treatment response include: frequency and duration of attacks, duration since onset of the cluster period, the duration expected for a cluster, and the average duration after the start of the cluster period when the patient was enrolled (11). Cluster headache is considered by many to be the most severe pain disorder possible to experience (3, 6). During an active cluster bout, due to the intensity of pain and the frequency of the attacks, the patient's quality of life is seriously impaired; 25% of patients report suicidal intentions during the course of their illness (12), although suicide itself is rare (4). There is increased psychiatric comorbidity in these patients, with higher rates of depression, anxiety and aggressive behavior (4, 6, 12). However, it remains unclear whether this is a reactive phenomenon to the burden of the headaches or linked to common pathophysiology such as a low serotonergic state (4). Beyond the psychological burden, there is a large overall cost associated with this disease. There is a paucity of Canadian data on this disease, but in other countries with similar health care systems, when direct and indirect costs were considered, the total cost was estimated to be €6,000 per six months. Per patient, this is 20% more than diabetes, which is estimated to have direct and indirect costs totaling €5000 per six months (13).

CURRENT MANAGEMENT OPTIONS FOR CLUSTER HEADACHE

Management of cluster headache is based on clinical expertise and evidence from clinical trials; acute treatment and prevention are typically discussed as different components of patient care. A 2010 systematic review of randomized controlled trials studied the benefits and harms of interventions for cluster headache (14), as did a subsequent update (15), though both are now several years old.

Table 1.1 Acute and preventive therapy of cluster headache: evidence summary

Treatment and dosage	Assessed for episodic (E), chronic (C), or both (E&C)?	Described as effective therapy (Y/N/U)?	Level of Evidence AHS Guideline Robbins et al, 2016(15)	References
ACUTE THERAPY				
Sumatriptan (subcutaneous) 6mg	E&C	Y	Level A, established effective	(16, 17)
Sumatriptan (nasal) 20mg	E&C	Y	Level B, probably effective	(18)
Zolmitriptan (nasal) 5mg	E&C	Y	Level A, established effective	(19, 20)
Zolmitriptan (oral) 5mg	E&C	Y	Level B, probably effective	(21)
Oxygen 6-12L/min	E&C	Y	Level A, established effective	(22–25)
Lidocaine/cocaine 100mg and 50mg (sphenopalatine ganglion application)	E&C	Y	Level C, possibly effective	(26)
SPG stimulation	C	Y	Level B, probably effective	(27, 28)
DHE 1mg (nasal)	E&C	U	Level U, insufficient evidence	(29)
Somatostatin 25µg (intravenous)	E&C	U	Level U, insufficient evidence	(30)
Prednisone 60mg taper (oral)	NA	U	Level U, insufficient evidence	(31)
nVNS	E&C	Y (only E)	NA	(32, 33)
PREVENTIVE THERAPY				
Suboccipital steroid (injection)	E&C	Y	Level A, established as effective	(34, 35)
Civamide 100µLof 0.025% (nasal)	E	Y	Level B, probably effective	(36)
Lithium 900mg (oral)	E&C	U	Level C, possibly effective	(37, 38)
Verapamil 360mg (oral)	E&C	Y	Level C, possibly effective	(38, 39)
Warfarin to INR 1.5-1.9 (oral)	C	Y	Level C, possibly effective	(40)
Melatonin 10mg	E&C	Y	Level C, possibly effective	(41)
Frovatriptan 5mg (oral)	ECH	N	Level U, insufficient evidence	(42)
Capsiacin 0.025% cream (intranasal)	E&C	N	Level U, insufficient evidence	(43)
Nitrate tolerance 30mg TID (oral)	C	N	Level U, insufficient evidence	(44)

Treatment and dosage	Assessed for episodic (E), chronic (C), or both (E&C)?	Described as effective therapy (Y/N/U)?	Level of Evidence AHS Guideline Robbins et al, 2016(15)	References
Prednisone 60mg taper (Oral)	NA	Y	Level U, insufficient evidence	(31)
Sodium valproate 1000-2000mg daily (oral)	E&C	N	Level B, probably ineffective	(45)
Sumatriptan (oral)	E&C	N	Level B, probably ineffective	(46)
DBS unilateral hypothalamus	C	N	Level B, probably ineffective	(47)
Cimetidine/chlorpheniramine	E&C	N	Level C, possibly ineffective	(48)
Misoprostol 300 µg daily (oral)	E&C	N	Level C, possibly ineffective	(49)
Hyperbaric oxygen (100%)	E&C	N	Level C, possibly ineffective	(50)
Candesartan 32mg (oral)	E	N	Level C, possibly ineffective	(51)
Galcanezumab 300mg (injection)	E	Y	NA	(52)
Galcanezumab 300mg (injection)	C	N	NA	(53)

Abbreviations: AHS, American Headache Society; DHE, dihydroergotamine; NA, not available; nVNS, non-invasive vagal nerve stimulation, SPG=sphenopalatine ganglion block.

The level of evidence used in the American Headache Society Guidelines are from the American Academy of Neurology guideline practice manual (54):

A - Established as effective, ineffective, or harmful for this disorder. To qualify for Level A rating requires at least two consistent Class I studies.

B - Probably effective, ineffective, or harmful for this disorder. To qualify for Level B rating requires at least one Class I study or at least two consistent Class II studies.

C - Possibly effective, ineffective, or harmful for this disorder. To qualify for Level C rating requires at least one Class II study or two consistent Class III studies.

U - Data available is conflicting or of poor quality; treatment is unproven for this disorder. Studies not meeting criteria for Class I-Class III are considered poor quality.

Study classes (Class I-IV) are established based on methodological issues and risk of bias in the same document (54): "Studies rated Class I are judged to have a low risk of bias; Class II, a moderate risk of bias; Class III, a moderately high risk of bias; and Class IV, a very high risk of bias."

For acute treatment of episodic and chronic cluster, we summarize the evidence for available interventions from these past reviews (14, 15) in **Table 1.1.** Existing reviews reported the treatment as being effective when compared to placebo for sumatriptan (both injectable and nasal spray), zolmitriptan nasal spray, and oral zolmitriptan, oxygen, cocaine or lidocaine, and subcutaneous octreotide (Table 1.1). For acute therapy in

chronic cluster, they found having evidence of benefit for sphenopalatine ganglion stimulation (SPG). The authors found insufficient evidence to support the use of dihydroergotamine nasal spray, somatostatin, and prednisone oral.

For preventive therapy of episodic and chronic cluster headache, we summarize the evidence for available interventions from past systematic reviews (14, 15) in **Table 1.1**. The authors noted the treatment as being effective when compared to placebo for suboccipital steroid injections with local anesthetics, civamide nasal spray, lithium, verapamil, and melatonin. For the prevention of chronic cluster headache, warfarin was noted to be effective. There was insufficient evidence to support the use of frovatriptan, capsaicin intranasal, nitrate tolerance, or prednisone. Additionally, each of valproate, sumatriptan oral, deep brain stimulation, cimetidine/chlorpheniramine, misoprostol, hyperbaric oxygen, and candesartan were found to be ineffective.

Since the publication of these systematic reviews (14, 15), there have been new studies of acute (24, 25, 28, 32, 55) and preventive therapies (52, 53). There is therefore a need to update evidence syntheses and incorporate these new studies.

While past literature reviews have included pairwise meta-analyses comparing the effects of various interventions for both indications with placebo, such analyses do not constitute a unified analysis of available data that can better inform clinical decision-making. Additionally, there are multiple therapies including acute (nVNS) and preventive (galcanezumab) that have not been considered in previous analyses, and there are new trials that can be incorporated, for example for SPG stimulation. New trials of oxygen presently raise questions whether low flow (7-12L/min) or high flow (12-15L/min) oxygen is more likely to be effective (24). There is also a trial evaluating new masks (25). This direct evidence may be incorporated into NMA. Lastly, we want to assess if there are additional non-randomized studies that can be incorporated into our analysis given the paucity of randomized data in this field, and the recommendations which are often based on non-randomized studies and expert opinion (3, 4).

The use of methods to generate updated comparative data for interventions related to acute treatment and prevention of cluster headache will provide clinicians with a greater ability to compare first line approaches to treatment in terms of efficacy and safety. Looking at all available data systematically, including observational studies, may provide further therapies to consider for management in refractory cases and for further study.

STUDY METHODS TO ADDRESS KNOWLEDGE GAPS REGARDING INTERVENTIONS FOR CLUSTER HEADACHE

This thesis was designed to characterize the evidence base for therapies in cluster headache in consideration of the limitations outlined in Section 1.3. In establishing a basis for intervention comparisons based upon currently available evidence, two forms of knowledge synthesis were pursued: (a) a ***scoping review*** of intervention studies for cluster headache; and (b) ***network meta-analyses*** to compare interventions for cluster headache. Brief descriptions of the intent and value of both approaches are provided in the following sections.

Scoping Reviews: Overview and Relevance to this Work

Scoping reviews are an approach to exploratory research used to establish the working boundaries and evidence gaps of interventions in a particular field (56–58). Scoping reviews are typically undertaken to address broad research objectives rather than to address a specific question about effectiveness or safety. In addition to informing the identification of research gaps, this type of review aids researchers in surveying the characteristics and key findings from literature in research areas where evidence is plentiful. Scoping reviews can also serve as a valuable approach for mapping the reporting of outcomes and study characteristics to highlight commonalities and variations amongst a body of research, and therefore can also be informative in the planning of systematic reviews.

In achieving the objectives for this thesis, a scoping review of intervention studies was performed to assess the feasibility of a network meta-analysis of interventions to inform treatment comparisons for acute treatment and prevention of cluster headache. Through

scoping and mapping the features of eligible studies identified from a systematic search, this helped to identify a set of commonly reported outcomes for acute treatment and prevention that could form a basis for comparisons. We also were able to collect data on patient enrollment criteria and important effect modifiers to establish the similarity (or lack thereof) for the studied populations. As we identified reported outcomes, we were able to establish the connectivity of evidence networks. Additionally, we reviewed the extent of observational literature available and considered the suitability of inclusion of these data in evidence networks and possible benefits.

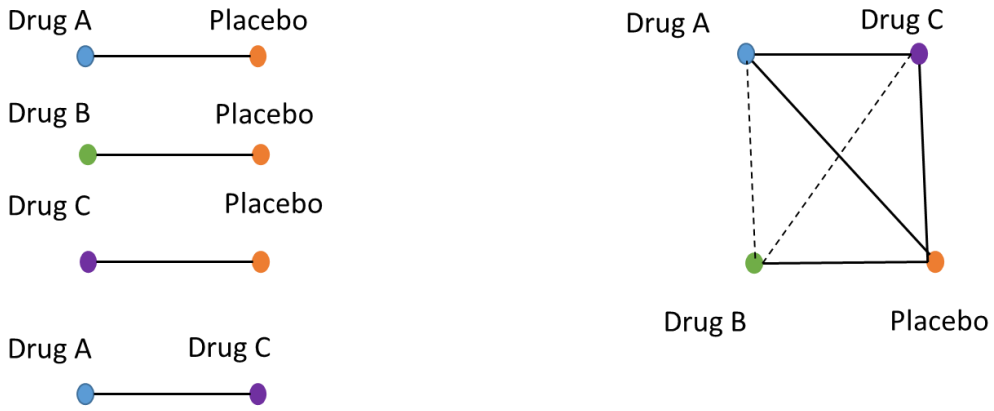
Network Meta-Analysis: Overview and Relevance to this Work

While traditional pairwise meta-analysis (i.e., focused on the comparison of two interventions) is recognized as a useful technique to combine data from multiple trials in many situations, there are many medical conditions wherein an array of available treatment options exists. For disorders like cluster headache 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 (59–63). 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 (64, 65). 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 (64). The solid lines in Figure 1.1 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 example of comparisons between drugs A, C and placebo)

in situations where there are head-to-head comparisons (Drugs A and C), we can combine the direct estimates (from head-to-head comparisons) with results of indirect comparisons, thereby considering a broader evidence base, to get more robust estimates of treatment effects. Both Bayesian and Frequentist approaches to NMA are available.

Figure 1.1 Graphical representation of a pairwise meta-analysis versus NMA



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 RCTs. For systematic reviews involving NMA (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).

Regarding the objectives for this thesis, NMA was used to synthesize evidence on multiple treatments to compare them in terms of their relative benefits and harms. This was done to develop evidence regarding the relative benefits and harms of therapies to inform clinical practice, including those that were not directly compared to each other in clinical trials. Additionally, the NMA allowed us to assess a dose response relationship within the same type of therapy, such as oxygen therapy (22–24).

THESIS OBJECTIVE AND STRUCTURE

The objective of this thesis was to characterize the treatment responses and safety of interventions used for the acute treatment and prevention of cluster headache. This thesis has been reported in manuscript format, consisting of an introductory chapter (**Chapter 1**), two prepared manuscripts (**Chapter 2** focusing on the scoping review and **Chapter 3**

focusing on the NMAs), and a discussion chapter (**Chapter 4**) to contextualize the implications of study findings. This work will be a valuable addition to the literature by providing timely, methodologically rigorous evidence that can inform clinical decision-making and future guideline development for the management of cluster headache.

CHAPTER 2

Effects of Acute and Preventive Therapies for Episodic and Chronic Cluster Headache: A Scoping Review of the Literature

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ABSTRACT

Background: Cluster headache is the most common primary headache disorder of the trigeminal autonomic cephalalgias. It is a highly disabling primary headache disorder associated with unilateral headache of brief duration and autonomic features. The treatments for this disorder are few and are poorly defined, with limited underlying evidence.

Objective: To undertake a scoping review to characterize evidence of benefits and harms for therapies to prevent and acutely treat cluster headache, characterize trial methodology utilized in acute and preventive studies in this disorder and recommend future trial "good practices", and assess homogeneity of studies and the feasibility for future network meta-analyses to compare acute and preventive treatments for cluster headache.

Eligibility Criteria: We sought studies of adult patients with cluster headache as identified by accepted diagnostic criteria. Both randomized controlled trials (RCT) and observational studies (with a control group) were included. The interventions of interest were medications, procedures, devices, surgeries, or behavioral/psychological interventions. The comparators of interest were placebo, sham, or other active treatments. The outcomes of interest were predefined; however, we did not exclude studies without these outcomes.

Sources of Evidence: A systemic search was conducted by an experienced librarian in Ovid, Embase and Cochrane. We also undertook a limited search for conference abstracts from publications of journals prominent in the field. We searched for English, French, Italian, and Spanish language publications.

Results: We identified 55 studies: 44 RCTs, 4 studies only available in clinical trial registries, and 7 observational studies. Of the 44 RCTs, 20 focused on acute therapies and 24 on preventive therapies. Overall, we determined that it is feasible to pursue an NMA for acute therapy focusing on 15 or 30min headache reduction for acute trials, as we identified 11 trials in the combined population of episodic and chronic cluster headache patients (2 trials in chronic cluster headache only were also found). For preventive therapy of cluster headache, we identified trials with common outcomes that may be considered for NMA, however these trials had different timelines of study enrollment, with some including patients who were much earlier in a bout than others. We

identified this as a possible treatment effect modifier, the patients included later in a bout may have spontaneous resolution due to natural remission and as such the treatment responses would not be comparable, and in keeping with this assertion placebo response rates are also much higher in trials where patients are allowed later enrollment. Unfortunately, as most trials do not report a timeline of study enrollment as a variable, a meta-regression on this is also not possible. We have identified new studies looking at nVNS, SPG and oxygen since the prior systematic review, but these acute treatments were previously identified as effective. However, for CGRP monoclonal antibodies, two published preventive trials both looking at galcanezumab demonstrating effectiveness in episodic cluster headache and a lack of effectiveness in chronic cluster headache, and unpublished registry identified studies that show fremanezumab is not effective for episodic and chronic cluster. This finding highlights that CGRP monoclonal antibodies may not show a class effect in cluster headache prevention and need to be considered individually.

Conclusions: We describe the treatment landscape of cluster headache for both acute and preventive treatments and highlight new studies since prior systematic reviews. We also identify and highlight possible treatment effect modifiers and recommend their reporting in future trials. Lastly, we present the network meta-analyses we will undertake in acute therapies of cluster headache.

INTRODUCTION

Background

Trigeminal autonomic cephalalgias are associated with unilateral headache and ipsilateral autonomic features such as lacrimation, conjunctival injection, rhinorrhea, miosis, ptosis, hyperhidrosis, eyelid edema and flushing. They are thought to be due to aberrant pain signal generation arising mostly out of the hypothalamus, given the associated autonomic features. Cluster headache is the most common primary headache among the trigeminal autonomic cephalalgias (TACs), although it is overall rare with a yearly prevalence of 1 per 1,000 (3, 6). Cluster headache can be identified by its characteristic duration of 15 minutes to three hours and its particularly severe intensity (3, 6).

Rationale for this Work

There are few evidence-based treatments available in cluster headache (15, 66), as it is a rare condition that has been under-studied (3). In terms of acute therapy, there are 5 modalities of treatment: triptans (injection or nasal spray given time of onset of effect), oxygen, sphenopalatine ganglion (SPG) stimulation in chronic cluster headache, cocaine/lidocaine 10% nasal spray, and octreotide injection (15, 66). Preventive therapy currently has 6 treatments available: suboccipital steroid injections with local anesthetics, civamide nasal spray, lithium, verapamil, warfarin in refractory chronic cluster headache, and melatonin (15, 66).

While two past systematic reviews (15, 66) used traditional pairwise meta-analyses (i.e., comparing two treatments at a time) to assess evidence from randomized trials regarding benefits and harms of therapies, they did not report comparisons of the efficacy and safety of the various treatments relative to each other, a step which can be accomplished using a network meta-analysis (NMA). Additionally, they did not consider evidence regarding treatment comparisons made in the context of study designs other than randomized controlled trials.

The current scoping review was designed to expand upon past reviews in several ways. First, we sought to identify new studies published since the prior reviews were completed. Second, with the data gathered in this scoping review, we aimed to assess the feasibility of pursuing NMAs (67, 68) to inform comparisons of multiple treatments based on available direct and indirect evidence in the field; we planned to systematically evaluate study and population features to establish the potential for rigorous NMAs, by confirming appropriateness of the assumptions of homogeneity and similarity (69). Third, in addition to identifying and reviewing RCTs of interventions for cluster headache, we also set out to assess the value of observational studies in this clinical area and the potential for their inclusion in future meta-analyses. There are many who lament that RCTs are limited in the field, and there is considerable “real world” data to be used (70). Several past narrative

reviews from clinical experts in the field have included non-randomized trials in their recommendations (4) given the paucity of randomized trial data available.

Research Objectives

In this scoping review, we: (1) establish a collection and mapping of the available evidence underlying the evaluation of relative benefits and harms of interventions for cluster headache; (2) gather data that will inform an assessment of the homogeneity of study populations in randomized trials, as well as the relevant outcomes as a precursor toward performance of NMAs. We characterize clinical outcomes that are more uniformly used across trials, assess the extent to which the interventions of interest are represented within evidence networks for each outcome, and assess how homogenous the populations are with regard to the transitivity assumption necessary for network meta-analysis (56). We also provide a qualitative assessment of the benefits and safety associated with different interventions for the treatment and prevention of cluster headache. The reporting of this review and its protocol adhere to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols statement and the related extension for scoping reviews (71–73).

METHODS

The objectives of interest for this work were addressed by answering the three following research questions:

1) What treatment comparisons have been studied in controlled studies of acute and preventive treatment of cluster headache?
2) Is the homogeneity of the studies sufficient to establish a ranking of treatments using NMAs?
3) In studies of cluster headache, what are the benefits and harms of various treatments?

A protocol for this scoping review was prepared a priori and was registered on OSF registration: osf.io/54wjz

Study Eligibility Criteria

Eligibility criteria to identify relevant studies were developed according to the PICOS (Population – Interventions – Comparators – Outcomes – Study design) framework and are described below.

Population

We sought studies involving outpatient community, emergency room visitors as well as inpatient populations of adults (over 18 years old) with cluster headache, as identified by Ad Hoc (74), IHS (75) definition or other modern diagnostic criteria (ICHD2, ICHD3beta and ICHD3) (7, 76, 77). Chronic cluster patients were defined according to the criteria used in the trial where the sub-population was identified, as this definition has changed between iterations of the ICHD (7, 76). No restrictions regarding treatment history, disease duration, or durations since time of onset of cluster period were used. However, given the importance of these factors in terms of the ability to appraise the similarity of study populations (78), these data were gathered to inform evaluation of the comparability of populations across studies.

Interventions and Comparators

We sought studies related to medications, as well as procedural and surgical techniques, devices, and behavioral and psychological interventions. Specifically, the following interventions were sought:

- Medications - Pharmacological management with a potentially active treatment administered by a variety of routes (IM, SC, PO, PR, nasal spray, etc.).
- Procedures - Procedures such as nerve block (greater occipital nerve block) used for management.
- Surgical techniques - Surgical approaches such as DBS, insertion of stimulator (spheno-palatine ganglion stimulator, occipital nerve stimulator) used for management.
- Devices - Non-procedural devices (i.e., external vagal nerve stimulator) used for management;

- Behavioral or psychological interventions - Cognitive behavioral therapy, mindfulness-based relaxation, and similar techniques for management.

There were no restrictions on medication doses, frequency, or duration of treatment. We sought studies that had a comparator arm, which was either a placebo pill, a sham treatment placebo tailored to be similar to the treatment (saline injections for injectable therapies, sham current for stimulation therapies) or standard of care. Studies of interventions were stratified for inspection based upon the intent of the therapies being compared, namely according to those for acute headache resolution and those for prevention. In observational studies there was no placebo comparator, but rather most often it was standard of care or another active comparator.

Study Outcomes

The review was undertaken with a set of known outcomes that were a priori defined. We also collected information regarding the availability of additional outcomes reported within individual studies.

The *a priori* outcomes of interest for acute treatment trials were:

1. Headache response at 15 or 30 minutes after treatment administration - decrease in headache from very severe, severe, or moderate to mild or no pain.
2. Being pain-free at 15 or 30 minutes;
3. The overall number of patients reporting AEs.

The *a priori* outcomes of interest for preventive trials were:

1. Days from treatment start to cessation of CH attacks;
2. Count of number of days with at least one CH attack;
3. Mean headache day reduction;
4. Mean cluster attack reduction;
5. The overall number of patients reporting AEs.

Data collection summarized endpoints of established clinical importance so that the research team could explore the findings and potentially compare multiple treatments in future NMAs if deemed appropriate. Although some outcomes of interest in studies of cluster headache have been established (78), we were also interested in the identification of additional outcomes, to consider their clinical significance (if any), in order to better inform future reviews and clinical trials.

Study Design

Randomized controlled trials, open label trials, and observational studies (both prospective and retrospective cohort studies) assessing the effects of either acute treatments or prophylactic interventions (as outlined below) were sought. As noted earlier, only studies that included a comparator arm were sought.

Language of Publication

Studies published in English, French, Italian, Spanish or Farsi were eligible for inclusion. Studies in other languages were excluded due to limitations related to the ability to adequately translate their content. The research team had support from individuals speaking these languages who also possessed an understanding of epidemiology and study design to assist in addressing any identified foreign language publications.

Information Sources

A systematic search strategy was conducted in OVID MEDLINE (inception to present), EMBASE (1950 to present) and Cochrane (1950 to present) for published papers and conference proceedings on August 2019. Publications were also sought through a hand-search of journals and of the America Headache Society (AHS) and International Headache Society (IHS) conference proceedings for the past 10 years (1999-2019). The reference lists of included studies and prior systematic reviews in the field were reviewed to identify additional articles that may have been missed by the search. Grey literature searches were limited to what a team member could identify within 40 hours (i.e. 5 working days) of searching, as this makes the search easily reproducible if needed in the

future. specifically, we searched trial registries and abstracts from the American Headache Society and International Headache Society meetings for the last 10 years.

Search Strategy

The search strategy for all databases is provided in Appendix 1.1. All searches were constructed by an information specialist with systematic review experience, in collaboration with the research team, and were reviewed using the PRESS framework by a second librarian (79) prior to implementation. MeSH terms were used to capture each of the principal elements of the research question. The search strategy was expanded from a prior systematic review and meta-analysis looking at cluster headache treatment (66) to also include observational studies, and the search covered the time period from inception to August 2019.

Management of Study Records

Study Selection Process

Abstracts were exported from the electronic databases following implementation of the electronic search, duplicates were removed, and the remaining citations were imported into Covidence (Veritas Health Innovation, Melbourne, Australia, v1846), an established software tool for systematic review management.

The titles and abstracts of all citations were reviewed by two reviewers independently (IM, SC), and studies were excluded if they failed to meet our selection criteria described earlier. When there was disagreement between reviewers over trial exclusion at the abstract stage, this was resolved by discussion. At the full text stage, study inclusion was decided by two reviewers. During full text screening, we recorded all reasons for exclusion of the studies assessed. When there was disagreement between reviewers over trial exclusion at the abstract or full text stage, this was resolved by discussion. The process of study selection was documented with a flow diagram, as recommended by PRISMA guidance (71, 72).

Data Collection Process

Data collection from the set of included studies was performed by one reviewer. A data extraction form was prepared *a priori* and was piloted prior to extraction, with slight modifications incorporated to maximize its flexibility. Information was collected regarding publication traits (e.g. authors, year, journal), study methods (e.g., design, duration of follow-up), population (e.g. eligibility criteria, demographic measures), interventions (including methods of administration, dosages and other details as appropriate), and outcomes reported (including definitions, directionality of findings, and availability of data necessary for meta-analysis). For some studies, we contacted the authors to obtain additional information regarding trial results including raw numbers of participants experiencing outcomes of interest (24). No risk of bias assessments were performed, as is common practice in scoping reviews (72).

Mapping and Synthesizing the Evidence

Synthesis of the evidence was conducted using various approaches to address the three objectives for this scoping review.

Research question 1 (regarding identification of treatment comparisons) and research question 2 (regarding investigation of outcomes and study characteristics) were addressed based on recommended approaches (69) to evaluate an evidence base with regard to feasibility of NMA. This included:

- Generation of evidence network diagrams for key outcomes (including inspection of definitions and time points), to establish the presence of connected networks.
- Inspection of the details of treatment administration for each intervention, in evidence tables, to monitor for important differences that could influence treatment effect.
- Inspection of patient characteristics (including diagnostic criteria, percentage with episodic versus chronic cluster, male to female ratio, age), inspection of recommended covariates to consider based on past guidance (78), and review of patient enrollment criteria and baseline risk. We used a combination of tables and bar plots to assess for the presence of important differences that could influence treatment effect.

- Inspection for differences in treatment effects where multiple studies for an outcome evaluated the same treatment comparison.

We planned to stratify these inspections by intent of intervention (acute treatment versus prevention), type of cluster headache (episodic versus chronic cluster), study design (randomized trial versus observational studies), and possible effect modifiers (78).

To answer question 2, effect modifiers that were compiled and inspected based on past expert recommendations (78) consisted of:

- *Placebo response* for a given outcome. We decided to look at placebo response rates as these are an informative marker of potential differences in study populations in NMA that may need adjustment when there is variability. This is important as unadjusted variability across placebo response in studies in NMAs can produce misleading treatment effects (80).
- *Frequency and duration of attacks*. Baseline measures for the population overall were noted. Additionally, some trials only included patients with duration >30min, and these trials were distinguished from those including patients with duration 15-30 min. This is of importance given variability between treatments as to the timeline of onset of medication, as it may be 15min or more (78). Most trials require a minimum baseline frequency of cluster headaches, and this measure was also recorded.
- *Duration since onset of the cluster period*. For preventive treatment trials, the duration of the episodic cluster period expected after randomization should be at least one month as recommended (78). The average duration after the start of the cluster period was recorded where available.

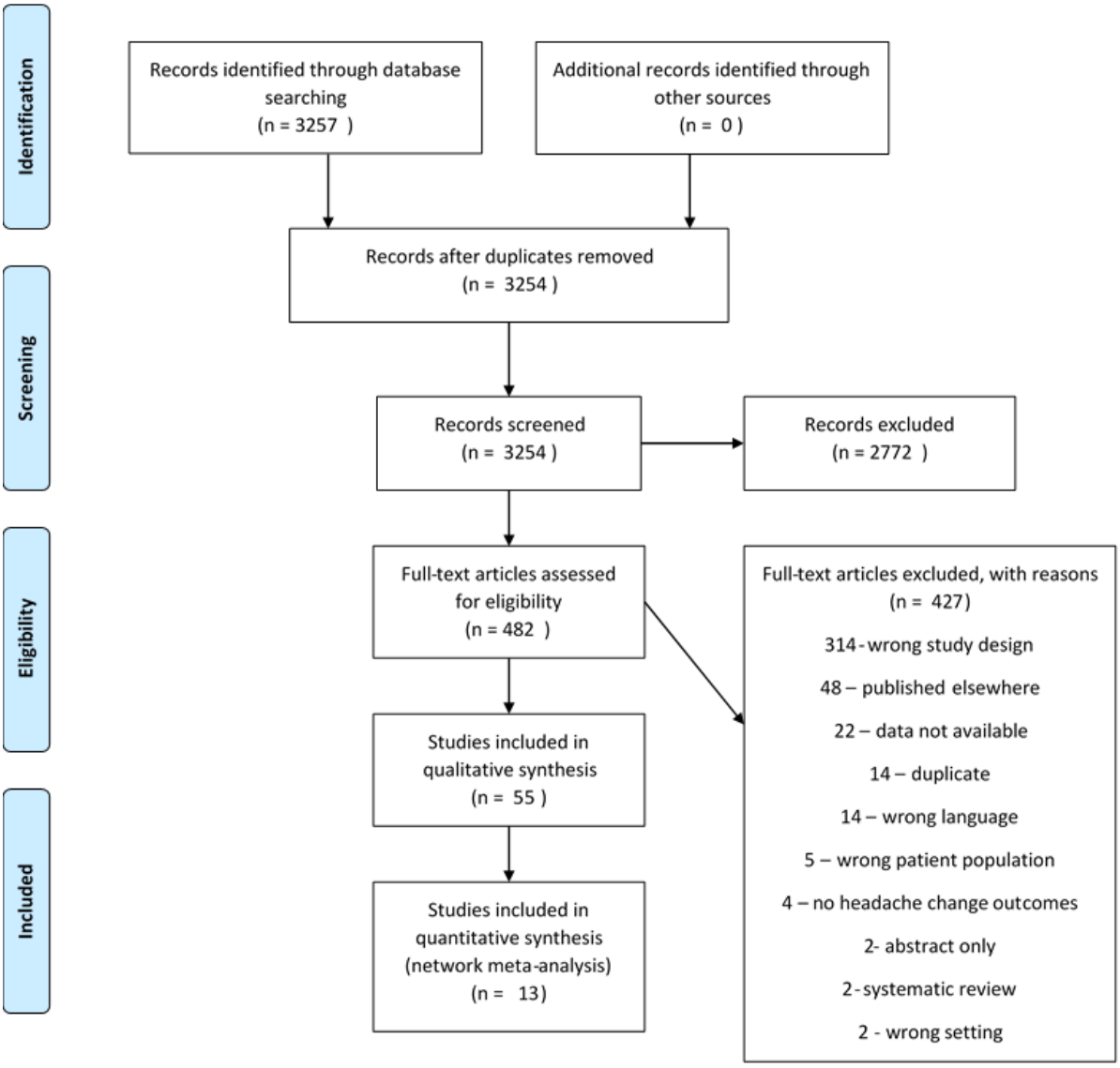
For research question 3, we used a descriptive approach supported by tables and figures to summarize directionality of findings regarding the relative benefits and harms associated with different interventions for acute treatment and prevention. Table-based approaches (81) were used to provide a visual summary of these data for readers.

RESULTS

Methods Used to Identify Relevant Literature

A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram that summarized the process of study selection is presented in **Figure 2.1**. After an initial review of 3,254 citations (following removal of duplicates), a total of 55 studies (16–21, 23–26, 28–31, 34–53, 82–102) were selected for inclusion. These studies included 44 published RCTs, four RCTs that were available only in clinical trial registries (91, 93–95), and seven observational studies (96–102), with publication dates from 1978 to 2019.

Figure 2.1 PRISMA flow diagram



Characteristics of Study Populations in the RCTs

The characteristics of the patients enrolled in the 44 RCTs included in our analysis are detailed in **Table 2.1a** (acute therapies) and **Table 2.1b** (preventive therapies). Most of the studies enrolled patients according to standard diagnostic criteria and included a mixed population of patients with both episodic and chronic CHs. Patient enrollment in these studies ranged from those with all episodic to all chronic CHs; in studies with mixed populations, the interquartile range (IQR) was from 65% to 75% episodic CH. Patient outcomes were only rarely reported by CH subtype. Of the 44 published RCTs, 20

focused on acute therapies used for headache relief and 24 focused on headache prevention. As a group, these studies enrolled adult patients only, and most of them included more males than females (median 82%, range 75% to 88% male) with a mean age of 42.65 years (IQR 40.33 to 45.00; range 36.20 to 49.00 years). Most of the trials included in our study were conducted in Europe (61%) or North America (17%) or both (9%); 9% of trials reported no specific location. While the largest trial included 327 patients (117 and 120 patients per study arm), most trials were small (median total sample size 26, IQR 14–54 patients). Reporting was limited regarding several of the characteristics that might be used to assess the homogeneity of study populations (see **Tables 2.1a** and **2.1b**). Likewise, baseline information regarding the number of weeks from the onset of CH was provided in only 25% of prophylaxis trials and none of the trials focused on acute treatment strategies. Data regarding disease severity, measured by the number of attacks per week at baseline, were reported in only one-third of the acute treatment trials and 64% of the trials focused on headache prevention. However, only one-third of acute treatment trials reported they targeted the inclusion of only patients whose attacks were longer than 45 min.

Only 7% of studies (all published before 1990) included no information on the specific diagnostic criteria used for enrollment. Most trials (87%) reported the proportions of enrolled patients diagnosed with episodic and chronic CHs. There were only five studies that focused specifically on either episodic or chronic CHs only (40, 52, 84, 94, 95). No exclusion criteria were reported in 36% of the studies included in our analysis (26, 29, 31, 34, 36, 41, 43, 45, 48, 50, 83, 88, 89, 103). Detailed study exclusion criteria are provided in **Appendix 1.2**. These criteria were reviewed systematically to identify differences between studies and any clear differences between the study populations. No specific differences were identified.

Although most of these studies were conducted with a mixed population of patients including those diagnosed with both episodic and chronic CH subtypes, the episodic subtype predominated; on average, 68% of the patients in a mixed population carried a diagnosis of episodic CH. The patients in most of these studies tended to be in their 40s.

Study patients were more likely to be male, a finding that was aligned with our current epidemiological understanding of this disease (3). The studies included in our analysis were conducted in Europe and North America. Unfortunately, the risk factors representing the most critical elements needed to evaluate clinical homogeneity were poorly reported. Our consideration of the available data and our assessment of the feasibility of performing an NMA revealed that these populations were relatively similar to one another. However, we needed to assume that there was balance across studies specifically for characteristics that had not been reported routinely.

Table 2.1a Characteristics of RCTs that examined acute treatments for CHs

Study Characteristics				Population Characteristics									Co-Interventions Permitted	
Trial and location	**Treatment (n)**	**Comparator (n)**	**CH Diagnostic criteria**	**ECH %**	**Male %**	**Mean Age**	**Illness duration**	**Onset <wks**	**Attacks/wk**	**Attack duration**	**Bout duration**	**>45min**	**Acute Rescue**	**Prophylaxis**
Andersson 1986; Europe	DHE NS (n=133)	Placebo (n=137)	ad hoc	100	80	40	9 y	na	na	na	na	na	na	na
Bahra 2000; Canada, UK, Sweden	Zolmitriptan PO (n=114)	Placebo (n=115)	IHS	73	86	43.8	na	na	na	na	na	yes	no	no
Cittadini 2006: Europe	Zolmitriptan NS (n=65)	Placebo (n=61)	IHS	64	87	40	12 y	na	na	na	8 wk	yes	yes, simple analg + O_2	na
Cohen 2009; London UK	Oxygen 12L/min (n=76)	Placebo (n=76)	IHS	75	82	39	11.3 y	na	12	83 min	na	na	yes	no
Costa 2000; Pavia, Italy	Lidocaine/cocaine (n=9)	Placebo (n=9)	IHS	40	87	37.2	8.2 y	na	na	na	na	na	yes	na
Di Sabato 1993; NA	Hyperbaric O_2 (n=6)	Room (n=7)	ad hoc	100	93	na	na	na	na	na	na	na	na	no
Dirkx 2018; Denmark	Oxygen 7L/min (n=70)	Oxygen 12 L/min (n=70)	ICHD2	68	61	43	new onset	na	14	60 min	na	na	yes	yes
Ekbom 1991; Europe	Sumatriptan SC (n=39)	Placebo (n=39)	IHS	56	80	42	na	na	na	na	na	yes	yes	no
Ekbom 1993; Europe	Sumatriptan SC (n=92)	Placebo (n=88)	IHS	72	87	41	na	na	na	na	na	na	yes	na
Fogan 1985; USA	Oxygen 6L/min (n=15)	Air (n=17)	ad hoc	na	na	na	na	na	na	na	na	na	yes	no
Goadsby 2018; Europe	nVNS (n=50)	Sham (n=52)	ICHD3B	71	72	45.4	na	na	10.5	73.7 min	na	na	yes	yes
Goadsby 2019_2; USA	SPG stim (n=45)	Sham (n=48)	ICHD3B	0	Na	48	11–14 y	na	14	45 min	na	na	yes	yes
Hardebo 1998; Sweden	Sumatriptan NS (n=25)	Sumatriptan SC (n=25)	IHS	88	88	na	na	na	1–3 /day	na	na	yes	yes	yes
Matharu 2004; UK	Octreotide SC (n=46)	Placebo (n=45)	IHS	73	79	40	14 y	na	na	na	na	yes	yes	no
Petersen 2017; Denmark	Oxygen 15L/min, DVO (n=32)	Placebo (n=11)	ICHD2	53	74	45	13.2 y	na	7.7	na	>2 wk	na	yes	yes

Study Characteristics				Population Characteristics									Co-Interventions Permitted	
Trial and location	**Treatment (n)**	**Comparator (n)**	**CH Diagnostic criteria**	**ECH %**	**Male %**	**Mean Age**	**Illness duration**	**Onset <wks**	**Attacks/wk**	**Attack duration**	**Bout duration**	**>45min**	**Acute Rescue**	**Prophylaxis**
Rappaport 2007; USA	Zolmitriptan NS (n=52)	Placebo (n=50)	ICHD2	71	69	45.2	na	na	na	na	na	yes	no triptans or ergot	yes
Rozen 2013; NA	DVO (n=na)	Oxygen 15 L/min na	ICHD2	0	75	na	na	na	na	na	na	na	yes	yes
Schoenen 2013; Europe	SPG stim (n=32)	Sham (n=32)	ICHD2	0	84	45	na	na	19.2	na	na	no	yes	yes
Sicuteri 1983; NA	SST/DHE (n=na)	Placebo na	na	75	100	36.2	na	na	na	na	na	na	no	no
Silberstein 2016; ISA	nVNS (n=60)	Sham (n=73)	ICHD2	67	84	47.87	na	na	na	na	na	na	yes	yes
Van Viet 2003; USA	Sumatriptan 20 mg NS (n=118)	Placebo (n=118)	IHS	75	82	43	13 y	na	na	na	>8 wk	yes	0_2 or simple analgesia	no

Abbreviations: CH, cluster headache; ECH, episodic CH; NS, nasal spray; SC, subcutaneous; PO, by mouth; HIS, International Headache Society; ICHD, International Classification of Headache Disorders; O_2, oxygen; analg, analgesic; DVO, demand valve oxygen; na, not available; DHE, dihydroergotamine; SST, somatostatin; nVNS, non-invasive vagal nerve stimulation; SPG, sphenopalatine ganglion.

Table 2.1b Characteristics of RCTs that examined interventions for prevention of CHs

Study Characteristics				Population Characteristics									Co-Interventions Permitted	
Trial and location	**Treatment (n)**	**Comparator (n)**	**CH Diagnostic criteria**	**ECH %**	**Male %**	**Mean Age**	**Illness duration**	**Onset <wks**	**Attacks per week**	**Attack duration**	**Bout duration**	**>45min**	**Acute Rescue**	**Prophylaxis**
Ambrosini 2005; Europe	Betamethasone injection (n=13)	Placebo (n=10)	IHS	70	87	40.1	na	<1 wk	11.3	na	>4wk	na	yes	yes
Anthony 1978; Australia	Cimetidine alone and with chlorpheniramine (n=20)	Placebo (n=20)	na	na	na	47.4	na	na	na	na	na	na	na	na
Bussone 1990; Italiy	Verapamil (n=15)	Lithium (n=15)	IHS	0	90	43	na	na	na	na	na	na	yes	no
Christiansen 2000; Denmark	Nitrate tolerance (n=5)	Placebo (n=5)	IHS	0	88	53.1	>2 y	na	na	na	na	na	yes	no
Di Sabato 1993; NA	Hyperbaric O_2 (n=6)	Room air (n=7)	ad hoc	100	92	na	na	na	na	na	na	na	na	no
El Amrani 2002; Europe	Valproate (n=50)	Placebo (n=46)	IHS	77	88	45.4	na	na	12.1	na	na	na	Sumatriptan SC or O_2	no
Evers 1998; Europe	Misoprostol (n=8)	Placebo (n=8)	IHS	0	Na	44.5	14 y	na	14.4	64.4 min	na		Sumatriptan SC or O_2	yes
Fontaine 2010; Europe	DBS (n=11)	Sham (n=11)	ICHD2	0	73	44.1	12.1 y	na	17.8	na	na	na	yes	yes
Gaul 2016; Europe	nVNS + SOC (n=48)	SOC (n=49)	ICHD3B	0	69	43.8	4.9 y	na	17.7	99.3 min	na	na	yes	yes
Goadsby 2019; Europe and North America	Galcanezumab (n=49)	Placebo (n=57)	ICHD3B	100	83	45.9	16.8y	na	17.5	na	>6 wk	na	yes	mo
Hakim 2011; Italy	Warfarin (n=11)	Placebo (n=11)	ICHD2	0	76	44.6	7 y	na	21	48.8 min	na	na	yes	no
Jammes 1975; USA	Prednisone (n-18)	Placebo (n=19)	na	na	na	na	na	na	na	na	na	Na	na	na
Leone 1996; Italy	Melatonin (n=10)	Placebo (n=10)	IHS	90	75	36.4	na	<10 days	19.95	na	na	yes	yes	no
Leone 2000 Italy	Verapamil (n=15)	Placebo (n=15)	IHS	100	90	43.5	15.5 y	<1 wk	11.5	na	na	yes	yes	no
Leroux 2011; Paris, France	Cortivazol injection (n=19)	Placebo (n=18)	ICHD2	65	88	41.4	na	na	28.2	na	na	na	yes	nes
Marks 1993; USA	Capsaicin (n=9)	Placebo (n=8)	IHS	Na	77	na	na	na	na	na	na	na	na	na
Monstad 1995; Europe	Sumatriptan PO (n=89)	Placebo (n=79)	IHS	54	89	40	na	na	≥7	na	na	na	yes	no

Study Characteristics				Population Characteristics									Co-Interventions Permitted	
Trial and location	**Treatment (n)**	**Comparator (n)**	**CH Diagnostic criteria**	**ECH %**	**Male %**	**Mean Age**	**Illness duration**	**Onset <wks**	**Attacks per week**	**Attack duration**	**Bout duration**	**>45min**	**Acute Rescue**	**Prophylaxis**
Nilsson 2002; Stockholm, Sweden	Hyperbaric O_2 (n=14)	Sham - hyperbaric air (n=16)	IHS	75	75	42.7	14.9 y	na	range only	na	>4 wk	yes	yes	no
Oakes 2019; Europe and NA	Galcanezumab (n=117)	Placebo (n=1120)	ICHD3B	0	73	45	na	na	18.82	na	na	na	yes	yes
Pageler 2010; Europe	Frovatriptan PO (n=5)	Placebo (n=6)	ICHD2	100	na	na	na	>1 wk	15.6	na	>6 wk	na	no	yes
Russel 1979; USA	Cimet + chlorpheniramine (n=12)	Placebo (n=12)	ad hoc	na	na	49	na	na	na	na	na	no	Simple analgesia	na
Saper 2002; USA	Civamide nasal drops (n=18)	Placebo (n=10)	IHS	100	90	44.7	na	na	na	na	na	no	yes	no
Steiner 1997; USA	Lithium (n=14)	Placebo (n=13)	Their own - similar to IHS	100	100	36.4	13.4 y	<3 wk	15.75	na	na	>30	yes	no
Trovnik 2013; Europe	Candesartan (n=19)	Placebo (n=13)	ICHD2	100	85	42.7	16.3 y	<2 wk	17.85	na	na	na	Suma only	no

Abbreviations: CH, cluster headache; ECH, episodic CH; NS, nasal spray; SC, subcutaneous; PO, by mouth; IHS, International Headache Society; ICHD, International Classification of Headache Disorders; O_2, oxygen; analg, analgesic; na, not available; Suma, sumatriptan; nVNS, non-invasive vagal nerve stimulation; SPG, sphenopalatine ganglion; SOC, standard of care.

RCTs of Acute Treatments for Chronic and Episodic CHs

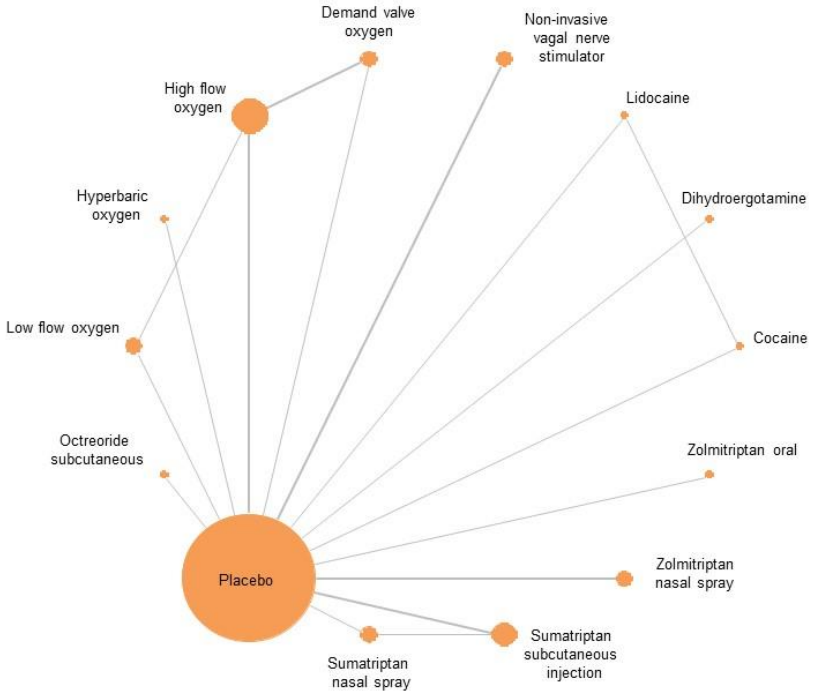
Interventions Compared

As none of the studies included in this analysis reported individual endpoints for the subgroups of patients diagnosed with chronic or episodic CHs, the results presented were based on a comparison of the combined subtype groups *versus* control. Outcomes from the following acute treatment interventions were evaluated:

1) Dihydroergotamine (DHE) NS (n=2) (29, 30);
2) Triptans (n=7) (16–21, 85) including zolmitriptan NS, sumatriptan injectable, and sumatriptan NS;
3) Low flow (83) or high flow (23) oxygen (n=5), comparisons of low *versus* high level flow (24), and new modes of delivery including demand valve oxygen (DVO) (25, 92);
4) nVNS (n=2) (82, 90);
5) Invasive SPG stimulation (n=2) (28, 89);
6) Somatostatin (n=1) (30), related formulations (n=1) (86), and pasireotide (n=1) (91);
7) Lidocaine/cocaine (n=1) (26);
8) Hyperbaric oxygen (n=1) (50).

A network diagram of all the available RCT evidence for acute treatment of CHs (before consideration of specific outcomes) is shown in **Figure 2.2**. The control group for most of the studies was a placebo (57%, n=12/21). Other control interventions included high flow compared to low flow oxygen (24), high flow compared to DVO (25), sham procedures or devices as placebo in cases in which an insertion procedure or external stimulating device was used (19%, n=4/21) (28, 82, 89, 90), air inhalation through a mask as a placebo (83), a hyperbaric room alone compared to inhalation of hyperbaric oxygen (50), and NS *versus* SC sumatriptan (85). The same treatment doses were used in all cases in which results from multiple trials were combined at a single node.

Figure 2.2 Network diagram of acute treatments for CHs

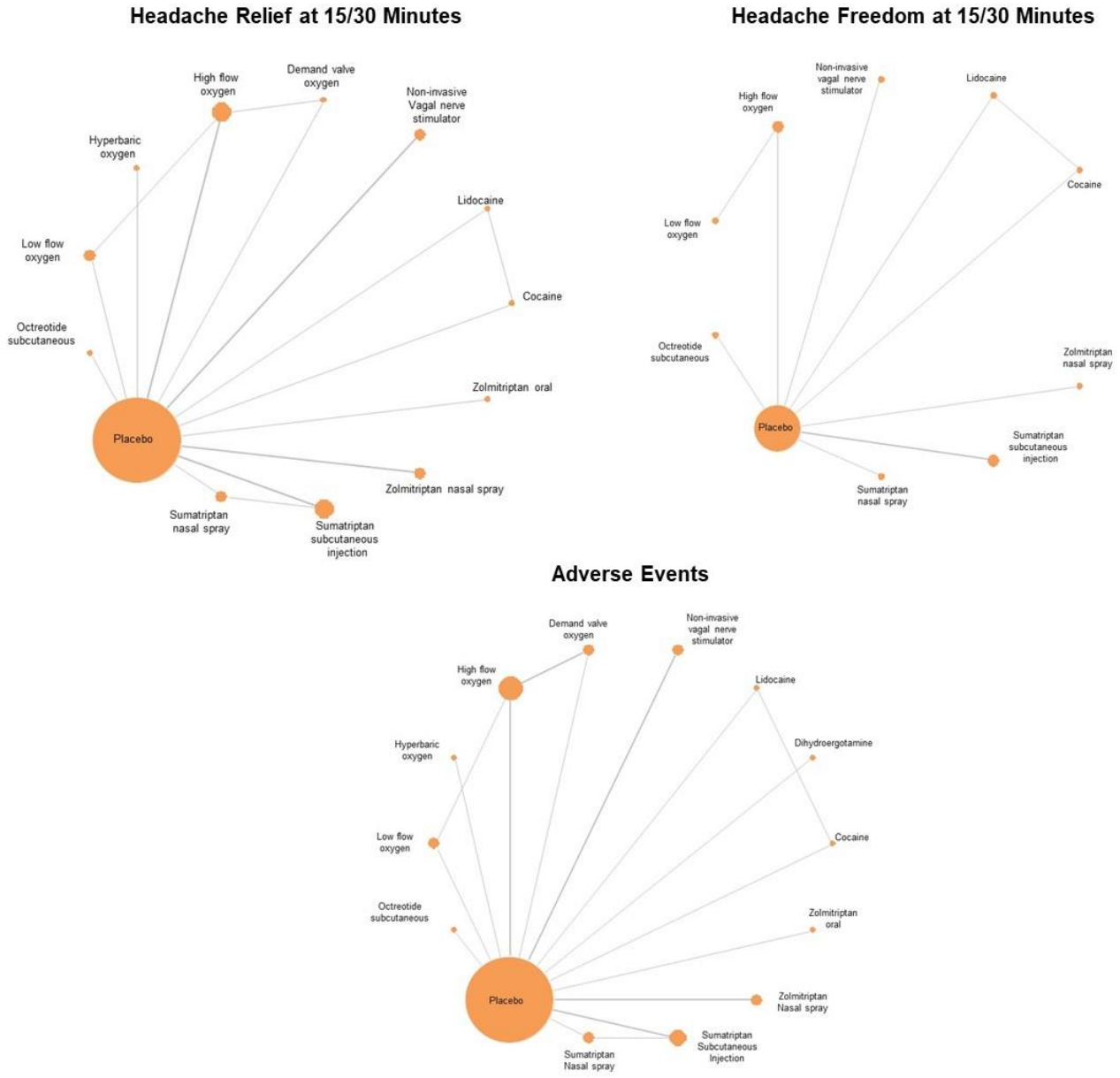


The network diagram for trials of acute treatments for CHs was as shown**.** Nodes were sized proportionately to reflect the number of patients provided with each intervention. The lines connecting the interventions have widths that reflected the number of studies evaluated for each comparison. Overall, 14 interventions were compared from a total of 21 studies (n=2,059 patients).

Outcomes

Table 2.2 provides a summary of the outcomes reported in the set of trials included in this study**.** Most trials assessed pain intensity as measured on an ordinal scale and all but two trials (29, 83) reported headache relief as a decrease from moderate to very severe pain to mild or no pain at 15 or 30 min; others reported freedom from headache at 15 or 30 min. The two trials that did not report these data were older and conducted before these measures became standard criteria in acute therapy trials. All but one of the studies reported adverse events (29). **Figure 2.3** presents network diagrams for each of these endpoints.

Figure 2.3 Common outcomes encountered in acute treatment trials for CHs



Network diagrams documenting three possible outcomes from acute treatment trials, including headache relief, freedom from headaches, and adverse events were as shown**.** Nodes were sized proportionately to reflect the number of patients provided with each intervention. The lines connecting the interventions have widths that reflected the number of studies evaluated for each comparison. The number of studies, treatments, and patients varied between the outcome measures presented.

Table 2.2 Outcomes reported for acute treatment trials

Trial ID	Treatment	Comparator	HA relief at 15min	HA relief at 30min	Pain-free at 15 min	Pain-free at 30 min	Other efficacy measures	Adverse Events
Andersson 1986	DHE NS	Placebo					Attack controlled, strongly reduced, or slightly reduced as per timeline provided	NA
Bahra 2000	zolmitriptan PO	Placebo		Yes				Yes
Cittadini 2006	zolmitriptan NS	Placebo	Yes	Yes		Yes		Yes
Cohen 2009	Oxygen 12L/min	Placebo	Yes	Yes	Yes	Yes		Yes
Costa 2000	Lidocaine/cocaine	Placebo	Yes	Yes	Yes	Yes	Pain extinction times in minutes were 31.3 for cocaine, 37 for lidocaine, and 59.3 for saline	Yes
Di Sabato 1993	Hyperbaric O_2	Room	Yes					Yes
Dirkx 2018	Oxygen 7L/min	Oxygen 12L/min	Yes§		Yes§			Yes
Ekbom 1991	sumatriptan SC	Placebo	Yes		Yes	Yes		Yes
Ekbom 1993	sumatriptan SC	Placebo	Yes		Yes		HA response at 10 min	Yes
Fogan 1985	Oxygen 6L/min	Placebo	Yes§				Subjective relief score expressed by the patient	Yes
Goadsby 2018	nVNS	Sham	Yes§		Yes		Proportion per subject of attacks with a response and who were pain-free at 30 min, pain score as per subject.	Yes
Goadsby 2019	SPG stim	Sham	Yes		Yes		Sustained pain relief from 15 min to 1 h, 50%, 75%, and 100% responder rate in patients treated for >6 attacks.	Yes
Hardebo 1998	sumatriptan SC	Sumatriptan NS	Yes	Yes				Yes
Matharu 2004	Octreotide SC	Placebo		Yes		Yes		Yes
Petersen 2017	Oxygen 15L/min, DVO	Placebo	Yes	Yes				Yes
Rappaport 2007	Zolmitriptan_NS	Placebo		Yes				Yes
Rozen 2013	DVO	Oxygen 15L/min		Yes				Yes
Schoenen 2013	SPG stim	Sham	Yes	Yes	Yes			Yes
Sicuteri 1983	Somatostatin/DHE	Placebo					The maximal pain intensity was moderately reduced, no timepoints were provided.	Yes
Silberstein 2016	nVNS	Sham	Yes				50% responders at 15 min	Yes
VanViet 2003	Sumatriptan NS	Placebo		Yes		Yes		Yes

Abbreviations: O_2, oxygen; DVO, demand valve oxygen; PO, by mouth; SC, subcutaneous; nVNS, non-invasive vagal nerve stimulation; NS, nasal spray; suma, sumatriptan; zolmi, zolmitriptan; DHE, dihydroergotamine; SPG = sphenopalatine ganglion, ECH, episodic CH; CCH, chronic CH. §Study characteristics obtained by communication with authors or by calculations based on available data.

Considerations for NMA and Outcomes Selected

We identified 18 suitable acute treatment trials that reported headache relief at 15–30 min as an outcome. We visually inspected the homogeneity of these trials as shown in **Appendix 1.3**. Of this set, five trials were identified as outliers that were excluded from the NMA for the following reasons:

- One trial was an open-label study (85) that compared two active treatments (sumatriptan SC and NS). We excluded this trial due to the risk of potential biases associated with the open-label design.
- One trial featured a sumatriptan oral formulation and recorded headache responses at 30 min (18). Oral formulations were not recommended for acute treatment of CHs (104) given that the time of onset was slow and, on average, these headaches were brief. It may not be appropriate from a methodological perspective to expect a response to oral sumatriptan at these early time points as it typically takes 2 hours to reach maximal systemic concentrations of this drug when administered via this route. This could be compared to the responses to sumatriptan injections, in which responses are typically seen within 15 min (105). Furthermore, this trial had a significantly lower placebo response rate (9%) for headache response at 30 minutes than was observed in the other trials. The average placebo response in all other trials was 27% (CI 23% to 31%).
- One trial that featured the use of DVO compared to simple mask and high flow oxygen was not appropriately blinded, as placebo treatment was always provided after DVO, which was hypothesized as likely to be the more effective of the treatments evaluated. The results included a placebo response rate of 45% for headache response at 30 minutes, which was much higher than the average at 27% (CI 23% to 31%). This high placebo response rate may be due to the direct temporal association of the potentially more effective treatment vis à vis the placebo (25).
- Another (92) was a pilot trial of DVO *versus* high flow oxygen involving only four CH patients. Because this would have been the only DVO trial in our analysis and the very small sample size might misrepresent the true treatment effect, this study was omitted from the formal analyses.

- One trial involving treatment with lidocaine and cocaine (26) warranted further consideration for exclusion from NMAs because (a) it included a substantially larger population of chronic CH patients (60%) compared to all other trials (range 25%–43.6%), and (b) there was no observed placebo response in 9 episodes of treated CHs. As noted above, in all other placebo-controlled trials the average placebo response was 27% (CI 23% to 31%).

Based on these considerations, 13 trials were identified as suitable for inclusion in an NMA of treatments used for CH relief with a 15–30 min outcome point. Of these, 11 studies compared acute therapies for all subtypes of CH. These trials compared injectable and NS formulations of triptans (n=5) (16–20), oxygen administered in high and low flow (n=3) (23, 24, 83), octreotide (n=1) (86) and nVNS (n=2) (82, 90). For an NMA, we planned to evaluate either the 15 min or the 30 min time point depending on the anticipated clinical onset of the effect of each therapeutic regimen. For example, the onset of the effect of sumatriptan SC is typically within 15 min, while the onset of the effect of sumatriptan NS was within 30 min. Recent data revealed that maximal blood concentrations of injectable triptans were achieved at <15 min (105) and that the clinical response occurs within this timeline (85). By contrast, some patients experience relief in response to NS triptans after 15 min or more (85). We created two treatment nodes for oxygen as there was clinical consensus (23, 106) suggesting a differential treatment effect as well as published findings that were consistent with this trend (24). We evaluated all reported side effects pooled per individual treatment as a secondary outcome. Another two trials were included in the subgroup analysis of outcomes associated with SPG stimulation in cases of chronic CH only (28, 89). The findings presented in **Table 2.3** are a summary of the group-level data for studies with common outcomes of responses of CHs at clinically appropriate time points together with safety outcomes that were considered in the NMA.

Table 2.3 Studies with clinically relevant shared outcomes that were considered in the NMA.

Two outcomes commonly included in these studies were headache responses at clinically appropriate time points and safety.

Study	Placebo	Suma SC	Zolmi NS	O_2 low	O_2 high	Suma NS	Octreotide SC	nVNS	Headache Response Timeline Analyzed	Safety	
										Adverse Events Therapy	Adverse Events Placebo
Ekbom 1991	25%, n=39	74%, n=39							15 min	35%, n=49	26%, n=47
Ekbom 1993	35%, n=88	75%, n=93							15 min	37%, n=92	16%, n=88
Cittadini 2006	23%, n=61		42%, n=65						30 min	2%, n=65	0%, n=61
Rappoport 2007	30%, n=59		50%, n=52						30 min	25%, n=52	16%, n=50
Fogan 1975	33%, n=63			68%, n=74					15 min	0%, n=67	0%, n=46
Cohen 2010	20%, n=148				78%, n=150				15 min	0%, n=148	0%, n=150
Dirks 2018				14%, n=14	33%, n=15				15 min	0%, n=14	0%, n=14
Van Viet 2003	26%, n=77					57%, n=77			30 min	23%, n=77	1%, n=77
Matharu 2004	36%, n=45						52%, n=46		30 min	57%, n=46	24%, n=45
Silberstein 2016	15%, n=73							27%, n=60	15 min	14%, n=73	30%, n=77
Goadsby 2018	30%, n=44							38%, n=48	15 min	40%, n=50	27%, n=52

Abbreviations: O_2, oxygen; SC, subcutaneous; nVNS, non-invasive vagal nerve stimulation; NS, nasal spray; Suma, sumatriptan; Zolmi, zolmitriptan.

Subgroup Analysis: Episodic and Chronic CHs

Our review of the data indicated that it was feasible to evaluate episodic CH patients and their acute responses in four trials that focused on zolmitriptan (n=2) (19, 20, 107) and nVNS (n=2) (82, 90, 108). It was also possible to perform a subgroup analysis with data on chronic CH patients treated with zolmitriptan (n = 2) (19, 20, 107), nVNS (n = 2) (82, 90, 108) and SPG stimulation (n = 2) (28, 89).

RCTs for Prevention for Chronic and Episodic CH

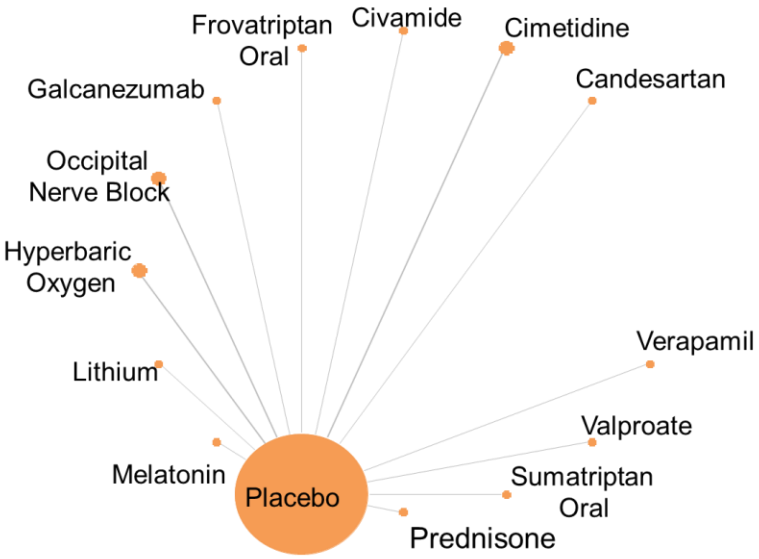
Interventions Compared

The RCTs focused on preventive therapies for CH included comparisons of the following interventions:

1) Nerve block injections with steroids/local anesthetic (n=2) (34, 35);
2) Verapamil (n=2) (38, 39);
3) Valproate (n=1) (45);
4) Galcanezumab (n=2) (52, 53);
5) Fremanezumab (n=3) (93–95);
6) Deep brain stimulation (DBS; n=1) (47);
7) nVNS (n=2) (82, 90);
8) Warfarin (n=1) (40);
9) Melatonin (n=1) (41);
10) Capsaicin (n=1) (43);
11) Misoprostol (n=1) (49);
12) Hyperbaric O_2 (n=1) (87);
13) Triptans (frovatriptan and sumatriptan (n=1 each) (42, 46);
14) Civamide (n=1) (36);
15) Lithium (n=2) (37, 38);
16) Candesartan (n=2);
17) Cimetidine (n=2) (48, 88); and
18) Nitrate tolerance (n=1) (44).

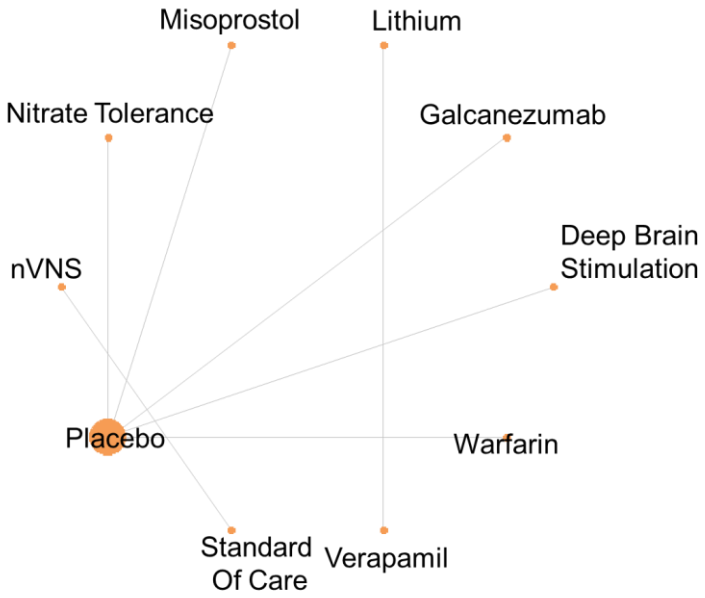
The network diagrams shown in **Figures 2.4** and **2.5** illustrate the current evidence regarding preventive treatments used for episodic or non-selective and chronic CHs, respectively, before focusing on the common outcomes reported. Placebo was used as the comparator in most of the trials (76%, n=19/25). Other notable comparators included a DBS procedure in which the device was not turned on (47), lithium *versus* verapamil (39), standard of care *versus* nVNS (84), and hyperbaric air in a room or via a mask *versus* hyperbaric oxygen treatment (50, 87).

Figure 2.4 Preventive treatments used in studies of patients with CHs including episodic disease



A network diagram documenting preventive trials is shown. Nodes were sized proportionately to reflect the number of patients subject to each intervention. The lines connecting the interventions have widths that reflected the number of studies per comparison. Overall, 14 interventions were compared in a total of 17 studies (n=758 patients).

Figure 2.5 Preventive strategies used in studies of patients with chronic CH



A network diagram documenting comparison performed in preventive trials for patients with chronic CH is shown. Nodes were sized proportionately to reflect the number of patients subject to each intervention. The lines connecting the interventions have widths that reflected the number of studies per comparison. Overall, 10 interventions were compared in a total of 7 studies (n=460 patients).

Outcomes

Table 2.4 presents a summary of the outcome measures assessed in all the included trials of preventive therapy. Overall, there was wide variability between studies with respect to the choice of primary outcome and timing of measurements. The guidelines for the design of clinical trials focused on CHs recommended that the primary efficacy should be measured as the frequency of attacks per week (78). However, there were no recommended or commonly accepted criteria for evaluating the duration of baseline headaches and the number of weeks used to define a response period. In this table, we listed the more commonly reported outcomes used in these studies to assess the feasibility of performing an NMA.

Table 2.4 Outcomes reported in preventive trials.

Trial and Year	Treatment	Comparator	Cluster Type	Baseline	Mean change in the number of headache days at 2 weeks	50% Reduction in Headache Days	Primary Outcome Measures
Ambrosini 2005	betamethasone injection	Placebo	69.5% ECH	1 week	no	no	From 72h to 1-week attack free, from 72h to 4 weeks attack free
Anthony 1978	cimetidine, cimet + chlorpheniramine	Placebo	NA	none	no	no	Headache free during 3weeks
Bussone 1990	verapamil	Lithium	CCH	3 weeks placebo	no	no	The number of headache attacks and changes in intensity during 12 weeks of treatment.
Christiansen 2000	nitrate tolerance	Placebo	CCH	1 week	no	no	Mean cluster attacks/week comparing placebo to active treatment for 1 week.
Di Sabato 1998	hyperbaric O2	Room	ECH	None	no	no	Freedom from CHs for 3 mo duration.
El Amrani 2002	valproate	Placebo	77% ECH	1 week	no	no	50% reduction in the number of headaches from run in to the second week of treatment
Evers 1998	misoprostol	Placebo	CCH	2 weeks	no	no	Number of attacks over 2 weeks of treatment *vs.* placebo
Fontaine 2010	DBS	Sham	CCH	4 weeks before implant and 4 weeks after implant but before randomization	no	no	Attacks in the last week on active *vs.* placebo in the 1 month of treatment
Gaul 2016	nVNS +SOC	SOC	CCH	2 weeks	yes	yes	Reduction in mean CH attacks in the last two weeks of a 4-week randomized phase
Goadsby 2019	galcanezumab 300 mg Qmo	Placebo	ECH only	1 week	yes	yes	Reduction in mean attacks in the 3 weeks compared to baseline, including week by week values
Hakim 2011	Warfarin	Placebo	CCH	4 weeks	no	no	Remission for 4 of 12 wk on treatment or placebo
Jammes 1975	Prednisone	Placebo	NA	NA	no	no	Complete relief of pain with prednisone and number of patients with duration of effect >2 mo.
Leone 1996	Melatonin	placebo	90% ECH	1 week	yes	no	Reduction in mean attacks in week 1 and 2 on treatment compared to baseline
Leone 2000	Verapamil	placebo	ECH only	5 days	yes	yes	Reduction in mean attacks in week 1 and 2 on treatment compared to baseline
Leroux 2011	Cortivazol	placebo	65.1% ECH	3 days	yes	yes	Attacks <2/day during the second, third, and fourth day after the third injection (days 9–12)
Marks 1993	capsaicin	placebo	62.5% ECH in rx, plac no ECH	3 days	no	no	The difference in the number of headaches and headache intensity at baseline *vs.* week 1 and 2

Trial and Year	Treatment	Comparator	Cluster Type	Baseline	Mean change in the number of headache days at 2 weeks	50% Reduction in Headache Days	Primary Outcome Measures
Monstadt 1995	sumatriptan 100 mg PO TID	placebo	53% ECH	1 week	no	no	50% responder rate between baseline week and week 1 of treatment
Nilsson 2002	hyperbaric O_2	Sham - hyperbaric air	75% ECH	1 week	no	no	Headache index reduction 50% at 1 wk
Oakes 2019	galcanezumab 300mg Qmo	placebo	CCH	2 weeks	yes	yes	Mean change in the number of cluster attacks from baseline to weeks 1–12
Pageler 2010	Frovatriptan 5mg daily	placebo	ECH	4–7 days	no	no	Mean change in the number of cluster attacks from baseline to weeks 1–2
Russel 1979	cimet + chlorpheniramine	placebo	NA	none	no	no	Mean change in the number of cluster attacks from baseline to weeks 1–12
Saper 2002	civamide nasal drop	placebo	ECH	3 days	yes	no	Mean change in the number of cluster attacks from baseline to weeks 1–3
Steiner 1997	Lithium	placebo	ECH	none	no	no	Percentage of patients whose attacks ceased at 1 week
Trovnik 2013	candesartan	placebo	ECH	none	yes	yes	Mean number of CH attacks from wk 1 to wk 3 of treatment

Abbreviations: cimet, cimetidine; PO, by mouth; SC, subcutaneous; O_2, oxygen; SOC, standard of care; TID, three times daily; DBS, deep brain stimulation; Qmo, administered once each month; nVNS, non-invasive vagal nerve stimulation; NS, nasal spray; SPG, sphenopalatine ganglion; rx, treatment; plac, placebo; wk, week; CH, cluster headache; ECH, episodic CH; CCH, chronic CH.

Many trials assessed freedom from headaches over specific periods of time (34, 37, 40, 48, 50). A few older trials included a headache index, which was a compound measure of frequency and intensity (39, 87). Some trials did not include a baseline period in which headache frequency was measured in the absence of treatment; these studies used the first week of treatment as the effective baseline for comparisons with responses during the weeks to follow (48, 51, 103). Other trials featured various measures of headache attacks over a defined period compared to baseline, although the time recorded varied from 1–2 weeks in most trials, up to 12 weeks in trials for chronic CH (53).

Considerations for NMA and Outcomes Selected for Evaluation of Prevention of CHs

We initially identified six trials (35, 36, 39, 41, 51, 52) that included the common outcome of a reduction in the frequency of headaches in comparisons between pre-treatment baselines and two weeks of treatment for the prevention of CHs. However, there was one significant methodological difference identified specifically in one of these studies that evaluated the efficacy of cortivazol injections. In a 2011 study, Leroux et al. (35) treated all episodic CH patients with verapamil in addition to the target drug or placebo injections. However, none of the patients diagnosed with chronic CH were treated with verapamil. As it was unclear which patients did or did not receive verapamil, we were unable to assign these study subjects to the true placebo or verapamil node.

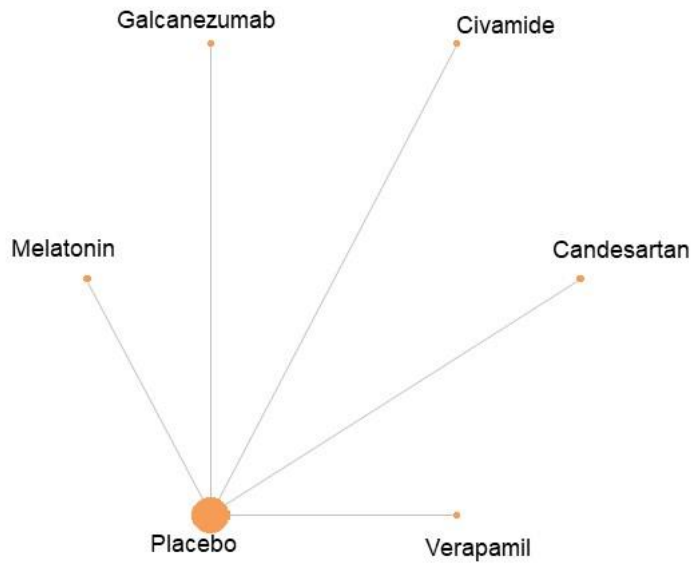
As shown in **Figure 2.6a**, we identified five trials for inclusion in NMAs as summarized in **Table 2.5**. All five studies reported decreases in headache parameters after two weeks of therapy, with four of them documenting a 50% response at two weeks; these findings are illustrated in **Figure 2.6b**. The findings presented in **Appendix 1.3** include possible effect modifiers and the placebo response rates reported in these trials. We noted that there was significant heterogeneity associated with these trials that may have an impact on the validity of NMA. As shown in **Appendix 1.3** and **Figure 2.4**, there was considerable variability in the placebo responses for both headache change (range 1.7 to -6.2) and the 50% response rate (range 0% to 45%). This likely reflected differences in study design that would influence treatment response. Those studies where the placebo response was very low included patients in the first week of a bout only(39, 41), and those studies with

a larger response included patients later in a bout(36, 51, 52). Earlier in a bout as the headaches are beginning, there is commonly a ramp-up of the number of headaches (104, 109), and thus the placebo effect when measured early can be very low(39, 41), and treatment effects, if seen, may be more significant. Another trial(34), left out of our analysis as it had a different outcome and was not eligible for NMA, that also had inclusion early (<1 week) in a bout, also had a zero placebo response rate. It is possible that by including patients later in a bout, the placebo measured effect is higher as some patients have natural remission of their cluster bout which occurs between 6-10 weeks (110, 111). Both placebo and true treatment response may be increased in these trials compared to trials that included patients later in a bout(51), compromising the similarity of these trials. Additionally, clinically patients are often seen out of bout, and will be asked to start a medication at the onset of a bout, making this trial design more applicable clinically as well. Overall, given this extremely high variability and given that there were too few studies to conduct meta-regression analyses on the placebo response rate and bout duration in these trials, we believe that NMAs comparing preventive therapies could be prone to bias and limited validity. Therefore, NMAs for this class of therapies were not considered valuable to be pursued.

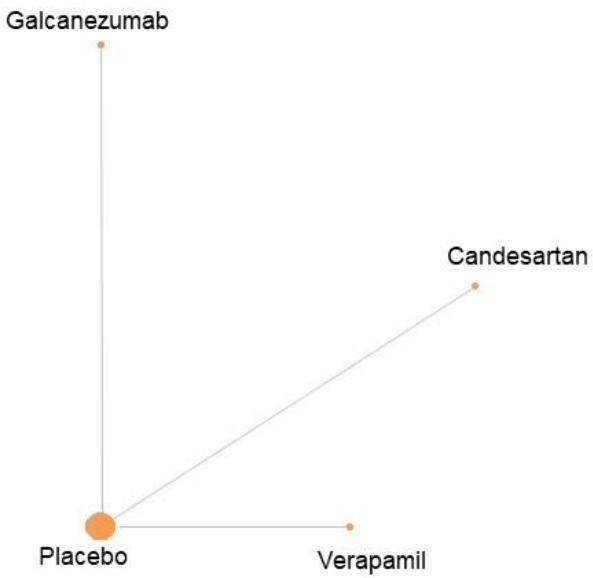
There were no data available from these preventive trials that facilitated subgroup analysis in episodic *versus* chronic CH patients. Four of the trials focused on episodic CHs only (36, 39, 51, 52); only one of the remaining two trials provide a clear and appropriate breakdown of the data (35). Seven reports focused on chronic CH patients only, although these studies did not include a common outcome (38, 40, 44, 47, 49, 52, 84).

Figure 2.6a (*left*). Studies reporting changes in the number of weekly headaches from baseline to 2 weeks in episodic CH patients

Figure 2.6b (*right*). Studies reporting fifty percent responder rates in episodic CH patients



Nodes are sized proportionately to reflect the number of patients involved in each intervention. The lines connecting the interventions have widths that reflect the number of studies per comparison. Overall, 6 interventions were compared in a total of 5 studies (n=268 patients).



Nodes are sized proportionately to reflect the number of patients involved in each intervention. The lines connecting the interventions have widths that reflect the number of studies per comparison. Overall, 4 interventions were compared in a total of 3 studies (n=164 patients).

Table 2.5 Preventive trials that feature changes in headache frequency from baseline to 2-weeks, 50% responder rates, and adverse events.

Trial and year	Treatment	ECH	Baseline frequency active Rx per week ± SD	Rx reduction to week 2 ± SD	Baseline frequency placebo per week ± SD	Placebo reduction to week 2 ± SD	Active Treatment 50% response	Placebo 50% resp	AE RX	AE PLAC
Goadsby 2019	galcanezumab	All	17.3±-10	-8.8±12.1, n=57	17.8+/-10.1	-4.5±10.5, n=49	39%, n=57	25%, n=49	25/57	16/49
Leone 1996	melatonin	90%	23.1	-12.7±16.0, n=10	16.73	0.8±11.4, n=10	NA	NA	0/10	0/10
Leone 2000	verapamil	All	13.4	-9.2±9.1, n=15	9.59	1.7±8.7, n=15	80%, n=15	0%, n=15	8/15	0/15
Saper 2002	civamide nasal drop	ECH	12.5	-8.4±9.1, n=18	10.8	-3.6±8.7, n=10	NA	NA	17/18	7/10
Trovnik 2013	candesartan	ECH	14.3±9.2	-8.7±9.1, n=19	16.8	-6.2±8.7, n=13	63%, n=19	46%, n=13	12/19	3/13

Abbreviations: ECH, episodic clusuter headache; RX, treatment; AE, adverse events; PLAC, placebo; NA, not available.

Table 2.6 Characteristics of two-arm observational studies of therapies used to treat CHs

Trial, year and location	Treatment	Diagnostic criteria	ECH %	Male %	Mean Age	Onset <wks	Attacks per day	Attack duration	Attack >45 min	Illness Duration	Prophylaxis	Rescue
De Carolis 1988 Italy	prednisone 50 mg/day for 30d	na	100	92	na	<1wk	na	>3wk	na	na	yes	yes
	nimodipine 30 mg QID											
	lithium 300 mg TID											
	methysergide 2 mg TID											
Favoni 2017 Italy	GON-B Methylprednisolone 80 mg + lidocaine 2 mg 2% 1X	na	68	na	na	na	na	na	na	na	na	na
	GON-B Methylprednisolone alone - 3 applications every 48h											
Fusco 1994 Italy	10% capsaicin applied only until desensitized ipsilateral to ECH	ad hoc	73	80	46+	>15 days	na	na	na	>3 y	na	Na
	Contralateral to ECH			80	49							
	Contralateral 1 mo and then ipsilateral 1 mo for CCH			100	51							
Gantenbein 2012 Switzerland	unilateral GON-B with 3 ml betamethasone + 2 ml 2% lidocaine	ICHDII	52	87	42	ECH 34 days	2.9+/-1.8	na	na	na	yes	na
	bilateral GON-B escalation					CCH	3.2+/-2.8					
	ECH											
	CCH											
Gregor 2005 USA	sumatriptan 6 mg SC	IHS	63	83	43	na	na	na	na	na	yes	yes
	sumatriptan 3 mg SC											
	sumatriptan 2 mg SC											
	Oxygen >7 L/min											
Kudrow 1981 NA	Ergotamine	ad hoc	72	84	44	na	na	na	na	na	no	no
	O2 7 L/min											
Wei 2018 USA	oral steroids prednisone or dexamethasone for 2–14 days	ICHD3B	67	80	44	na	na	na	na	na	yes	yes
	GON-B 2 ml 2% lidocaine and 40 methylprednisolone											

Abbreviations: CH, cluster headache; ECH, episodic CH; SC, subcutaneous; PO, by mouth; his, International Headache Society; ICHD, International Classification of Headache Disorders; O_2, oxygen; TID, three times daily; QID, four times daily; NA, not available; GON-B, greater occipital nerve block.

Characteristics of Study Populations in Non-Randomized Studies

Our literature search identified seven observational studies that included control arms (96–102). The characteristics of these studies are summarized in **Table 2.6**. Five out of the seven non-randomized studies evaluated preventive interventions (96–100), while two assessed interventions for acute treatment (101, 102). The interventions compared in the preventive studies included steroids with nimodipine, lithium, and methysergide (96); greater occipital nerve (GON) injections with steroids both with and without local anesthetic (98); administration of capsaicin in the ipsilateral *versus* contralateral nostril (97); unilateral *versus* bilateral GON injections (99); and oral steroids *versus* GON injection (100). Diagnostic criteria were provided in most of these studies (71% n=5/7), as were the percentages of patients diagnosed with episodic CHs. The percentage of male patients was reported in all trials (median = 84%, IQR 81% to 87%). Exclusion criteria were reported in only 29% of studies. Prophylaxis was accepted in 71.4% and disallowed in 14% of these studies; another 14% did not report this information. Rescue therapy was allowed in 42.9%, not allowed in 14%, and not reported in 28% of these trials. The average age of patients in these studies was similar to the average ages of patients enrolled in the RCTs (median 43.4, IQR 43.4 to 46.25 years); this information was not available in one study. It was unclear whether therapy was discontinued in any of the studies. Time of onset of the current cluster period was not reported in 42% of trials; 71.4% of the studies did not report the number of headache attacks per week. The durations of the headache attacks were reported in only 14% of the trials. It was also unclear whether any of the acute trials limited their evaluation to attacks that persisted for longer than 45 min. Duration of illness was reported in only 14% of these trials.

The outcomes assessed in the observational studies are presented in **Table 2.7**. For trials focused on preventive therapies, all studies reported complete cessation of attacks within a given timeline; however, as baseline frequencies were not available, the data provided by these trials were not sufficient for use in NMAs. Among the two-arm observational studies, de Carolis (96) found that, although prednisone treatment was effective, frequent relapses in a single cluster period were observed in patients treated with this medication. Of note, they did report that, regardless of the specific drug used, medications were less

likely to be effective when administered later during a cluster period. Favoni (98) found that 3 steroid injections without local anesthetics administered over a 72 h period were as effective in terminating headache clusters as was a single injection of steroids with an anesthetic. Fusco (97) found that the application of capsaicin in the ipsilateral nostril was effective in terminating a cluster in patients with both episodic and chronic cluster CHs. Gantenbein (99) reported that unilateral steroid injections with local anesthetics were effective for both episodic and chronic CHs; however, bilateral injections might be more effective in promoting complete resolution in those diagnosed with chronic CH. Wei et al. (100) found that steroid injections with local anesthetics were effective less frequently than were oral steroids. However, as they note in their publication, steroid injections with local anesthetics were provided as single and lower doses than those evaluated in the RCTs (34, 35).

While both acute treatment studies measured headache responses at 15 min, there were significant methodological limitations associated with these trials. In one trial, oxygen was administered at >7L/min (101), although the exact value was not reported by the authors and could not be determined. This study could not undergo further consideration for inclusion in the quantitative analyses. In the other trial, the authors reported treatment success if 7 of 10 attacks were relieved within 15 min (102). This endpoint was different from those used elsewhere; these findings could not be combined with those reported in other studies.. Given that risk of bias for these studies was not appraised nor were they included in further analyses, we do not give further comment on the strength of evidence of these trials. Instead the directionality of findings observed is reported, as is common for a scoping review giving a wide angle view of the field.

Table 2.7 Outcomes reported in observational studies.

Trial and Year	Treatment	Primary Outcome	Other Outcomes
De Carolis 1988	prednisone 50 mg/day for 30 d	No attacks after 7 days of therapy	
	nimodipine 30 mg QID		
	lithium 300 mg TID		
	methysergide 2 mg TID		
Favoni 2017 abstract	Methylprednisolone 80 mg + lidocaine 2mg 2%	Responders were in remission >1 mo	
	Methylprednisolone only three times every 48h		
Fusco 1994	10% capsaicin applied only until desensitized	Complete cessation of headaches over 60 days	50% response over 60 days
	Ipsilateral to ECH		
	Contralateral to ECH		
	Contralateral 1 mo and then ipsilateral 1 mo for CCH		
Gantenbein 2012	Ipsilateral GON-B with 3 ml betamethasone + 2 ml 2% lidocaine	No attacks within 24h of therapy	>25% decrease in the frequency of attacks after 24h
	bilateral GON-B with escalation		
	ECH		
	CCH		
Gregor 2005	sumatriptan 6 mg SC	HA relief at 15 min	
	sumatriptan 3 mg SC		
	sumatriptan 2 mg SC		
	O_2 >7L/min		
Kudrow 1981	Ergotamine	HA relief at 15 min	Headache freedom at 15 min
	O_2 at 7L/min		
Wei 2018	Oral steroids prednisone or dexamethasone for 2–14 days	Complete cessation of headaches with 7 days of treatment	A decrease in headaches within 7 days of treatment
	GON-B with 2 ml 2% lidocaine and 40 mg methylprednisolone		

Abbreviations: CH, cluster headache; ECH, episodic CH; SC, subcutaneous; PO, by mouth; IHS, International Headache Society; ICHD, International Classification of Headache Disorders; O_2, oxygen; TID, three times daily; QID, four times daily; GON-B, greater occipital nerve block; HA, headache.

Synopsis of Findings

For the present review, we identified 55 studies that fit our search criteria. Of these, 44 were RCTs, 4 were unpublished trials available from clinical registries, and 7 were observational studies. We noted that there was evidence of the efficacy of numerous therapies used for treatment of CHs, including oxygen, triptans (injectable and NS), nVNS (for episodic CH); SPG stimulation (for chronic CH), DHE NS and infusion, somatostatin and its analog, octreotide, and nasal application of lidocaine and cocaine (**Table 2.8**). For preventive therapy (**Table 2.9**), there was evidence supporting the efficacy of steroid injections with local anesthetics to the greater occipital nerve, galcanezumab (in episodic

CH), verapamil (39) (in episodic CH), oral prednisone (31), nVNS (for chronic CH) (84), lithium (38) (equivalent to verapamil for chronic CH) and warfarin (for chronic CH) (40). We were unable to report comparative data derived from some of the observational studies as they did not provide objective comparisons of the outcomes, but instead performed statistical analyses of the responses to each of these modalities individually (96, 98). In cases in which active treatments were compared directly to one another, the following were the conclusions for studies of acute therapy for CH:

(1) Sumatriptan injections in doses from 2 to 6 mg were effective in most patients. More patients responded to sumatriptan injection *versus* oxygen at flow rates >7L/min, although this was not stated explicitly (101);
(2) Sublingual ergotamine and low flow oxygen were equally effective (102).

Regarding directionality of findings, the following observations were made from observational studies focused on preventive therapy. It should be noted that these findings are subject to limitations due to inherent bias of observational studies (and as we did not assess their risk of bias formally):

(3) Capsaicin applied to the ipsilateral nostril (97) was more effective than its application to the contralateral nostril in preventing both episodic and chronic CHs;
(4) Bilateral steroid injections with local anesthetics into the greater occipital nerves were more effective than unilateral injections (if the latter were shown to be ineffective) especially for chronic CH patients (99);
(5) Oral steroids were found to be more effective than GON injections in one study, although in this study, an injection dose of only 40 mg of methylprednisolone was used. This dose is lower than the 80 mg that would be considered as equivalent to what was used in the randomized trials (34, 35) and other observational studies (98).

Table 2.8 Summary of findings and acute treatment interventions

Author and Year	Treatment	Comparator	Design	Directionality of Findings of Treatment *vs.* Comparator			
				Reports Efficacy	HA Relief	Pain-Free	Other primary Endpoints[§]
Andersson 1986	DHE NS	Placebo	RCT	Yes			↑
Bahra 2000	zolmitriptan PO	Placebo	RCT	Yes	↔		↔
Cittadini 2006	zolmitriptan NS	Placebo	RCT	Yes	↑		
Cohen 2009	Oxygen 12L/min	Placebo	RCT	Yes	↑	↑	
Costa 2000	Lidocaine/cocaine	Placebo	RCT	Yes	↑	↑	↑
Di Sabato 1993	Hyperbaric O2	Room	RCT	Yes	↑		
Dirkx 2018	Oxygen 7 L/min	Oxygen 12L/min	RCT	Yes			↑
Ekbom 1991	Sumatriptan 6 mg SC	Placebo	RCT	Yes	↑	↑	
Ekbom 1993	Sumatriptan 6 mg SC	Placebo	RCT	Yes	↑	↑	
Fogan 1985	Oxygen 6 L/min	Placebo	RCT	Yes			↑
Goadsby 2018	nVNS	Sham	RCT	ECH subgroup only		↔	
Goadsby 2019	SPG stim	Sham	RCT	Yes	↑	↑	↑
Gregor 2005	Sumatriptan 6 mg, 3 mg, 2 mg	Oxygen >7L/min	Observational	Yes			↑
Hardebo 1998	sumatriptan SC	Sumatriptan NS	RCT	Yes	↑		
Kudrow 1981	Ergotamine sublingual	Oxygen 7L/min	Observational	Yes			↔
Matharu 2004		Placebo	RCT	Yes			↑
Petersen 2017	Oxygen 15L/min, DVO	Placebo	RCT	No	↔		
Rappaport 2007	Zolmitriptan NS	Placebo	RCT	Yes	↑		
Rozen 2013	DVO	Oxygen 15L/min	RCT	No	↔		
Schoenen 2013	SPG stim	Sham	RCT	Yes	↑	↑	
Sicuteri 1983	Somatostatin/DHE	Placebo	RCT	Yes			↑
Silberstein 2016	nVNS	Sham	RCT	ECH subgroup only	↔		
VanViet 2003	Sumatriptan NS	Placebo	RCT	Yes	↑		

Abbreviations: CH, cluster headache; ECH, episodic CH; SC, subcutaneous; PO, by mouth; O_2, oxygen; DVO, demand valve oxygen; HA, headache; [§]Please see Table 2.2 for full explanations of these outcomes.

Table 2.9 Summary of findings and interventions used as preventive treatments

Author and Year	Treatment	Comparator	Design	Directionality of Findings Treatment *vs.* Comparator			
				Reports Efficacy	Mean change HA days	50% Reduction	Other primary Endpoints[§]
Ambrosini 2005	betamethasone injection	placebo	RCT	Yes			↑
Anthony 1978	cimetidine, cimet + chlorpheniramine	placebo	RCT	No			↔
Bussone 1990	verapamil	lithium	RCT	Yes			↑
Christiansen 2000	nitrate tolerance	placebo	RCT	No			↔
Di Sabato 1998	hyperbaric O_2	room	RCT	Yes			↑
El Amrani 2002	valproate	placebo	RCT	No			↔
Evers 1998	misoprostol	placebo	RCT	No			↔
Fontaine 2010	DBS	Sham	RCT	No			↔
Fusco 1999	10% capsaicin ipsilateral nostril	10% capsaicin contralateral nostril	Observational				
Gaul 2016	nVNS+SOC	SOC	RCT	Yes, CCH	↑	↑	
Goadsby 2019	galcanezumab 300 mg monthly	placebo	RCT	Yes	↑	↑	
Hakim 2011	warfarin	placebo	RCT	Yes			↑
Jammes 1975	prednisone	placebo	RCT	Yes			↑
Leone 1996	melatonin	placebo	RCT	Yes	↑		
Leone 2000	verapamil	placebo	RCT	Yes	↑	↑	
Leroux 2011	cortivazol	placebo	RCT	Yes	↑	↑	
Marks 1993	capsaicin	placebo	RCT	Yes			↑
Monstadt 1995	sumatriptan 100 mg PO TID	placebo	RCT	No			↔
Nilsson 2002	hyperbaric O2	Sham – hyperbaric air	RCT	No			↔
Oakes 2019	galcanezumab 300 mg monthly	placebo	RCT	No	↔	↔	
Pageler 2010	frovatriptan 5 mg daily	placebo	RCT	No			↔
Russel 1979	cimetidine + chlorpheniramine	placebo	RCT	No			↔

Author and Year	Treatment	Comparator	Design	Directionality of Findings Treatment *vs.* Comparator			
				Reports Efficacy	Mean change HA days	50% Reduction	Other primary Endpoints[§]
Saper 2002	civamide nasal drops	placebo	RCT	Yes	↑		
Steiner 1997	lithium	placebo	RCT	No			↑
Trovnik 2013	candesartan	placebo	RCT	No	↔	↔	↑
Wei 2019	oral prednisone 2–14 days	GON 40mg methylprednisolone	Observational	Yes			↑

Abbreviations: CH, cluster headache; ECH, episodic CH; CCH, chronic CH; cimet, cimetidine; nVNS, non-invasive vagal nerve stimulation; SOC, standard of care; SC, subcutaneous; PO, by mouth; TID, three times daily; O_2, oxygen; GON-B, greater occipital nerve block; HA, headache; [§]Please see full explanations in Table 2.4.

DISCUSSION

In summary, we have looked at patient and study characteristics across trials of preventive and acute treatment interventions of cluster headache and identified areas of deficiencies in reporting of these baseline characteristics in randomized controlled trials. We have made some recommendations for consideration in future trials to comply with common outcomes recommended by guidelines on cluster headache trials (78), and additionally for trial duration in preventive trials of episodic and chronic cluster.

After we ensured baseline characteristics were similar and there were no methodological concerns as to the trials (69), we established a possible network architecture for NMAs to derive comparisons between acute treatments for cluster headache using headache relief and side effects as outcome measures, and we identified thirteen trials to be included in the network. For trials of acute treatments, we can look at episodic cluster headache patients and their acute response for two therapies, and in chronic cluster we can look at response to three therapies. For preventive trials, we identified 6 trials utilizing headache count at baseline at two weeks, and five trials with 50% responder rate that we can utilize in NMA. However, given the high variability in placebo response seen across trials, exploring this network may produce difficult to interpret results that may mislead readers. We saw a very low placebo response in those trials enrolling in the first week of

a bout (34, 39, 41), likely reflecting an initial ramp-up where number of headaches increase. In contrast, trials that allowed enrollment up to week 3 or 4 of a bout had larger placebo responses (51, 52), as there was possibly also natural remission of the disease reflected in these rates (51). This may be related to possible differences in treatment effects as well. As clinically patients are often encountered out of bout and are asked to start treatment on bout commencement, trialists need to consider this paradigm for future trial design.

Collectively, these steps highlight that we have connected networks for acute therapies, which were found to have populations and settings which are comparable, making for the basis of viable network meta-analyses to compare treatments. The network architecture of the acute trials is such that most studies are connected through placebo, except for two situations where the comparisons are of two active treatments (24, 85). There were no large degrees of separation of trials through multiple nodes, however we have a sparse network (i.e. few studies informing treatment comparisons in the network), and there will be some uncertainty due to lack of direct treatment comparisons and the small studies of studies (69).

A limitation of the current study is that, as is typical for scoping reviews, we did not assess the risk of bias and we do not give recommendations on the available therapies. We informally assessed methodological limitations of the various trials as described above while appraising their characteristics to judge appropriateness of their inclusion in NMA in light of the transitivity assumption. studies included in NMAs were subsequently appraised for risk of bias. However, for the scoping review we have described the treatment landscape to provide the clinical community with a bird's eye perspective of current studies and interventions, while aiming to inform the planning of network meta-analysis and establishing past compliance with recommendations for trial design (78, 112). By not assessing the risk of bias of these studies, we caution the reader to not interpret all treatment comparisons we present to be on the same footing in terms of evidence of treatment efficacy, and as such we are not making recommendations on treatment to use for this condition as much as delineating the landscape.

Reporting of possible effect modifiers is important (78), and we would recommend the following be reported by the authors of clinical trials in the future: percentage of episodic versus chronic and reporting results by these subgroups, gender of participants, exclusion criteria, whether there was allowed prophylaxis and acute therapy, the mean age of participants, the location of the trial, the discontinuation rates, the onset of current cluster period, the frequency of attack/week in a baseline period and in subsequent weeks, the duration of individual cluster headaches and if there was a minimum headache duration for inclusion (commonly 45min). These effect modifiers may have a significant effect on study results, and without this information, generally readers are unable to judge if there are design weaknesses in the trials, if findings are applicable in all trials, and if formal synthesis is appropriate. For example, having more chronic cluster patients in a study may decrease treatment response as these patients tend to be more resistant to treatment, including patients with headaches <45min may decrease treatment response and increase placebo as patient who have shorter headaches may have natural cessation of episode by 30min. If these data are not reported, readers are not able to judge the comparability of populations and designs across studies, and in the future efforts to account for differences between studies in evidence syntheses cannot be pursued.

Since the last systematic review in 2016 (15), which only included RCTs, we identified 9 new studies(24, 25, 52, 53, 82, 82, 93, 94, 94). Amongst these, there were 4 studies of acute treatments utilizing noninvasive vagal nerve stimulation VNS (82), sphenopalatine ganglion stimulation SPG (28) and oxygen (24, 25). There were also two studies of preventive therapies that have been published of an anti-calcitonin gene related peptide CGRP molecule monoclonal antibody galcanezumab which is positive on primary outcome in episodic cluster and negative on primary outcome in chronic cluster headache (52, 53) and 3 unpublished negative studies with fremanezumab (93–95) in episodic and chronic cluster.

Notably, for new studies in episodic cluster headache, CGRP monoclonal antibodies do not seem to have a class effect, with only galcanezumab being positive (52) and

fremanezumab being negative (95), and trials of these in prevention of chronic cluster are both negative (53, 94). Dosing may have played a role in episodic cluster, as the galcanezumab trial used much higher doses than in migraine (52), whereas fremanezumab trial did not increase doses compared to migraine (93–95). Given the negative trial results of CGRP monoclonal antibodies in chronic cluster, perhaps chronic cluster headache is only associated with CGRP pathology in some patients, and there is some data to support this (113).

CONCLUSION

In this scoping review, we describe the treatment landscape of cluster headache for both acute and preventive treatments. We highlight new studies reported since prior systematic reviews and identify and highlight possible treatment effect modifiers and recommend their reporting in future trials. Lastly, we present the acute therapies for which we will undertake a network meta-analyses for cluster headache.

CHAPTER 3

Network Meta-analysis of Therapies for Cluster Headache: Effects of Acute Therapies for Episodic and Chronic Cluster

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ABSTRACT

Background: There are few evidence-based acute treatments available for cluster headache. As most treatments were compared only against placebo in clinical trials, few head-to-head comparisons of treatments are available. We used network meta-analysis (NMA) to characterize the relative effectiveness and harms of acute treatment options for cluster headache.

Methods: A systematic scoping exercise 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 30min, and also the occurrence of adverse events. We report odds ratios of relative treatment effects along with corresponding 95% credible intervals (CrI), as well as measures of treatment ranking.

Results: A total of 13 RCTs informed NMAs. We found high flow oxygen to be the most effective therapy for headache response at 15/30 minutes (OR 9.03, 95% CrI 5.27 to 15.93 versus placebo), with injectable sumatriptan demonstrating the next highest effect (OR 6.39, 95% CrI 3.75 to 11.13 versus placebo). High flow oxygen was also more effective than low flow oxygen (OR 2.55, 95% CrI 1.13 to 5.76), nasal spray zolmitriptan (OR 3.75, 95% CrI 1.72 to 8.35), octreotide (OR 4.53, 95% CrI 1.64 to 12.47) and nVNS (OR 5.21, 95% CrI 2.29 to 11.93). 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 5.88), octreotide (OR 3.20, 95% CrI 1.17 to 8.80) and nVNS (OR 3.69, 95% CrI 1.63 to 8.37). Regarding adverse events, octreotide (OR 4.13, 95% CrI 1.71 to 10.49) and sumatriptan (OR 2.40, 95% CrI 1.39 to 4.21) were associated with greater risk compared to placebo, while other treatments did not demonstrate increased risk. For subgroup analyses, non-invasive vagal nerve stimulation (nVNS) was significantly better than placebo in episodic cluster headache patients (OR 4.93, 95% CrI 1.89 to 14.11).

Conclusions: Our findings suggest that high flow oxygen is more efficacious when compared to low flow oxygen for headache relief. Patients who fail low flow oxygen and can tolerate increased flow rates should be tried on high flow oxygen. Additionally, 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.

INTRODUCTION

Rationale

There are few acute evidence-based treatments available for cluster headache. Few head-to-head comparisons of the effectiveness of these treatments are available. This study was undertaken to compare the acute treatment response in cluster headache 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 was previously available.

Objectives

This is the second of two reviews performed to evaluate studies of current interventions for cluster headache. 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 cluster headache as well as their key findings. 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, and study designs and 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 cluster headache while assessing the feasibility of network meta-analysis (NMA) to estimate between-treatment comparisons. In that work, we established that while NMAs were feasible to compare acute treatments for cluster headache, NMAs were not feasible to inform 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 cluster headache 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 looking at treatment response in episodic and cluster headache populations separately. The pathogenesis of chronic cluster headache may be such that they are a subgroup of cluster patients who are more treatment refractory. Instead of remitting on medications, they stay in bout (8); some have suggested this may be because there is a subtype that is distinct in pathophysiology that may require different treatments (9, 10), and specific analyses in this population of medications we currently use but have 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 of acute therapies, including drugs, procedures, surgeries, and devices, for decreasing cluster headache severity?

STUDY METHODOLOGY

The protocol for our scoping review and NMA was registered a priori on the Open Science Framework (114). In this manuscript, findings have been reported in consideration of the PRISMA extension statement for network meta-analysis (73).

Identification of Studies for Evidence Synthesis

The scoping review was used to identify the 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. A list of the commonly reported outcomes in acute trials was established, and feasibility of NMA for each outcome (based upon network

connectivity of treatments, availability of study data and homogeneity of study populations and methods) was assessed (69).

The population of interest for NMAs aligned with the target population of interest from our scoping review, namely adults with episodic or chronic cluster headache as defined by accepted diagnostic criteria. For each trial, during the scoping review data were gathered regarding patients' demographics and clinical characteristics that could influence treatment response. To assess clinical homogeneity of the available studies, we compared these characteristics across trials where available to inform assessment of the assumptions of homogeneity and similarity necessary for NMA (115). The outcomes we selected were headache response at 15 or 30 minutes as primary endpoints, and adverse events as secondary endpoints.

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 using the related scale from the American Academy of Neurology (AAN) (54). The AAN risk of bias (ROB) tool has been used in prior headache systematic reviews and clinical guidelines, and is well known and accepted by clinicians in the field (15, 66, 116) and this was the reason for its use in our review. However, it has not been validated. This is a four-tiered classification, wherein studies rated Class I are judged to have a low risk of bias; Class II denotes a moderate risk of bias; Class III denotes a moderately high risk of bias; and Class IV denotes a very high risk of bias and includes observational studies. The classification rating is also known as the level of evidence. These criteria evaluated randomization, masking or objective outcome assessment, baseline characteristics being presented or adjusted for, primary outcome definition, exclusion and inclusion criteria, accounting for dropouts and per-protocol analysis. To be class I, trials were required to have all criteria, and with missing criteria they dropped in the classification. 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 (i.e., pharmacological - sumatriptan IM) 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; for example, oxygen the 6L/min and 12L/min are represented by separate nodes, as there is no consensus that these treatments are equivalent (3, 24). The decision to avoid combining of interventions in this fashion was discussed by clinical experts on the team (IM, SC), 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 (117–119).There was a paucity of data in a few of the recommended criteria to identify in the trials, however there were no significant 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%(120)), we proceeded to the next stage. We used R (121) and RStudio (122) to conduct pair-wise meta-analyses (PMAs). The *pma()* function in R was used to perform traditional pairwise meta-analyses. We report odds ratios (OR; along with 95% confidence intervals) of response comparing treatment with placebo/other for categorical outcomes. Random effect models were used

for all meta-analyses. 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 R (121) and RStudio (122) using the BugsNet package for NMA (123–125). For dichotomous outcomes such as headache response at 15min, we used a binomial NMA model with a logit link function. 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 odds ratios and credible intervals looking at all treatments incorporating direct and indirect comparisons. Potential ordering/hierarches of therapies were also evaluated with the Surface Under the Cumulative Ranking curve (SUCRA)(126) 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 (59, 61, 115, 125). As there was no reason to prefer random effects, and in sparse networks like 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 (59, 115, 119). 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 (59, 119). 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 (119).

Evaluation of Meta-Biases

To assess for publication bias, we reviewed trial registries in search of negative trials that were not published. 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) (127).

RESULTS

Study Selection

As described in the accompanying manuscript, we initially reviewed 3,257 abstracts. This was followed by full-text assessments of 482 of these reports. Overall, 44 randomized controlled trials (RCTs) were evaluated as part of the scoping review. We identified 13 acute treatment trials that we used to perform the network meta-analyses (NMAs) featured in this review. Eleven of these trials enrolled mixed populations including patients diagnosed with both episodic and chronic cluster headaches (CHs) (16–20, 23, 24, 26, 82, 83, 86, 90). The two trials that included chronic CH patients only (28, 89) 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 2.1**. Findings from these assessments revealed Class II ROBs (i.e., moderate risk of bias) in nine of the 12 studies. Three of the 12 studies, one in which patients were treated with injectable sumatriptan (16) and two that featured vagal nerve stimulation (VNS) (82, 90) 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 CHs, two studies that featured sphenopalatine ganglion (SPG) stimulation were also scored as Class I (28, 89).

Findings and Comparisons of Acute Therapies

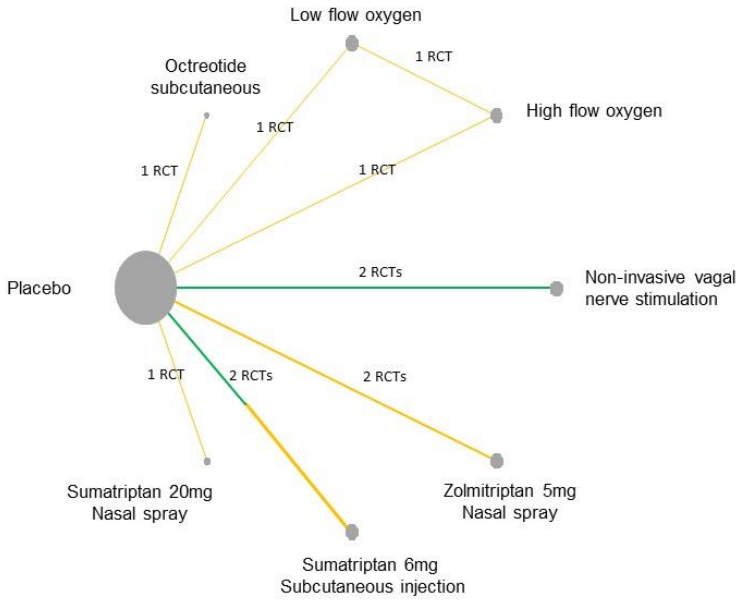
Headache response data at clinically meaningful time points (i.e., at 15 or 30 min, depending on the timing of the treatment effect) were available for 12 trials. Therapeutic

approaches studied in these trials included triptans as injectable and nasal spray (NS) formulations (n=6) (16–20, 85), oxygen at high (≥12 L/min) or low flow (>5 L/min and <12 L/min; n=3) (23, 24, 83), lidocaine (n=1) (26), octreotide (n=1) (86) and non-invasive VNS (nVNS; n=2) (82, 90). One trial was open-label (85) and included two active treatment arms and a placebo group. This latter study was excluded from primary analyses 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 was shown in **Figure 3.1**. The network included eight interventions studied in 11 trials involving 1,395 episodes of CHs with a total of 28 possible pairwise comparisons.

Outcome 1: Acute Headache Responses

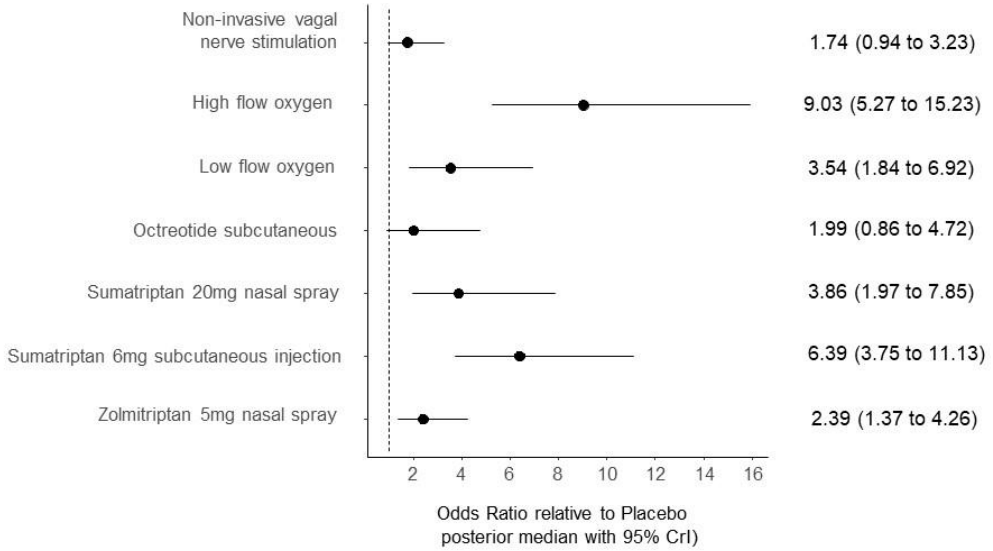
Characteristics of the studies used to formulate the evidence network were described in the accompanying scoping review. The findings presented in the forest plot in Figure 3.2 summarized the treatment effects resulting from active interventions *versus* placebo, while the findings presented in the league table in Figure 3.3 compared the treatment effects attributed to each of these therapies to one another. Figure 3.4 presents a bar plot of the surface under the cumulative ranking curves (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 (deviance information criterion [DIC]=37.14 *vs.* 39.03 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 2.1.

Figure 3.1 Network diagram of responses to treatments for acute CHs at 15 – 30 min



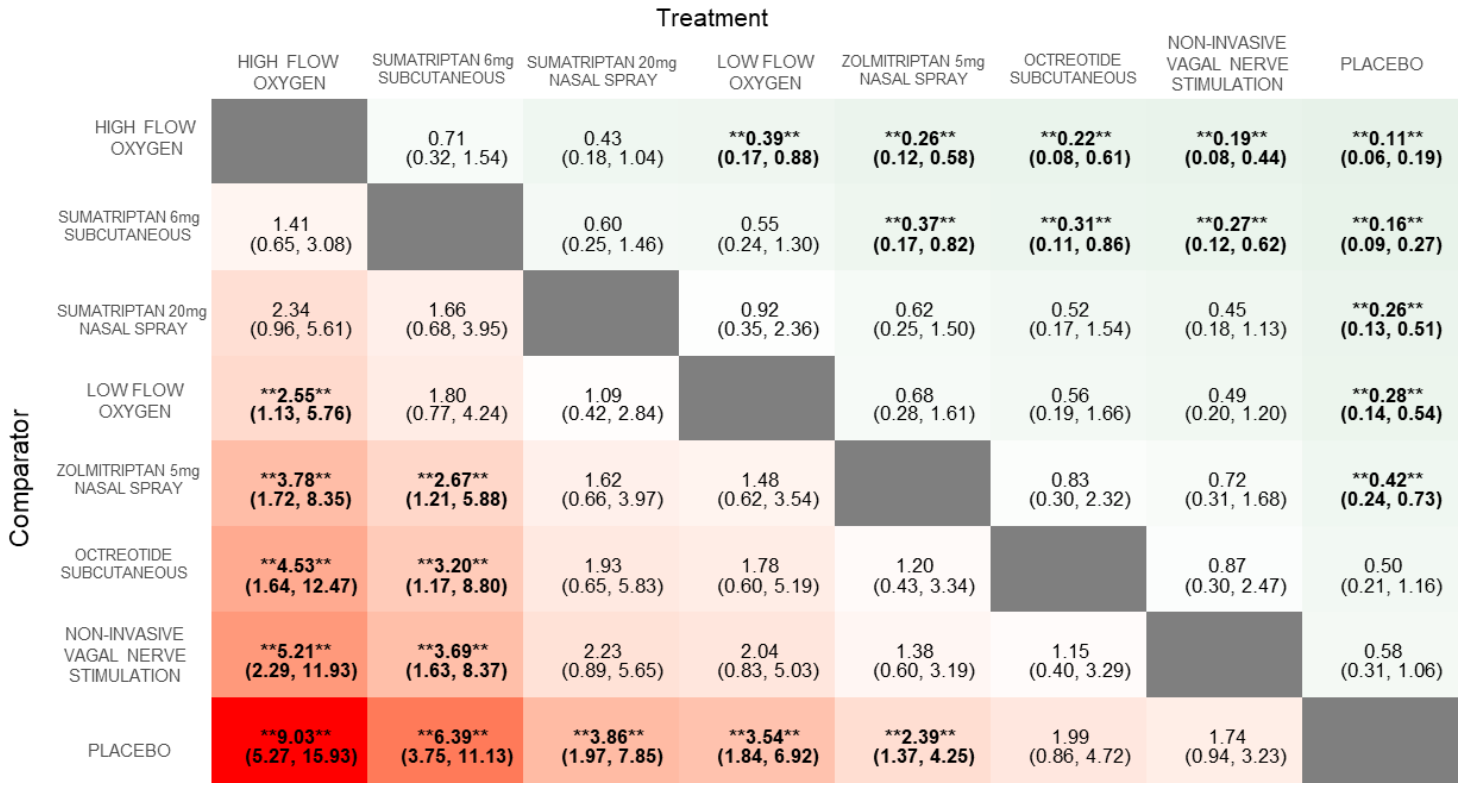
A network diagram for headache responses at 15-30 min is shown. Nodes were sized proportionately to reflect the number of attacks associated with each intervention. The lines connecting the interventions had widths that reflected the number of RCTs per comparison. The colors of the individual lines reflected the ROB assessments of each study as per the American Academy of Neurology (AAN), with Class I in green and Class II in yellow. Overall, eight interventions were compared from a total of 11 studies (n=1,395 CH events).

Figure 3.2 Odds ratios of treatment effects leading to headache responses at 15 and 30 min *versus* placebo



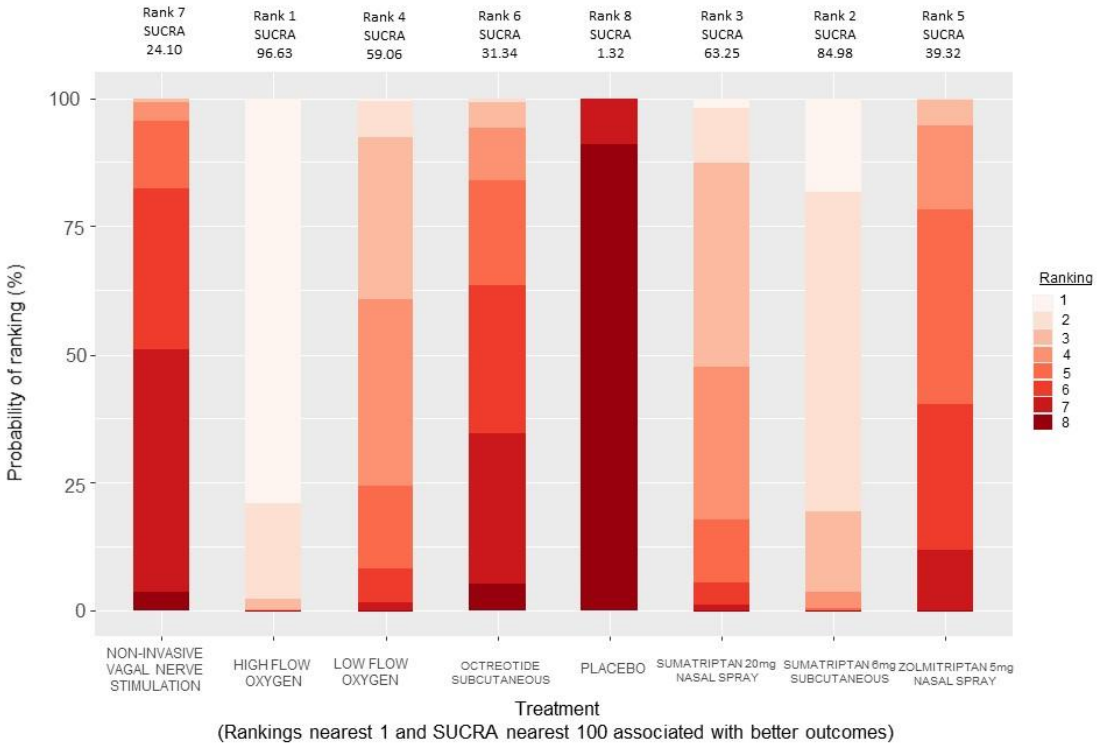
Treatment effects based on the NMA are shown. Values >1 favor active treatment compared to placebo.

Figure 3.3 Treatment effects and headache responses at 15 - 30 min



Odds ratios (ORs) and credible intervals (CrIs) for acute headache responses are presented; ** denotes statistically significant results. Below the diagonal, OR values > 1 favor the treatment in the column header.

Figure 3.4 Probability rankings of acute therapies and headache responses at 15 and 30 min



The probability rankings for each treatment are shown along with their respective SUCRA values. The individual probabilities per treatment associated with each ranking are shown as a function of 100% within the corresponding bars.

We considered headache responses 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). Statistically significant effects were also observed when responses to high flow oxygen were compared to those resulting from 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 4.53, 95% CrI 1.64 to 12.47), and nVNS (OR 5.21, 95% CrI 2.29 to 11.93). Low flow oxygen, which exhibited the fourth-highest probability ranking and SUCRA value, was significantly better than placebo (OR 3.54, 95% CrI 1.84 to 6.96), but was not better than nVNS, octreotide, sumatriptan injectable, sumatriptan NS, or zolmitriptan NS.

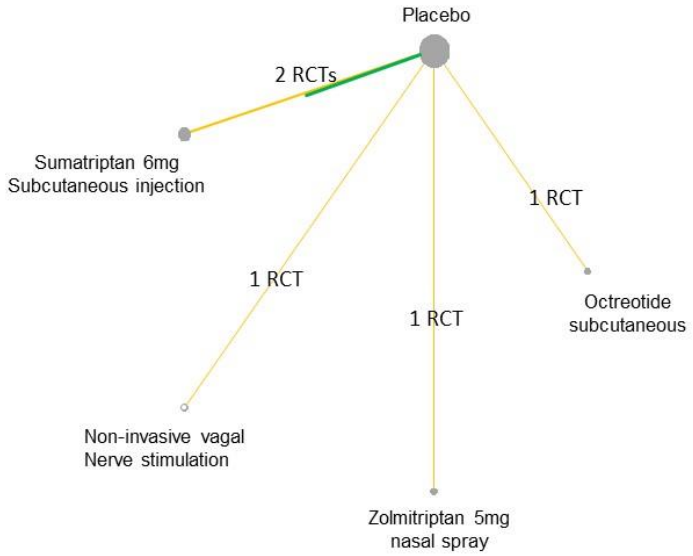
Injectable sumatriptan at doses of 6 mg subcutaneous (SC) was associated with the second-highest probability ranking and SUCRA value after high flow oxygen based on results from two trials in which it was compared to placebo (16, 17). Responses to sumatriptan (6 mg SC) were significantly better than those for nVNS (OR 3.69, 95% CrI 1.63 to 8.37), octreotide (OR 3.20, 95% CrI 1.17 to 8.80), zolmitriptan NS (OR 2.67, 95% CrI 1.21 to 5.88), and placebo (OR 6.39, 95% CrI 3.75 to 11.13).

Sumatriptan (20 mg NS; OR 3.68, 95% CrI 1.97 to 7.86) and zolmitriptan (5 mg NS; OR 2.39, 95% CrI 1.37 to 4.25) were both identified as significantly better than placebo, although no other statistically significant differences were observed involving these therapeutic regimens. The lowest-ranked intervention was placebo, followed by nVNS and octreotide SC. In **Appendix 2.6** we provide the ORs of headache responses to all treatments in the trials evaluated in direct treatment comparisons and pair-wise meta-analyses compared to the ORs based on our NMA. 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 2.6**).

Outcome 2. Acute Therapies and Adverse Events

After the elimination of five studies that reported no adverse events in any groups (17, 20, 23, 24, 83), we included the five remaining studies in an NMA that compared the frequencies of treatment-associated adverse events. The network diagram presented in **Figure 3.5** includes adverse events associated with the use of octreotide, zolmitriptan (5 mg NS), VNS, sumatriptan (6 mg injectable), and placebo. We used an FE model to analyze this outcome, as the difference in fit between the two models was negligible (DIC=19.68 for FE *vs.* 19.94 for RE). There was again no evidence of violations of the consistency based on inspection of measures of model fit (Appendix 2.6).

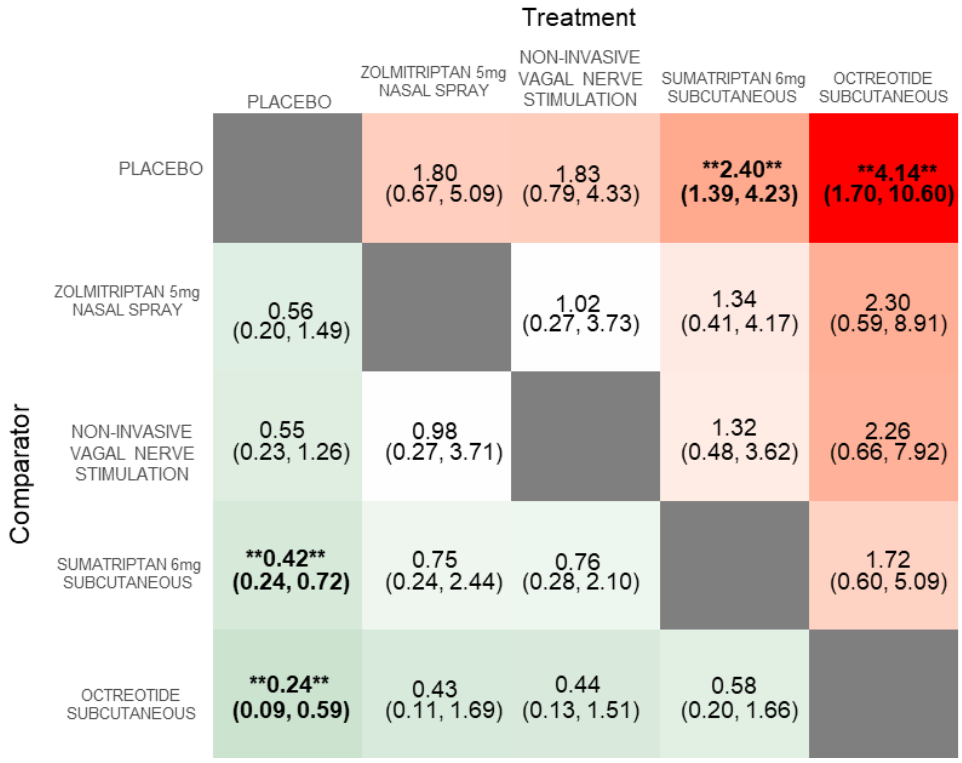
Figure 3.5 Adverse events associated with therapies for acute CHs



Shown is a network diagram for adverse events associated with acute treatments for CHs. Nodes were sized proportionately to reflect the number of events associated with each intervention. The lines connecting the interventions had widths that reflected the number of RCTs per comparison. The line colors reflected the ROB assessment as per AAN 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).

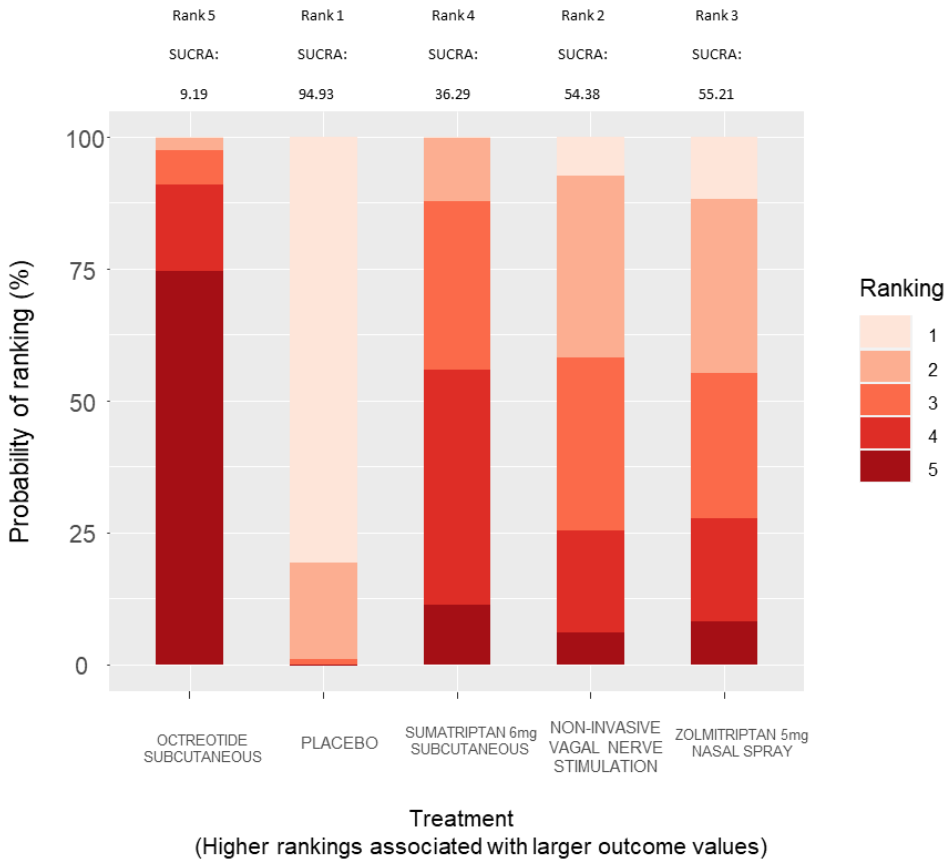
The accompanying league table is shown in **Figure 3.6** and the associated probability bar plot is shown in **Figure 3.7**. Placebo was least likely to be associated with adverse events, while octreotide and sumatriptan were the only treatments associated with significantly higher probabilities of adverse events. Octreotide had an OR of 4.14 (95% CrI 1.70 to 10.60) for adverse events compared to placebo, while sumatriptan injectable had an OR of 2.40 (95% CrI, 1.39 to 4.23) compared to placebo. Our analysis revealed no statistically significant differences in adverse events associated with nVNS or zolmitriptan NS compared to placebo. Overall, there were no reported deaths. Adverse events were mostly minimal and varied by intervention.

Figure 3.6 Treatments, comparators, and adverse events associated with acute CHs



ORs and CrIs for adverse events associated with treatment for acute CHs; **denotes statistically significant results. Below the diagonal, values <1 favor the treatment in the column header.

Figure 3.7 Probability rankings of adverse events associated with therapies for acute CHs



The highest probability ranking for each treatment is shown along with its respective SUCRA value. The individual probabilities associated with each treatment and of each ranking are shown as a function of 100% within its corresponding bar.

Subgroup Analysis: Responses of Patients Diagnosed with Episodic or Chronic CHs to Various Acute Treatments

Episodic CH

We identified three trials that specifically addressed the outcomes of acute treatments, including zolmitriptan 5 mg NS (20), nVNS (82, 90), and placebo for episodic CHs with data that could be used to perform an NMA of headache response (see **Appendix 2.4**) 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-analysis (108) of the two trials featuring nVNS (82, 90). Our findings suggested that nVNS was significantly better than placebo when evaluating

acute responses of episodic CH patients (OR 4.93, 95% CrI 1.89 to 14.11). Subgroup data for episodic CHs were available from one trial featuring treatment with zolmitriptan 5 mg NS (20). Our NMA revealed an OR of 2.10 (95% CrI 0.78 to 5.85) for this subgroup. Overall, nVNS ranked first, with no significant 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 10.05).

Chronic CH

We identified five trials with sufficient data that permitted us to assess treatment effects in patients with chronic CH (20, 28, 82, 89, 90) (see **Appendix 2.5**). In this case, we reported findings from an RE model, as this resulted in a better fit (DIC=114.34 for FE model *vs*. 20.07 for RE model).

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 significant differences. Two of the trials examined (28, 89) featured SPG stimulation that was only used in patients diagnosed with chronic CH. Compared to placebo, SPG stimulation was associated with an OR of 5.82 (95% CrI, 0.30 to 119.50). Zolmitriptan 5 mg NS had the second-highest probability rank and SUCRA value (OR of 2.44 *vs.* placebo, 95% CrI 0.03 to 202.76), although no significant differences were identified. Treatment with nVNS ranked lower than placebo, although this difference was also not statistically significant (OR 0.66, 95% CrI 0.03 to 14.41).

Meta-Biases

To address the issue of potential publication bias, we searched clinical trial registries and identified negative trials for two therapies that have not yet been published. Among these reports, we reviewed the results of negative trials involving treatment of episodic and chronic CHs with fremanezumab, a monoclonal anti-calcitonin gene-related peptide (CGRP) antibody, a drug that was in the same class as galcanezumab (93–95). We also identified a negative and as yet unpublished trial featuring the synthetic somatostatin analog, pasireotide (91). More formal methods, 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 cluster headache. Findings were suggestive that high flow oxygen was as effective as injectable sumatriptan for headache relief at 15 minutes. Furthermore, while comparisons of AEs 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 nor 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 liters per minute is better than low flow oxygen at 7 liters per minute, with both demonstrating more effectiveness for headache relief than placebo. For acute therapy of episodic cluster, we found that VNS may be as effective as zolmitriptan nasal spray, and this generally has fewer side effects. For chronic cluster headache, we found that SPG stimulation may be a viable treatment option, comparable or possibly better than zolmitriptan nasal spray. As has been shown by others (108, 128), VNS does not appear to be an effective treatment option for chronic cluster headache sufferers. Our approach to synthesizing the evidence as well as the inclusion of new trials and interventions represent important additions to the literature for clinicians.

Additionally, we considered the introduction of an open label randomized trial (85) comparing the effect of sumatriptan injectable to nasal spray, but the response was statistically significantly different compared to other trials utilizing the same interventions. There is evidence that the placebo effect is increased if there is the expectation introduced to the participant that the study drug will work (129), and with open label trials this may be more difficult to circumvent. It has been shown in migraine research that placebo effects on acute treatment are more likely with injection than other means of administration (130), and this may also hold true in cluster headache. We did not include this trial in NMAs, as the open label nature of it likely 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 cluster headache, most of the acute trials were crossover trials; patients were given an active treatment and placebo sequentially, and this merits different considerations (131). We felt it was appropriate to use a binomial model for this data as there were few trials (23, 82) where individuals received multiple treatments with the same intervention, and in those trials, it was not most individuals in the trial.

To contextualize our findings with the most recent systematic review and guideline for cluster headache (15, 66), 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. To our knowledge, this is the first review to identify this important clinical finding. This has clinical implications, as patients who fail 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 nasal spray, nVNS, and octreotide. Sumatriptan injectable is more likely to be effective when compared to zolmitriptan nasal spray, 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 novel and important findings worthy of additional study.

NMAs can play a vital role in establishing the relative benefits and risks of treatment modalities for a disease, though the importance of head-to-head RCTs remains high. In NMAs there can exist confounders such as differing trial characteristics that modify treatment response, and they can’t 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.

CONCLUSION

We showed that high flow oxygen is more efficacious when compared to low flow oxygen for headache relief. From a clinical standpoint, patients who fail low flow oxygen and can tolerate increased flow rates should be tried on high flow oxygen. Additionally, 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. Patients who fail nasal spray triptans should be tried on injectable triptans, as our data suggest that with injection patients have more chances of having a decrease in headache than with nasal spray. For episodic cluster headache nVNS is likely effective, whereas it is not effective in chronic cluster headache patients. In the chronic cluster headache subgroup, it is suggested by our results that SPG stimulation is effective.

Chapter 4
Discussion and Conclusion

Summary of Findings

We performed a scoping review of interventions for acute and preventive treatment for cluster headache as well as NMAs to compare interventions for acute treatment to achieve the overarching objective of this thesis, namely, to characterize evidence of treatment effects associated with different interventions for management of cluster headache, and to synthesize evidence that compares their relative benefits and harms. Since the last systematic review of acute and preventive therapy in 2016(4), which only included RCTs, we identified 9 new studies(24, 25, 52, 53, 55, 93–95, 132). Of these, 4 studies focused on acute headache treatment utilizing vagal nerve stimulation (55), sphenopalatine ganglion stimulation (132) and oxygen (24, 25). There were two studies of preventive interventions that focused on a humanized monoclonal antibody that potently and selectively binds to CGRP (galcanezumab), which has been found to be effective in episodic cluster but ineffective in chronic cluster headache (52, 53). We also identified 3 unpublished trials that reported negative results of fremanezumab (93–95) in episodic and chronic cluster.

Clinical Implications of this Work

In our scoping review, we categorized the currently available evidence for management of cluster headache, establishing a repository and mapping of published studies. NMAs were also performed to compare interventions for acute treatment of cluster headache, while such analyses were not undertaken for preventive treatments due to concerns over the validity of findings. Our review adds the following new findings to the clinical literature.

For acute treatment of cluster headache:

1) Higher flow oxygen 12L/min and above was found to be more likely to be effective than low flow oxygen 7L/min to 12L/min. We urge clinicians to consider a two-step process of trying oxygen at low flow, and if no response is observed, having the

patient increase the flow may be worthwhile, as there may be a dose response relationship.

2) In the triptan class, injectable sumatriptan is the most likely to be effective, with nasal spray formulations being less likely effective. We recommend that when nasal spray triptans fail, then injectable sumatriptan should be tried.
3) nVNS in episodic cluster headache was shown to be effective and should be considered, as there tends to be a minimal side effect profile.
4) SPG stimulation is effective in chronic cluster headache, but it is not available as the company who manufactures the device has presently gone out of business.
5) Somatostatin and analogue octreotide have some evidence of efficacy as an infusion but do have notable side effects.
6) Lidocaine and cocaine nasal application also have some evidence of efficacy, but the lidocaine is difficult to administer, and cocaine is a controlled substance with a high risk for addiction.

For preventive treatment of cluster headache:

1) Greater occipital nerve blocks using steroid/local anesthetic have two RCTs(34, 35) establishing their effectiveness. These should be recommended as first line preventive therapy.
2) Galcanezumab is effective in episodic cluster headache(52), but not in chronic cluster headache(53). This may not be a class effect, as fremanezumab failed to show benefit. However, in the fremanezumab trials, the dose used was lower equivalent dosing than the galcanezumab dose.
3) Verapamil has evidence for efficacy in episodic cluster (12) and has been recommended as first line preventive treatment (3)

   Verapamil is also equivalent when compared to lithium in chronic cluster headache(38), Change in headache index from baseline was statistically significant in both therapies.
4) Oral prednisone (31) can be considered as there is some evidence on its efficacy from one RCT (31), although this trial has a higher risk of bias overall and reporting issues.

5) We recommend that nVNS can be used in chronic cluster headache for prevention as there is evidence from an RCT (6).
6) We note that in certain select patients, especially if indicated clinically for other reasons, warfarin can be used in chronic cluster headache (40) for prevention as there is evidence from an RCT.

For preventive treatments, an older medication like verapamil is generally effective, but likely has more side effects than a newer medication like galcanezumab. A future direction of research would be a head-to-head trial of these interventions, for considerations of effectiveness and safety. Additionally, given the differential cost, we could consider cost-effectiveness analysis to better determine the place of these medications in the armamentarium of cluster headache treatment (which should be first line).

Our analysis primarily considered interventions in terms of effectiveness and safety. It is important for future work to consider the cost-effectiveness of interventions. For example, oxygen is generally more accessible than sumatriptan in terms of cost, but in the USA is not covered by Medicare. It may be important to highlight in an analysis why it may be advantageous to cover especially if performing on par with sumatriptan.

Future Directions in Cluster Headache

There are several challenges that exist when conducting RCTs and observational studies in patients with cluster headache. Patients are unlikely to accept the risk of being randomized to a placebo intervention, as the pain of cluster attacks is amongst the most severe acute pain conditions known. It is also difficult to recruit patients given the rarity of the condition and the small population size in the community, and thus trials often do not reach their targeted sample size (42). Both randomized trials and observational studies must carefully identify important attributes that may modify and confound treatment effects and should also utilize standard outcomes that are easily compared between trials. The latter is, in fact, a recommendation for good research practice as part of the COMET initiative (112), and the core outcome set (COS) of cluster headache (78) may be considered for further revision. In our study, we identified multiple issues to explore further

concerning trial design in cluster headache that are discussed next. Collectively, these considerations can serve to improve future trials as well as to improve the ability for robust evidence syntheses by researchers seeking to undertake systematic reviews.

Prior to the trial, the study investigators may want to consider a pilot study to delimit the timeline of treatment effect for both preventive and acute trials of cluster headache. For example, for preventive trials some treatments such as greater occipital nerve steroid/local anesthetic blocks have a treatment effect in 72 hours(34, 35), whereas the effect of galcanezumab in episodic cluster headache is only apparent in week 2(52). Similarly, for acute therapy trials, the treatment effect can be variable with the onset of effect of injectable triptans being quicker than nasal spray(85). A pilot study will give a clearer indication about when to expect a treatment response, how large this response may be so that sample size calculations are informed, and also how long it may take to recruit that large a study population.

Trials enrolling episodic cluster patients who have already been experiencing the current cluster attack for longer than 1-2 weeks may incur spontaneous remission in both treatment and placebo groups that will increase response rates, as attacks remit on average at 6 – 10 weeks(110, 111, 133) or earlier. There is evidence of this amongst the studies we have looked at in this thesis. The placebo response was near zero in those studies that restricted trial entry to patients who were within 1 week of the onset of an active cluster bout(34, 39, 41), and was larger in studies that allowed trial entry later into a bout(36, 51, 52). In one preventive trial, the issue of spontaneous remission in the placebo group is well identified and characterized, and they propose a Poisson model for analysis of data to no longer account for placebo patients that have likely had spontaneous remission(51). This may not be necessary if the trial includes patients at the beginning of an active bout, as the rate of active remission is close to nil, and a study may need a smaller sample size as had the trials that only allowed patients <1 week of an active bout and used very small sample sizes and still demonstrated a treatment effect (34, 39, 41).

To facilitate treatment comparisons, the frequency of attacks per week should be the main efficacy parameter in preventive trials as outlined by clinical guidelines(78). However, in addition, it is paramount that studies should consider the possibilities of natural remission and carefully monitor duration of present bout at trial enrollment and report information regarding this patient characteristic. Trials should report the frequency of attacks/week for treatment and placebo, the mean difference in this variable from baseline period to end of study, and the standard deviations of these measures, along with the 50% responder rate. These measures should be reported for each week in the trial.

In reviewing recent prophylactic trials that have been well conducted and were positive on their primary outcome, we believe that there should be different trial design requirements for episodic and chronic cluster. As noted earlier, episodic cluster patients are likely to reach the end of a bout in 6-10 weeks(110, 111, 133), and thus the measurements should be made at a time when active treatment response would easily differentiate from natural remission of disease. Looking at trials that included this measure in all weeks of the trials, (39, 41, 52), having the measurement of headache frequency between the baseline week and the second week of treatment seems to be the most sensitive measure. However, the onset of efficacy may be earlier in some treatments like occipital nerve blocks (34, 35). If the onset of study medication effect is thought to be more rapid, within 1 week, this would arguably still be reflected by the second week data and be distinguishable from placebo; we see this for one of the occipital nerve block studies which also reports the second week headache frequency(35). After the third week of trial entry, including a week of baseline and two weeks of active disease prior to study entry as most recruited patients are in this category, we are looking at six weeks of active disease, any measurement may be quite difficult to distinguish from a natural remission of the disease, which occurs possibly as early as 6 weeks(110, 111, 133).

For chronic cluster trials, longer baseline periods are feasible, as there is not likely to be remission, and additionally the measurement of treatment effect can be (and arguably should be) done over a longer time period, as the neural mechanism of chronification of

pain may need to be “turned” off(134), which may require a longer period of time. Trials in chronic cluster headache (39, 40, 53) generally used a longer baseline period of 2-4 weeks, and evaluated patients over the course of 8-12 weeks. Our recommendations would be to have a baseline period of at least two weeks and to evaluate headache frequency per week in patients during the 8-12 weeks of treatment. Within this timeline it is likely that treatments would show an effect if present, and if this effect was shown in the trial this would likely indicate the medication has a clinically meaningful and long lasting reduction.

As cluster headache is a somewhat rare disease with a prevalence at 1:1,000 (135), it is challenging to recruit study participants (24, 42). To overcome this issue, we recommend the development of larger networks of headache researchers to increase the feasibility of patient recruitment. The creation of regional cluster clinics may increase the population size for these trials, enhance the capacity to plan multi-center investigations, and also lead to better outcomes for a larger number of patients. Additionally, as randomized controlled trials of preventive therapies are difficult to recruit for because there is a requirement for placebo control, for non-regulatory trials investigators can consider non-inferiority designs as two therapies can be compared head-to-head, rather than subjecting some participants to placebo for a very painful disorder. The margins for these trials need to be established and the treatment of patients with known therapies such as verapamil can be compared to other therapies that show promise, but have thus far not had a positive trial such as candesartan (51).

Lastly, the methodology for the observational studies that were identified through our scoping review was highly variable. There were few two-armed studies identified that sought to compare outcomes between different management strategies. Furthermore, the designs of these studies were typically retrospective case series looking at either two treatments or a treatment and standard of care. These trials did not attempt to identify or correct for variables that may have affected treatment response. In the future, studies should use more advanced statistical approaches such as propensity score methods (136, 137), and multiple regression analysis (138). These methods can account for known

confounders, where RCTs are infeasible (138, 138–142); they allow observational studies to approximate the distribution of known baseline variables being similar between treated and untreated subjects, however it is not exactly equivalent to an RCT as it does not correct for unmeasured confounding factors (137).

Notably for new studies in cluster headache prevention utilizing CGRP monoclonal antibodies, dosing may have played an effect in episodic cluster, as the single galcanezumab trial used much higher doses than in migraine(52), and for all CGRP therapies, higher doses than in migraine may require future study. Additionally, it is plausible that CGRP pathology is only relevant for some of the cluster headache patients (113), as CGRP infusion only triggers cluster headaches in half of these patients. It may be possible that this group can be pre-selected by a biomarker for future trials.

There are some observational data (96) that long-term therapy in cluster headache with the same medication may not be effective, and some suggest that chronic cluster is due to increasing resistance to treatments as the disease progresses(8). In the future, observational studies or pragmatic randomized trials may be needed to explore if repeating treatment in subsequent bouts over time decreases likelihood of response to prevention. The importance of treatment cycling for patients in between bouts of cluster headache is currently unclear.

In clinical practice, headache centers are performing invasive procedures and inserting devices for management of treatment refractory disabled chronic cluster headache patients utilizing injections of onabotulinumtoxin A to the SPG(143), DBS to hypothalamus(144), and occipital nerve stimulation (145–147). Data from the real-world utilization of these various therapies should be carefully compared with standard of care treatment for refractory patients that are not currently getting any further invasive therapy to see if there is a likely benefit.

Conclusions

In this thesis, a scoping review of the literature summarizing a repository of evidence for acute and preventive treatments for cluster headache was completed that is based on evidence from randomized controlled trials as well as observational studies. Methodological challenges with observational studies were discussed. Based on a feasibility assessment conducted in the context of the scoping review, we subsequently undertook network meta-analyses and ranked acute treatments in terms of efficacy, safety and looking and episodic and chronic subgroup data, where available. We did not undertake a network meta-analysis in preventive therapy for episodic cluster headache as there were felt to be threats to the validity of such analysis. In light of the limitations observed in the existing studies, we propose clinical considerations and directions for future research in cluster headache.

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APPENDIX 1

Chapter 2 Appendices

Chapter 2 Appendices:

- **Appendix 1.1:** Literature Search Strategies
- **Appendix 1.2:** Overview of Study Inclusion and Exclusion Criteria
- **Appendix 1.3:** Bar Plots of Possible Effect Modifiers for Acute and Preventive Treatment
- **Appendix 1.4:** Completed PRISMA Checklist for Scoping Reviews

APPENDIX 1.1: SEARCH STRATEGY

Database: Embase Classic+Embase <1947 to 2019 August 05>, Ovid MEDLINE(R) ALL <1946 to August 05, 2019>, EBM Reviews - Cochrane Central Register of Controlled Trials <June 2019>

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1 exp Cluster Headache/ (8369)
2 ((episod* or cluster) adj2 (headache* or head ache*)).tw. (10387)
3 (episod* headache* or cluster headache*).kw. (1833)
4 trigeminal autonomic cephalalgia*.mp. or exp Trigeminal Autonomic Cephalalgias/ (9559)
5 or/1-4 (13754)
6 (randomized controlled trial or controlled clinical trial).pt. (1135499)
7 randomized controlled trials/ or random allocation/ or double-blind method/ or single-blind method/ (954017)
8 clinical trial.pt. (796833)
9 exp "Clinical Trials as Topic"/ or placebos/ or research design/ (2678825)
10 (clinic* adj25 trial*).mp. (3326093)
11 ((singl* or doubl* or trebl*) adj (mask* or blind*)).mp. (865701)
12 (placebo* or random*).mp. (4265580)
13 (latin adj square).mp. (10608)
14 comparative study/ or exp evaluation studies/ or follow-up studies/ or prospective studies/ or cross-over studies/ (5262698)
15 (control* or prospective* or volunteer*).mp. (17678196)
16 observational study/ (239689)
17 exp Cohort Studies/ (2518267)
18 (retrospective* or cohort*).tw. (2989318)
19 follow up.tw. (2518149)
20 or/6-19 (25609772)
21 5 and 20 (6100)
22 exp animals/ not humans/ (18614680)
23 21 not 22 (4258)

24 23 use medall (1803)
25 exp cluster headache/ (8369)
26 (cluster adj2 (headache* or head ache*)).tw. (7902)
27 exp trigeminal autonomic cephalalgia/ (9330)
28 Trigeminal Autonomic Cephalalgia*.tw. (747)
29 25 or 26 or 27 or 28 (11143)
30 random*.tw. or placebo*.mp. or double-blind*.tw. (3852260)
31 (clinical adj5 trial*).tw. (1028090)
32 latin square.tw. (10537)
33 *comparative study/ (17336)
34 *evaluation study/ (850)
35 *follow up/ or *''evaluation and follow up''/ (42764)
36 *prospective study/ (21090)
37 *crossover procedure/ (1332)
38 (control* or prospective* or volunteer*).tw. (10843680)
39 open study/ (36136)
40 open label.tw. (161457)
41 clinical trial/ or controlled clinical trial/ or randomized controlled trial/ (2106351)
42 clinical study/ (172129)
43 *observational study/ (9084)
44 *cohort analysis/ (26251)
45 *retrospective study/ (19428)
46 (Cohort* or retrospective* or follow up).tw. (4849543)
47 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 (16701111)
48 29 and 47 (3766)
49 (exp animal/ or nonhuman/) not exp human/ (11565034)
50 48 not 49 (3726)
51 (conference abstract or conference or conference review).pt. (4298343)
52 50 and 51 (662)

53 50 not 52 (3064)

54 52 use emczd (651)

55 53 use emczd (1744)

56 exp Cluster Headache/ (8369)

57 ((episod* or cluster) adj2 (headache* or head ache*)).tw. (10387)

58 (episod* headache* or cluster headache*).kw. (1833)

59 trigeminal autonomic cephalalgia*.mp. or exp Trigeminal Autonomic Cephalalgias/ (9559)

60 or/56-59 (13754)

61 conference abstract.pt. (3524305)

62 conference*.so. (584901)

63 "Journal: Conference Abstract".pt. (134496)

64 61 or 62 or 63 (3730157)

65 60 and 64 (1630)

66 60 not 65 (12124)

67 65 use cctr (112)

68 66 use cctr (387)

69 24 or 55 or 68 (3934)

70 remove duplicates from 69 (2721)

71 70 use medall (1782) Medline

72 70 use emczd (762) Embase

73 70 use cctr (177) Cochrane

74 52 or 67 (763)

Conference Abstracts

75 remove duplicates from 74 (699)

76 75 use emczd (641) Embase

77 75 use cctr (58) Cochrane

APPENDIX 1.2: OVERVIEW OF STUDY EXCLUSION CRITERIA

Study			Exclusion Criteria Across Studies				
	Prior treatments for cluster allowed?	History of migraines or other headaches?	History of vascular disease excluded?	History of drug or alcohol abuse excluded?	Abnormal laboratory or ECG studies excluded?	Pregnant women excluded?	Other noted criteria
Ambrosini 2005	NA	NA	NA	NA	NA	NA	NA
Andersson 1986	NA	NA	NA	NA	NA	NA	NA
Anthony 1978	NA	NA	NA	NA	NA	NA	NA
Bahra 2000	NA	NA	Yes	Yes	Yes	Yes	methysergide, methylergovine, AIDS, hypersensitivity to triptan and exposure to investigational drug in prior 30 days
Bougea 2016	NA	NA	NA	NA	NA	NA	NA
Bussone 1990	No	NA	Yes	NA	Yes	Yes	Not taking oral contraceptives
Christiansen 2000	NA	Yes	NA	Yes	NA	NA	NA
Cittadini 2006	No	NA	Yes	NA	NA	NA	Ear, nose or throat issue that may preclude use of nasal spray
Cohen 2009	NA	Yes	NA	NA	NA	Yes	Could not tolerate mask, had COPD or had tried oxygen before
Costa 2000	NA	NA	NA	NA	NA	NA	NA
Di Sabato 1993	No	NA	Yes	NA	Yes	NA	NA
Dirkx 2018	NA	Yes	NA	NA	NA	Yes	Could not tolerate mask, had COPD or had tried oxygen before, not able to provide consent

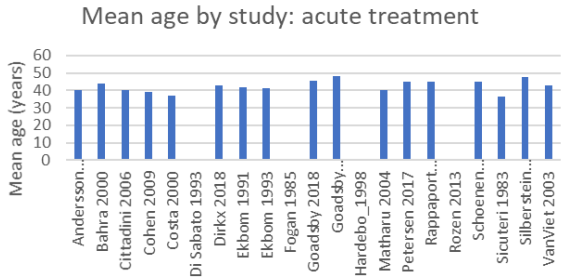
Study			Exclusion Criteria Across Studies				
	Prior treatments for cluster allowed?	History of migraines or other headaches?	History of vascular disease excluded?	History of drug or alcohol abuse excluded?	Abnormal laboratory or ECG studies excluded?	Pregnant women excluded?	Other noted criteria
Ekbom 1991	NA	NA	Yes	Yes	Yes	Yes	Epilepsy and psychiatric issues
Ekbom 1993	NA	NA	Yes	Yes	Yes	Yes	Epilepsy and psychiatric issues
El Amrani 2002	No	NA	NA	Yes	Yes	NA	Psychiatric disorder
Evers 1998	NA	NA	NA	NA	NA	NA	NA
Fogan 1985	NA	NA	NA	NA	NA	NA	NA
Fontaine 2010	NA	NA	NA	Yes	NA	NA	No contra-indication to surgery or anesthesia
Gaul 2016	Ok if change >1mo ago	NA	Yes	NA	NA	NA	Implanted electrical device, surgery at vagal nerve, syncope or epilepsy, metallic hardware
Goadsby 2018	NA	NA	Yes	NA	NA	NA	Implanted electrical device, surgery at vagal nerve, syncope or epilepsy, metallic hardware
Goadsby 2019_2	No	No	NA	NA	NA	NA	NA
Goadsby 2019	NA	No	NA	NA	NA	NA	Clinical trial in last year, MAB use or CGRP use, ischemic migraine variants
Hardebo_1998	NA	NA	NA	Yes	NA	Yes	NA
Hakim 2011	NA	NA	Yes	NA	NA	Yes	Increased risk of bleeding factors
Jammes 1975	NA	NA	NA	NA	NA	NA	NA

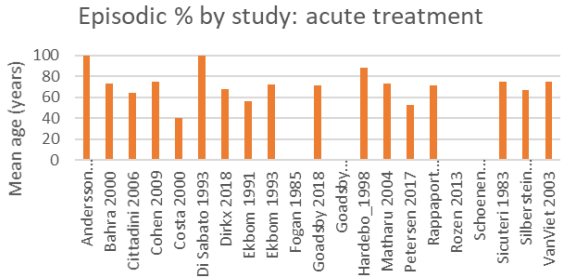
Study			Exclusion Criteria Across Studies				
	Prior treatments for cluster allowed?	History of migraines or other headaches?	History of vascular disease excluded?	History of drug or alcohol abuse excluded?	Abnormal laboratory or ECG studies excluded?	Pregnant women excluded?	Other noted criteria
Leone 1996	NA	NA	NA	Yes	Yes	NA	psychiatric disease or taking antidepressants or neuroleptics
Leone 2000	NA	NA	Yes	Yes	Yes	NO	Adynamic ileus, bradycardia, hypotension, psychiatric history
Leroux 2011	NA	Yes	NA	NA	NA	NA	Contra-indication to cortivazol or verapamil, anticoagulant use or bleeding history
Marks 1993	NA	NA	NA	NA	NA	NA	NA
Matharu 2004	Yes	Yes	NA	NA	NA	Yes	Diabetes or known cholelithiasis
Monstad 1995	Yes	NA	Yes	Yes	Yes	Yes	Severe psychiatric disease
Nilsson 2002	Yes	NA	Yes	NA	NA	Yes	Ear disease
Oakes 2019	NA	NA	NA	NA	Yes	Yes	Clinical trial over last month, CGRP use, indomethacin use, psychiatric disease
Pageler 2010	Yes	NA	NA	NA	NA	NA	NA
Petersen 2017	Yes	NA	NA	Yes	NA	Yes	COPD
Rappaport 2007	NA	NA	Yes	NA	NA	Yes	Major depression or medical illness
Rozen 2013	NA	NA	NA	NA	NA	NA	COPD, asthma, syncope with hyperventilation
Russel 1979	NA	NA	NA	NA	NA	NA	NA

Study			Exclusion Criteria Across Studies				
	Prior treatments for cluster allowed?	History of migraines or other headaches?	History of vascular disease excluded?	History of drug or alcohol abuse excluded?	Abnormal laboratory or ECG studies excluded?	Pregnant women excluded?	Other noted criteria
Saper 2002	NA	NA	NA	Yes	Yes	Yes	NA
Schoenen 2013	No change 1mo	yes	NA	NA	NA	NA	Surgery, botox, radiofrequency ablation or radiation to face
Sicuteri 1983	NA	NA	NA	NA	NA	NA	NA
Silberstein 2016	NA	NA	Yes	NA	NA	NA	Vascular neck surgery or electrical implant
Steiner 1997	NA	NA	NA	NA	NA	NA	Lithium contraindicated
Trovnik 2013	In 1 month prior	NA	NA	Yes	Yes	Yes	Use of anti-depressant or neuroleptic.
VanViet 2003	Yes	NA	Yes	NA	NA	Yes	Ear, nose or throat disease, serious adverse event with triptan in past.

APPENDIX 1.3: BAR PLOTS OF POSSIBLE EFFECT MODIFIERS FOR ACUTE AND PREVENTIVE TREATMENT

Figure A1.1 Bar plots for possible effect modifiers in trials of acute therapy





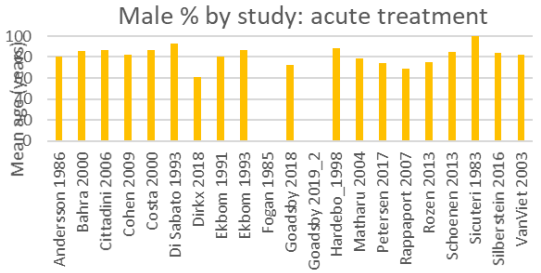


Figure A1.2 Bar plot placebo response in trials of acute therapy for headache relief

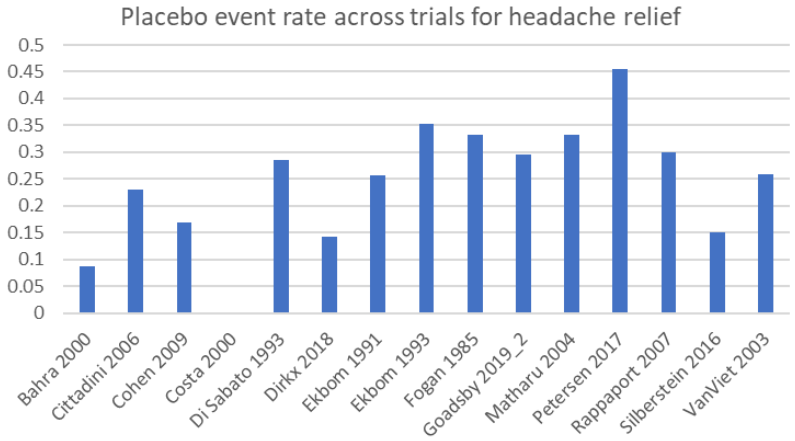


Figure A1.3 Bar plots for possible effect modifiers in trials of preventive therapy

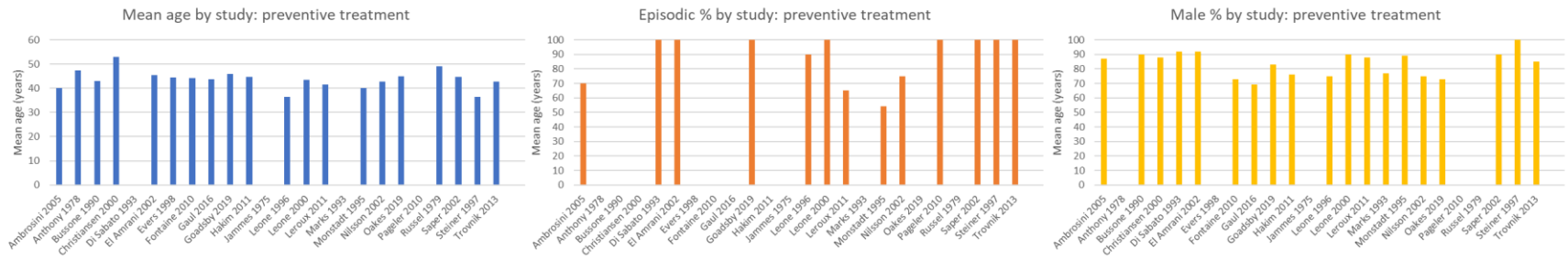
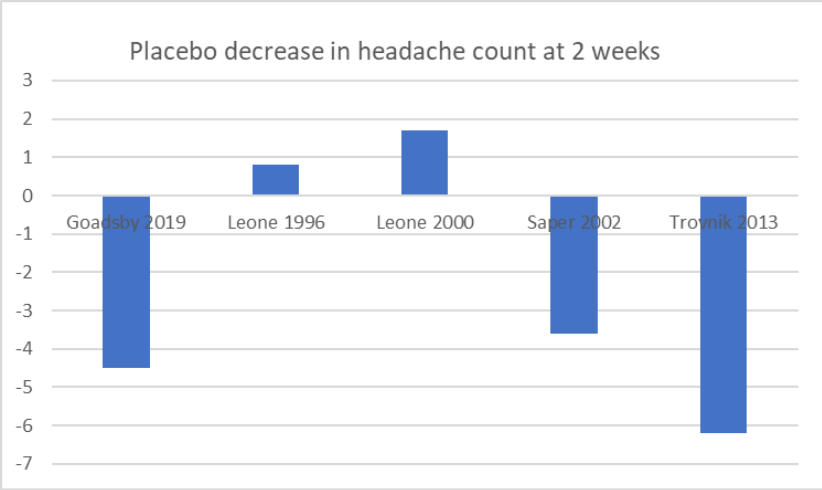
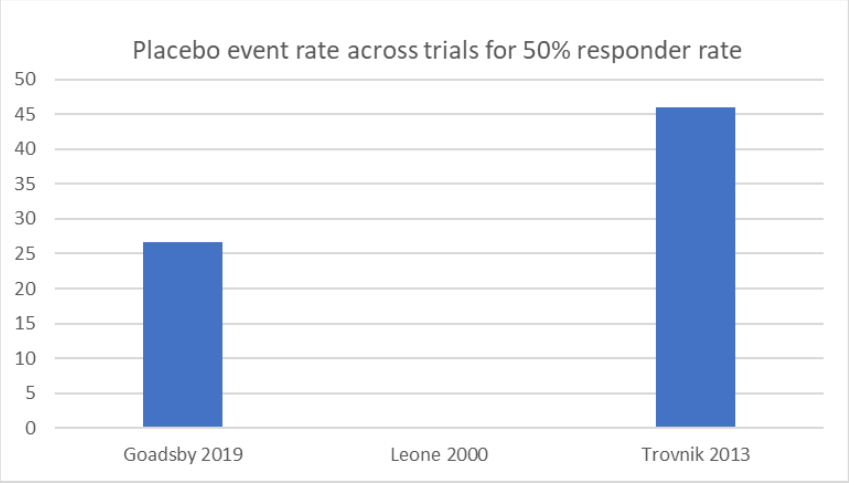


Figure A1.4 Bar plots placebo response in trials of preventive therapy for headache relief





APPENDIX 1.4: PREFERRED REPORTING ITEMS FOR SYSTEMATIC REVIEWS AND META-ANALYSES EXTENSION FOR SCOPING REVIEWS (PRISMA-SCR) CHECKLIST

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
TITLE			
Title	1	Identify the report as a scoping review.	20
ABSTRACT			
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	21
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	23
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	24
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	24
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	25
Information sources*	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	27
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	Appendix 1.1
Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	28
Data charting process‡	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	28
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	26 and 30
Critical appraisal of individual sources of evidence§	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	No
Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	29
RESULTS			
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	31
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	32-33
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	No
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	31-33

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	57
DISCUSSION			
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	61
Limitations	20	Discuss the limitations of the scoping review process.	62
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	64
FUNDING			
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	20

JBI = Joanna Briggs Institute; PRISMA-ScR = Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews.

* Where *sources of evidence* (see second footnote) are compiled from, such as bibliographic databases, social media platforms, and Web sites.

† A more inclusive/heterogeneous term used to account for the different types of evidence or data sources (e.g., quantitative and/or qualitative research, expert opinion, and policy documents) that may be eligible in a scoping review as opposed to only studies. This is not to be confused with *information sources* (see first footnote).

‡ The frameworks by Arksey and O'Malley (6) and Levac and colleagues (7) and the JBI guidance (4, 5) refer to the process of data extraction in a scoping review as data charting.

§ The process of systematically examining research evidence to assess its validity, results, and relevance before using it to inform a decision. This term is used for items 12 and 19 instead of "risk of bias" (which is more applicable to systematic reviews of interventions) to include and acknowledge the various sources of evidence that may be used in a scoping review (e.g., quantitative and/or qualitative research, expert opinion, and policy document).

From: Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMAScR): Checklist and Explanation. Ann Intern Med. 2018;169:467–473. doi: 10.7326/M18-0850.

APPENDIX 2

Chapter 3 Appendices

Chapter 3 Appendices:

- **Appendix 2.1:** Risk of Bias Appraisals
- **Appendix 2.2:** Findings from Random Effects Model for Headache Response at 15/30min
- **Appendix 2.3:** Findings from Random Effects Model for Adverse Events
- **Appendix 2.4:** Findings from Fixed Effects and Random Effects Model for Headache Response at 15/30min in Episodic Cluster
- **Appendix 2.5:** Findings from Fixed Effects and Random Effects Model for Headache Response at 15/30min in Chronic Cluster
- **Appendix 2.6:** NMA Model Fit Assessment Information
- **Appendix 2.7:** PRISMA NMA Checklist

APPENDIX 2.1: RISK OF BIAS APPRAISALS

Table A2.1 AAN risk of bias sample table

Study ID#:

Reviewed by:

Final Class:

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 (ie. 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 A2.2a 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 6mg SC	Placebo	IHS	56% ECH	3.88:1	Class II	Drop out at 20%; did not talk about allocation concealment
Ekbom 1993	Sumatriptan 6mg SC	Placebo	IHS	72% ECH	6.44:1	Class I	No downgrades applied
Cittadini 2006	Zolmitriptan 5mg 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.
Rapopport 2007	Zolmitriptan 5mg NS	Placebo	ICHD2	71%ECH	2.21:1	Class II	Crossover study, did not present baseline treatment order groups; did not talk about allocation concealment.
Fogan 1985	O2 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	O2 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	O2 Low	O2 High	ICHD2	67% ECH	1.57:1	Class II	Crossover, and no treatment order groups baseline presented
Van Viet 2003	Sumatriptan 20mg 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	ICHD2	67% ECH	5.25:1	Class I	No downgrades applied
Goadsby 2019	nVNS	Placebo	ICHD3B	71% ECH	2.52:1	Class I	No downgrades applied
Goadsby 2019_2	SPG	Placebo	ICHD3B	CCH	na	Class I	No downgrades applied
Schoenen 2013	SPG	Placebo	ICHD2	CCH	5:25:1	Class 1	No downgrades applied

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

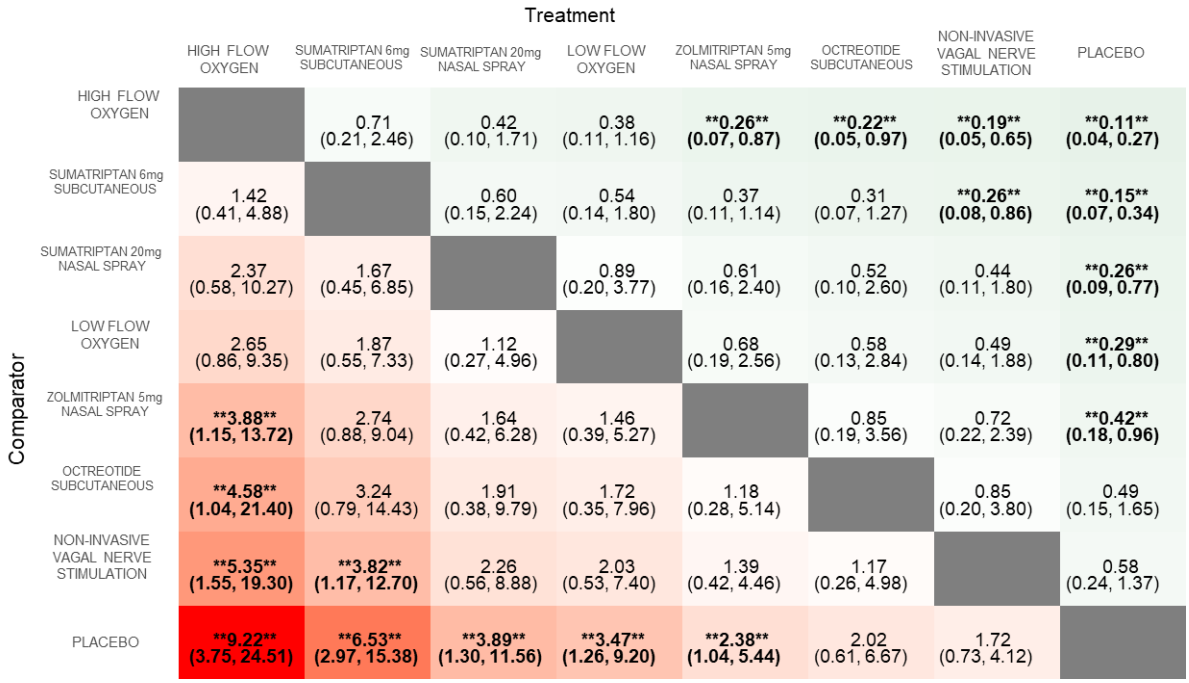
Table A2.2b Baseline demographics of trials not included in the NMA for preventive therapies

Preventive Treatment	Treatment	Comparator	Diagnostic criteria	ECH/CCH	M/F	AAN ROB	Reasons for downgrade
Goadsby 2019	galcanezumab	Placebo	ICHD3B	ECH only	4.89:1	Class I	No downgrades applied
Leone 1996	melatonin	Placebo	IHS	90% ECH	3:01	Class II	Did not discuss how they did randomization nor allocation concealment
Leone 2000	verapamil	Placebo	IHS	ECH only	9:01	Class II	Did not discuss how they did randomization nor allocation concealment
Leroux 2011	cortivazol	Placebo	ICHD2	65% ECH	7.06:1	Class I	No downgrades applied
Saper 2002	civamide nasal drop	Placebo	IHS	ECH	9:01	Class II	Did not discuss allocation concealment
Trovnik 2013	candesartan	Placebo	ICHD2	ECH	5.67:1	Class II	Drop out over 20% and did not talk about allocation concealment

Abbreviations: ECH, episodic cluster headache; IHS, International Headache Society; ICHD, International Classification of Headache Disorders

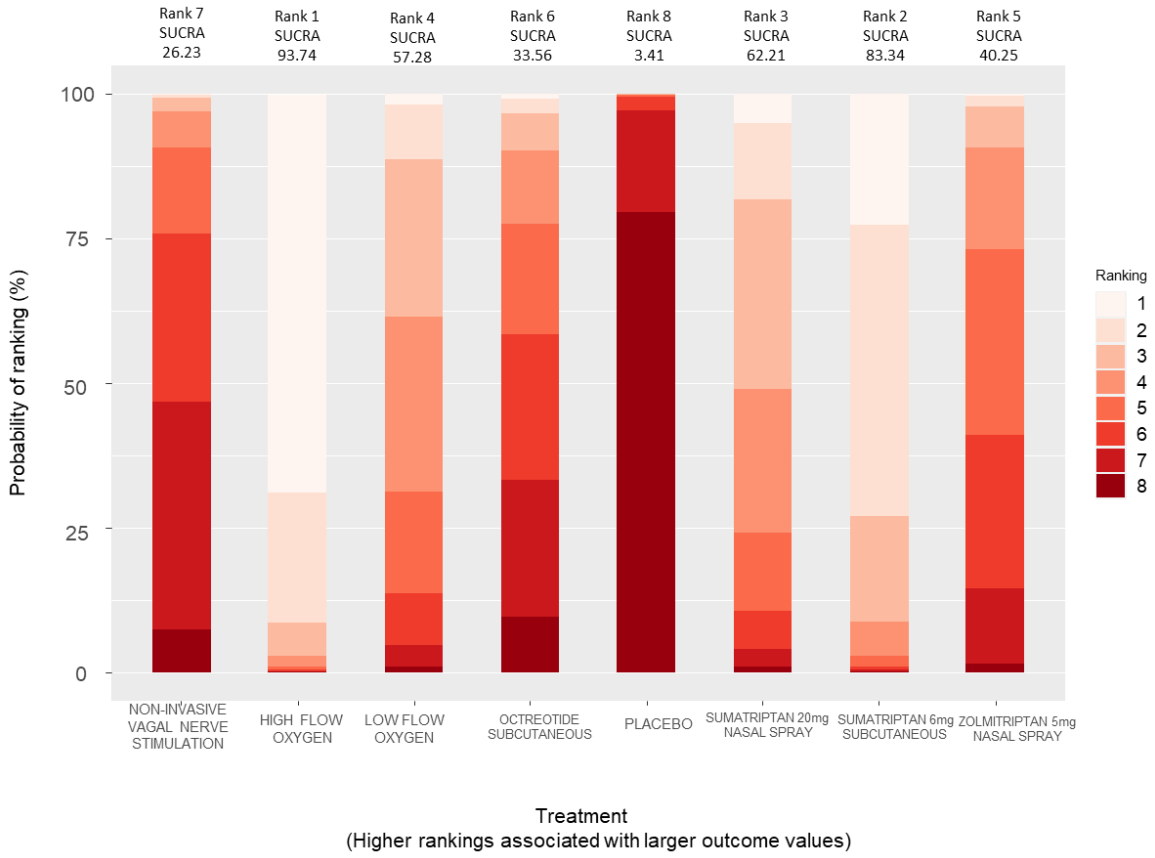
APPENDIX 2.2: FINDINGS FROM RANDOM EFFECTS MODEL FOR HEADACHE RESPONSE AT 15 OR 30MIN

Figure A2.1 League plots of treatment effect in network meta-analysis for each of the acute therapies and headache relief



Odds ratios and credible intervals for acute headache response are presented; ** denotes statistically significant results. Below the diagonal, values > 1 favor the treatment in the column header.

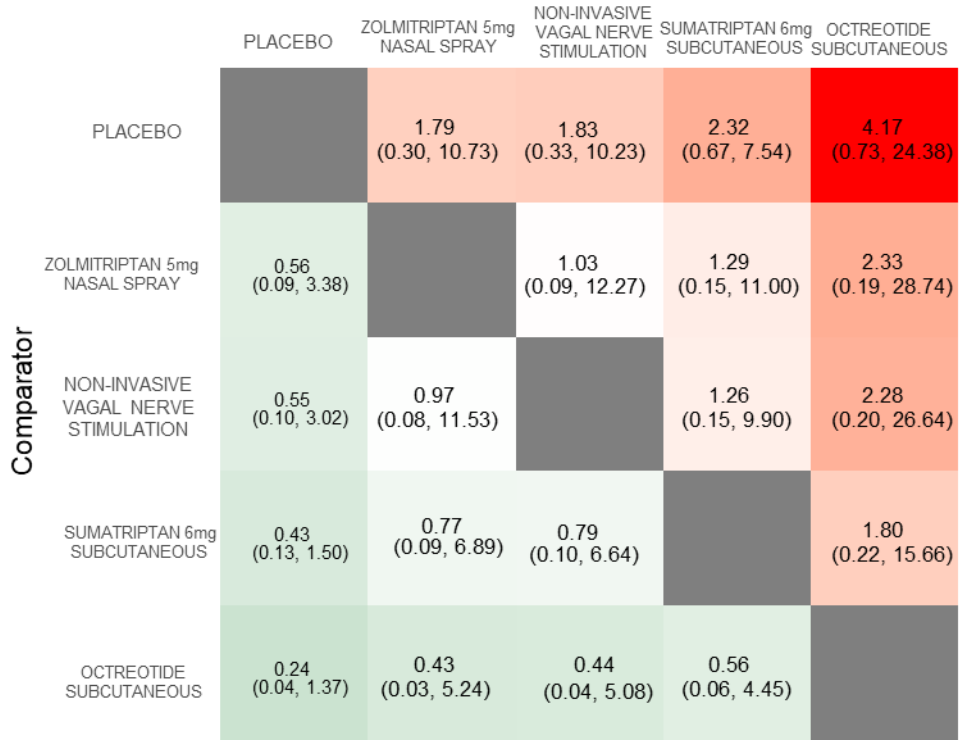
Figure A2.2 Probability bar plot of therapies for acute cluster headache and headache relief



For each individual treatment, the most probable ranking is shown at the top along with its SUCRA value. The individual probabilities per treatment of each ranking are shown out of 100% within its corresponding bar.

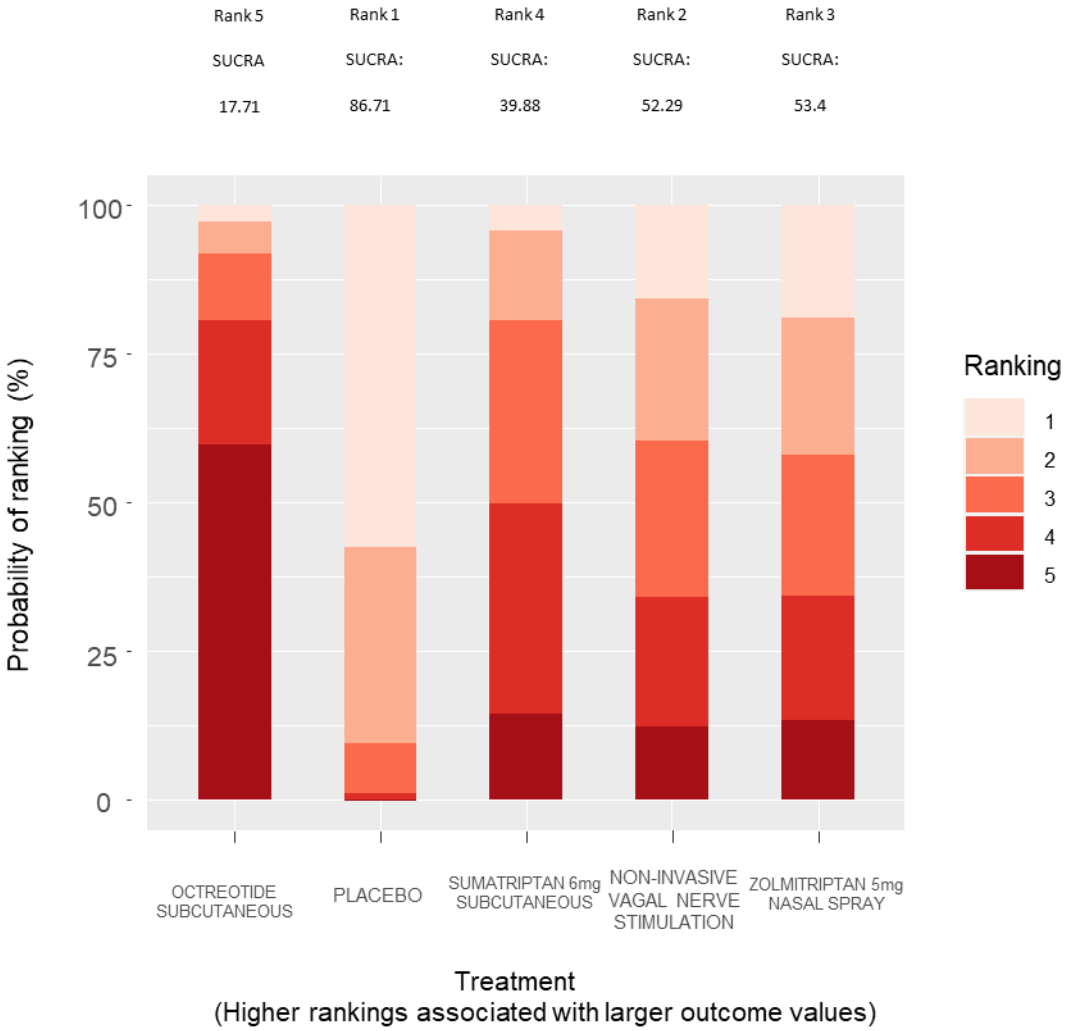
APPENDIX 2.3: FINDINGS FROM RANDOM EFFECTS MODEL FOR ADVERSE EVENTS

Figure A2.3 League plot of adverse events in acute treatments of cluster headache



Odds ratios and credible intervals for acute headache response are presented; ** denotes statistically significant results. Below the diagonal, values > 1 favor the treatment in the column header.

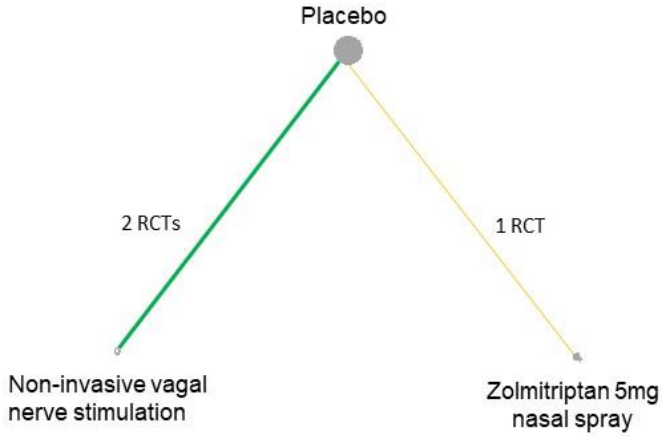
Figure A2.4 Probability bar plot of adverse events in acute treatments of cluster headache – Random Effects Model



For each individual treatment, the most probable ranking is shown at the top along with its SUCRA value. The individual probabilities per treatment of each ranking are shown out of 100% within its corresponding bar.

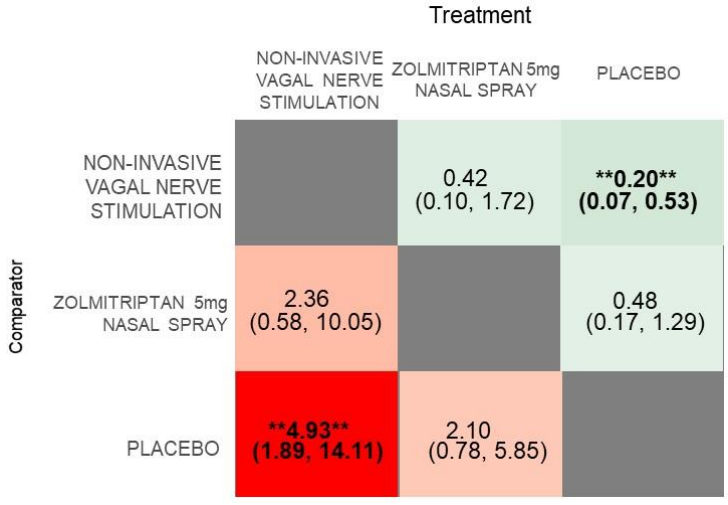
APPENDIX 2.4A: FINDINGS FROM FIXED EFFECTS AND RANDOM EFFECTS MODEL FOR HEADACHE RESPONSE AT 15/30MIN IN EPISODIC CLUSTER

Figure A2.5 Network of treatments with headache response available for acute cluster headache treatment in episodic patients



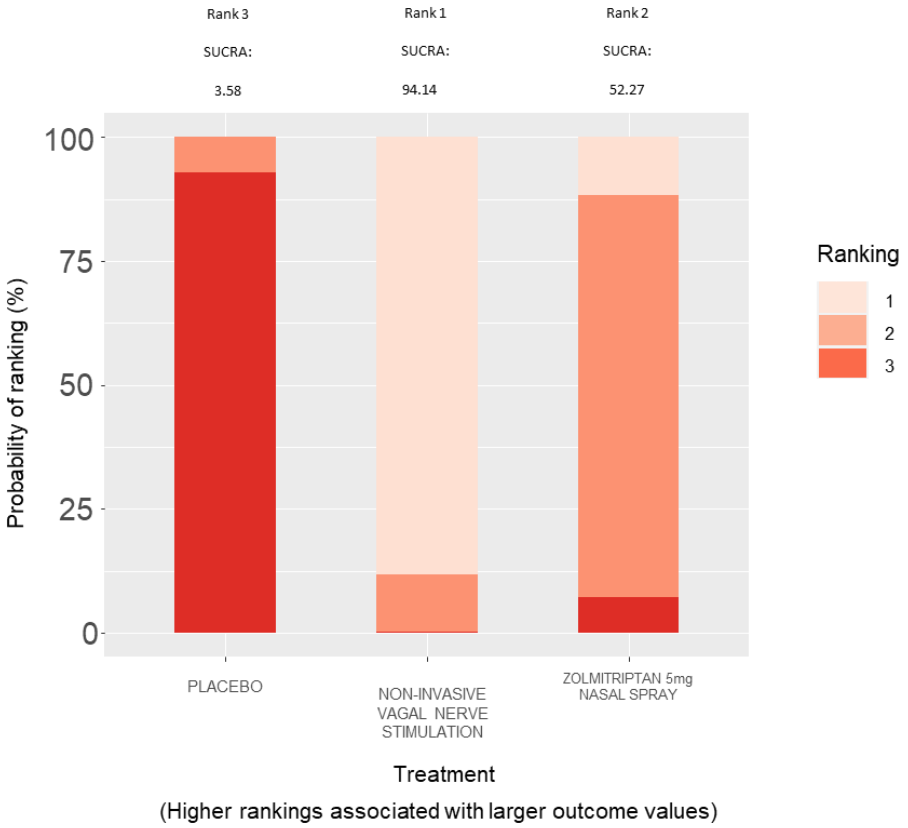
The network diagram for headache response at 15/30 minutes in episodic cluster headache subgroup is shown. Nodes are sized to proportionately reflect the numbers of attacks for each intervention, while edges joining interventions have widths to reflect the numbers of studies per comparison. The color of edges reflects the AAN ROB 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).

Figure A2.6 League plot of headache response in episodic cluster patients – fixed effects model



Odds ratios and credible intervals for acute headache response are presented; ** denotes statistically significant results. Below the diagonal, values > 1 favor the treatment in the column header.

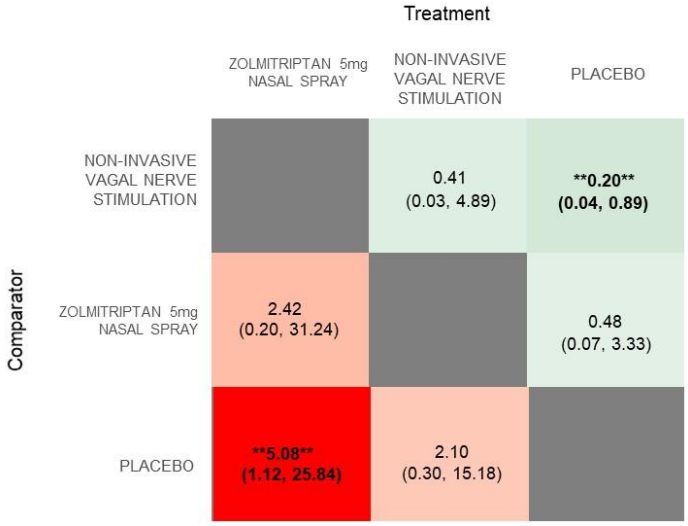
Figure A2.7 Probability bar plot of headache response in episodic cluster patients



For each individual treatment, the most probable ranking is shown at the top along with its SUCRA value. The individual probabilities per treatment of each ranking are shown out of 100% within its corresponding bar.

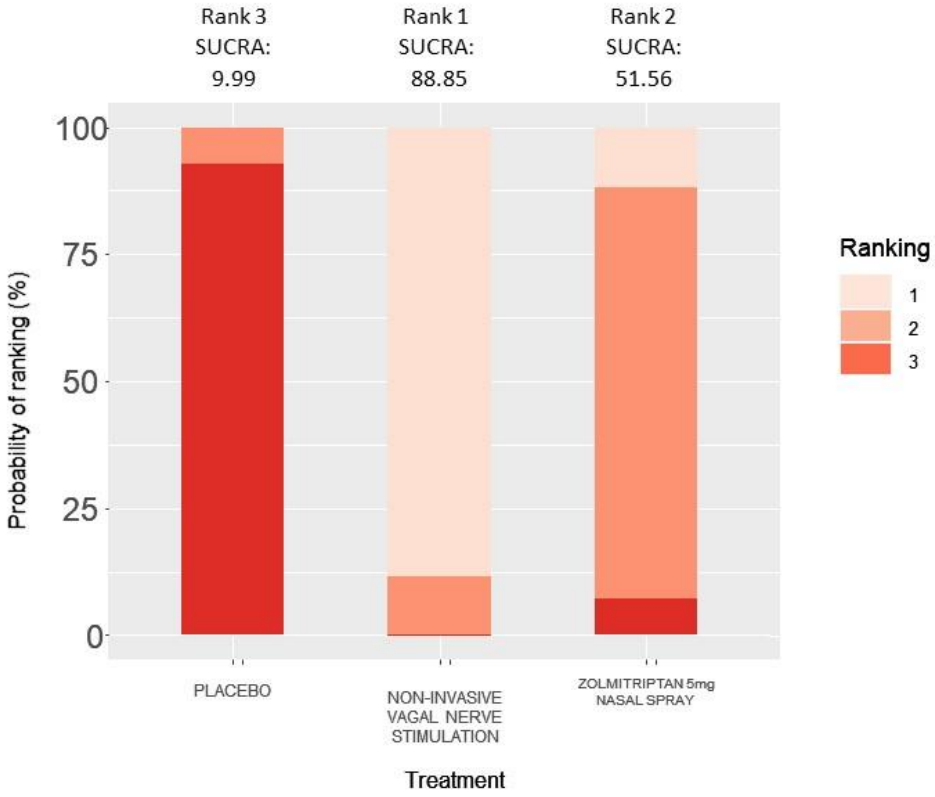
APPENDIX 2.4B: EPISODIC CLUSTER HEADACHE RELIEF AT 15 OR 30MIN: RANDOM EFFECTS MODELS

Figure A2.8 League plot of headache response in episodic cluster patients – random effects



Odds ratios and credible intervals for acute headache response are presented; ** denotes statistically significant results. Below the diagonal, values > 1 favor the treatment in the column header.

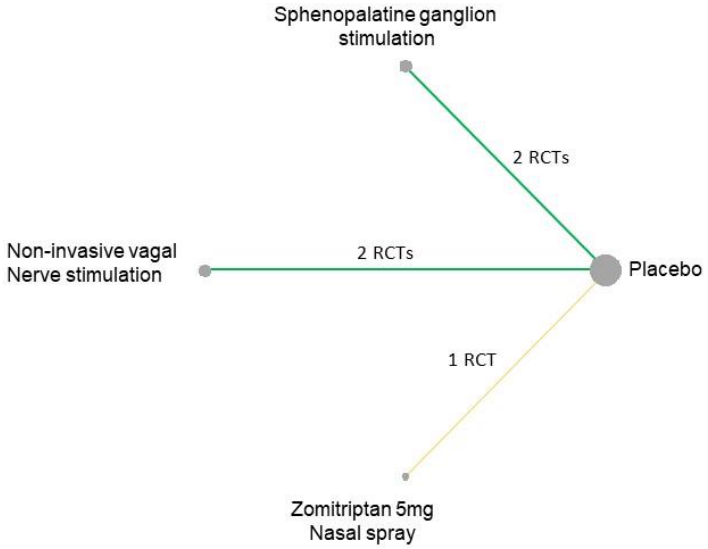
Figure A2.9 Probability bar plot of headache response in episodic cluster patients



(Rankings nearerst 1 and SUCRA nearest 100 associated with better outcomes)

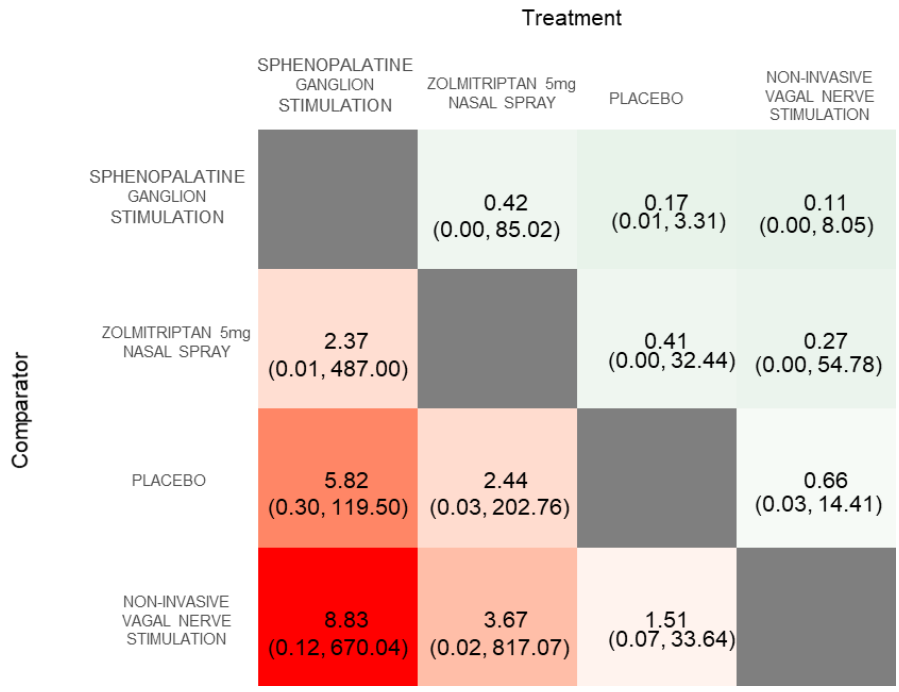
APPENDIX 2.5: CHRONIC CLUSTER HEADACHE RELIEF AT 15 OR 30MIN RANDOM EFFECTS MODELS

Figure A2.10 Network for acute headache relief in chronic cluster headache patients



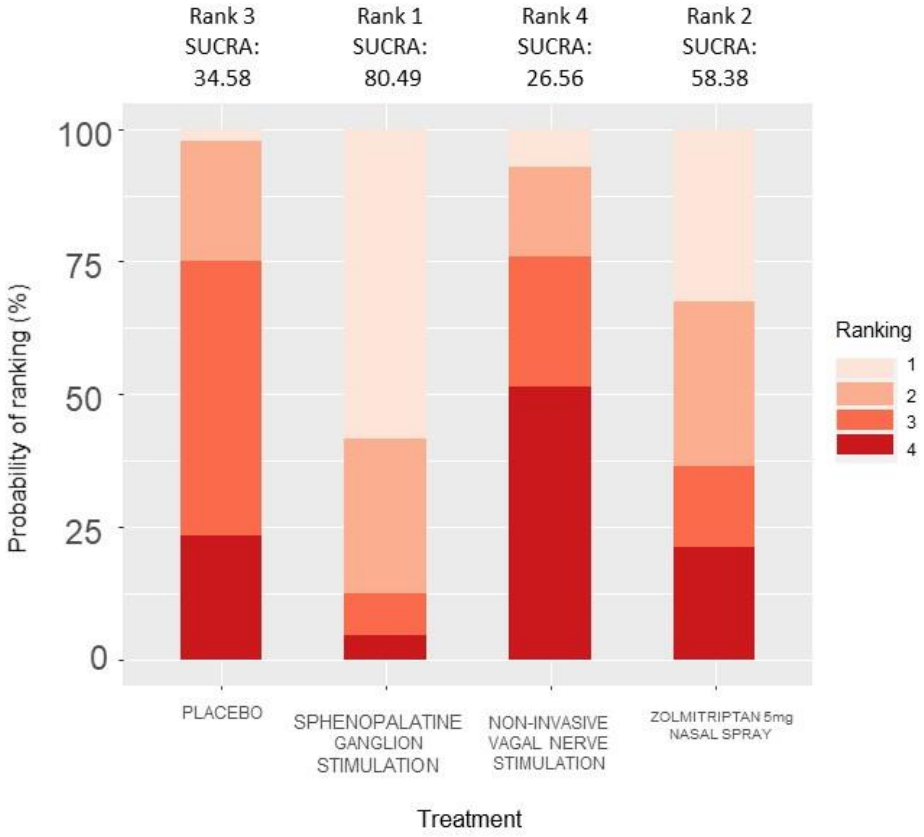
The network diagram for headache response at 15/30 minutes in chronic cluster is shown. Nodes are sized to proportionately reflect the numbers of attacks for each intervention, while edges joining interventions have widths to reflect the numbers of studies per comparison. The color of edges reflects the AAN ROB 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).

Figure A2.11 League table for acute headache relief in chronic cluster headache patients



Odds ratios and credible intervals for acute headache response are presented; ** denotes statistically significant results. Below the diagonal, values > 1 favor the treatment in the column header.

Figure A2.12 Probability bar plot of acute therapies for chronic cluster headache



(Rankings nearest 1 and SUCRA nearest 100 associated with better outcomes)

APPENDIX 2.6: NMA MODEL FIT ASSESSMENTS

Table A2.3 Comparison of RCT Treatment Effects versus NMA from best fitting models

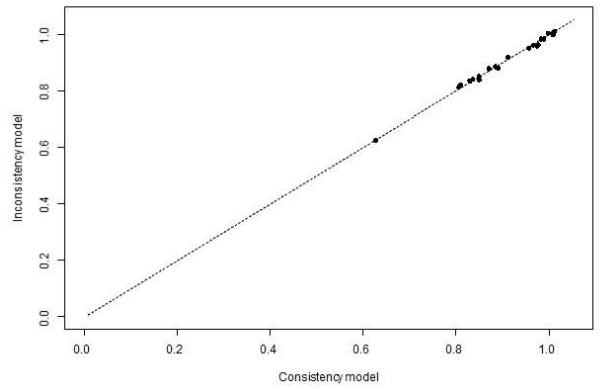
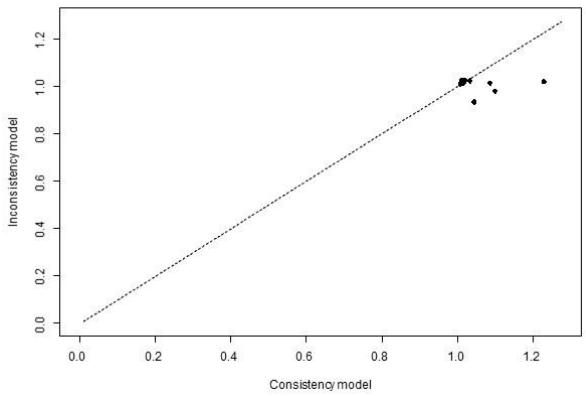
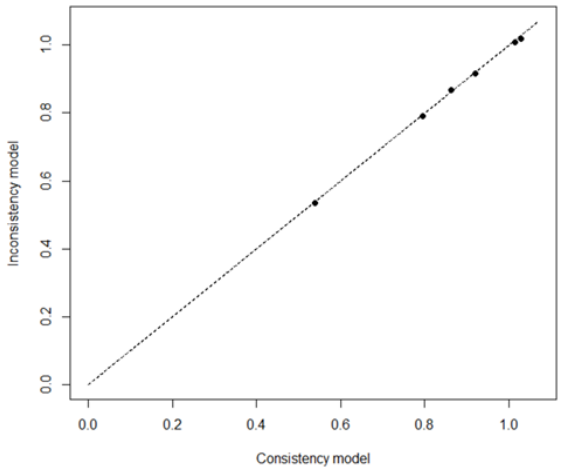
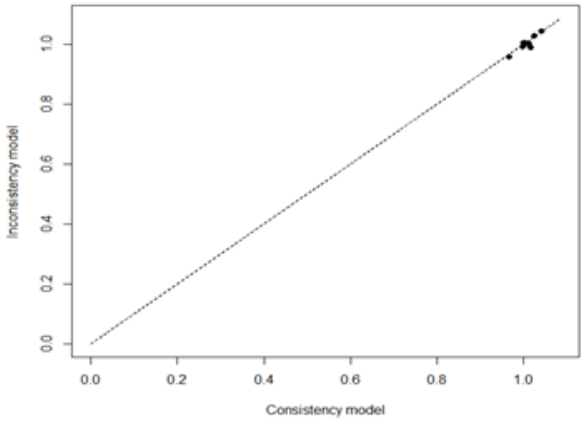
Active treatment	Comparison	OR Trial or PMA	Confidence Interval	I^2 - if PMA	P value	OR NMA	Credible Interval
Acute Therapy Cluster Headache - Headache Response							
O2 high	Placebo	3.95	2.48 to 6.29	NA	NA	9.03	5.27 to 15.93
O2 low	Placebo	1.90	1.04 to 3.47	NA	NA	3.54	1.84 to 6.94
O2 high	O2 low	2.33	0.39 to 14.04	NA	NA	2.55	1.13 to 5.76
Sumatriptan 5mg 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
Acute Therapy Cluster Headache - Adverse Events							
Octreotide….	Placebo	4.02	1.64 to 9.83	NA	NA	4.14	1.70 to 10.60
Sumatriptan 6mg SC	Placebo	2.33	1.17 to 4.55	30.60%	0.23	2.40	1.39 to 4.23
Zolmitriptan 5mg 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
Acute Therapy Cluster Headache – Episodic							
Zolmitriptan 5mg 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
Acute Therapy Cluster Headache – Chronic							
Zolmitriptan 5mg 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: PMA, pair-wise meta-analysis; O2, oxygen; SC, subcutaneous; NS, nasal spray; nVNS, non-invasive vagal stimulator; SPG-S, sphenopalatine ganglion stimulation, NA, not available.

Table A2.4 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

Figure A2.13 Scatterplots of residuals from consistency and unrelated means models from best fitting models per outcome

Headache resolution 15/30 mins	Adverse Events
	
Acute Response at 15/30min in Episodic Cluster Subgroup FE model	**Acute Response at 15/30min in Chronic Cluster Subgroup**
	

APPENDIX 2.7: 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 *incorporating a network meta-analysis (or related form of meta-analysis).*	64
ABSTRACT			65 and 66
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 *synthesis methods, such as network meta-analysis.* **Results:** number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; *treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.* **Discussion/Conclusions:** limitations; conclusions and implications of findings. **Other:** primary source of funding; systematic review registration number with registry name.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known, *including mention of why a network meta-analysis has been conducted.*	66
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	66
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 page 24
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. *Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged*	Accompanying manuscript page 24

		into the same node (with justification).	
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 page 24
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Accompanying manuscript page 24
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 page 24
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 page 25
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 page 25
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.	69 and 70
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.	69
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). *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.*	71
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: • *Handling of multi-arm trials;* • *Selection of variance structure;* • *Selection of prior distributions in Bayesian analyses; and* • *Assessment of model fit.*	70 and 71
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.	71
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).	72

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: • Sensitivity or subgroup analyses; • Meta-regression analyses; • *Alternative formulations of the treatment network; and* • *Use of alternative prior distributions for Bayesian analyses (if applicable).*	71
RESULTS†			
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.	72
Presentation of network structure	**S3**	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	74
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.	74
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 page 34-37
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	Appendix 2.1 128
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. *Modified approaches may be needed to deal with information from larger networks.*	75-80 and Appendix 2.6 page 143
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. *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.* If additional summary measures were explored (such as treatment rankings), these should also be presented.	82
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	Appendix 2.6 Page 144 and 145

		models, *P* values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	Appendix 1.1 Page 130-131
Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses, *alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses,* and so forth).	80 and 81
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).	82
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). *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).*	83
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	83
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.	64

PICOS = population, intervention, comparators, outcomes, study design.

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

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