Received: 21 March 2023 | Accepted: 23 June 2023

DOI: 10.1111/ene.15956

european journal of neurology
the official journal of the european academy of neurology

GUIDELINES

European Academy of Neurology guidelines on the treatment of cluster headache

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Abstract

Background and Purpose: Cluster headache is a relatively rare, disabling primary headache disorder with a major impact on patients' quality of life. This work presents evidence-based recommendations for the treatment of cluster headache derived from a systematic review of the literature and consensus among a panel of experts.

Methods: The databases PubMed (Medline), Science Citation Index, and Cochrane Library were screened for studies on the efficacy of interventions (last access July 2022). The findings in these studies were evaluated according to the recommendations of the European Academy of Neurology, and the level of evidence was established using GRADE (Grading of Recommendations Assessment, Development, and Evaluation).

Recommendations: For the acute treatment of cluster headache attacks, there is a strong recommendation for oxygen (100%) with a flow of at least 12 L/min over 15 min and 6 mg subcutaneous sumatriptan. Prophylaxis of cluster headache attacks with verapamil at a daily dose of at least 240 mg (maximum dose depends on efficacy and tolerability) is recommended. Corticosteroids are efficacious in cluster headache. To reach an effect, the use of at least 100 mg prednisone (or equivalent corticosteroid) given orally or at

up to 500 mg iv per day over 5 days is recommended. Lithium, topiramate, and galcanezumab (only for episodic cluster headache) are recommended as alternative treatments. Noninvasive vagus nerve stimulation is efficacious in episodic but not chronic cluster headache. Greater occipital nerve block is recommended, but electrical stimulation of the greater occipital nerve is not recommended due to the side effect profile.

KEYWORDS
cluster headache, guideline, TAC, treatment, trigeminal autonomic cephalalgia

INTRODUCTION

These guidelines provide evidence-based recommendations for the treatment of cluster headache. A brief clinical description of this primary headache disorder is included.

WHY IS A REVISION OF THIS GUIDELINE REQUIRED?

Guideline revision and update from time to time is an essential feature of their curation. Furthermore, given the development of innovative treatment options, both pharmaceutical and neuromodulatory, since the last edition [1], a revision is timely.

Moreover, although the clinical diagnosis of cluster headache—which is the most common of the trigeminal autonomic cephalgias (TACs)—might seem obvious, it has been proven that there is a delay [2–4], and when it comes to differentiating among the defined TACs, the complexity increases. Delayed diagnosis enhances the risk of not offering an appropriate treatment, with significant consequences for the patient: increase of possible acute medication overuse with the risk of gastrointestinal side effects, intoxication, et cetera, and of the burden for the individual, family, and society, which can eventually though rarely lead to suicidal behavior [5–7].

These guidelines aim to set out the management of cluster headache by providing evidence for specific treatment recommendations. They are based on an extensive revision of the existing European Federation of Neurological Societies (EFNS) guidelines [1].

BACKGROUND

The updated version of the International Classification of Headache Disorders, third edition (ICHD-3), describes different headache syndromes, including TACs [8], which are reviewed in Chapter 3. Headaches classified as TACs have two characteristics in common: relatively short-lasting pain attacks and associated cranial autonomic symptoms, both of which are overwhelmingly lateralized [9, 10]. Cranial autonomic symptoms such as lacrimation, conjunctival injection, rhinorrhea, nasal congestion, hyperhidrosis, and eyelid edema occur mostly on the ipsilateral side to the pain [11, 12] and are only absent in 3% of the cases [12]. According to the ICHD-3, cluster headache is the most prominent of the TACs, with a distinct pattern of duration, frequency, rhythmicity, and intensity of attacks, and associated cranial autonomic symptoms are more or less pronounced [10]. The cluster headache pathophysiology is not fully understood and is a topic of a number of research investigations [6, 13, 14].

Methods

The methodology for the development of these guidelines followed the framework provided by Grading of Recommendations Assessment, Development, and Evaluation (GRADE) and the Recommendations of the EAN on the Development of a Neurological Management European Academy of Neurology (EAN) [15, 16]. Given the rareness of the syndrome and consequently limited evidence available, the clinician authors recognize that the GRADE process may not result in outcomes that agree with clinical experience.

Research questions were developed using the PICO (population/intervention/comparison/outcome) format through a consensus during a task force meeting over the course of 1 year (Table 1).

For practical reasons, given the evidence available, the following principle was followed in deciding whether an evidence-based recommendation or a "research recommendation" or "good practice statement" is given:

Evidence-based recommendations:

- PICOs including systematic reviews with randomized controlled trials (RCTs) and crossover trials (CTTs);
- PICOs including RCTs, CTTs, or open label trials with ≥50 patients.

Good practice statements or research recommendations:

- PICOs including systematic reviews of case studies and case series;
- PICOs including only RCTs, CTTs, or open label trials with <50 patients
- PICOs including only other types of studies.

Data analysis and evaluation

Data extraction

Data from included studies was extracted through a predefined data frame. Two authors (A.M. and S.E.) extracted data, with disagreement resolved by consensus.

TABLE 1 PICO table for cluster headache.

Population	Patients with chronic or episodic cluster headache according to the current ICHD-3 classification [8] and earlier versions, treated in outpatient and inpatient clinics specializing in the diagnosis and treatment of headache disorders
Intervention	For acute treatment of cluster headache • Oxygen • Triptans • Ergotamine derivates • Lidocaine • Octreotide • Other interventions For prophylactic treatment of cluster headache • Verapamil • Corticosteroids • Lithium carbonate • Topiramate • Ergotamine • Triptans • Melatonin • OnabotulinumtoxinA • CGRP antagonists • CGRP monoclonal antibodies • Invasive nerve stimulation • Noninvasive nerve stimulation • Other interventions
Comparison	Placebo Usual care/best medical treatment/no treatment/sham treatment
Outcome	Decrease in 50% in the frequency of the attacks Pain relief Decrease in pain intensity Decrease in the frequency of attacks per week
Subgroup analysis	Chronic cluster headache Episodic cluster headache
Review type	Intervention review
Study design	Systematic reviews of RCTs RCTs or observational studies with control group with at least 50 participants

Abbreviations: CGRP, calcitonin gene-related peptide; ICHD-3, International Classification of Headache Disorders, third edition; PICO, population/intervention/comparison/outcome; RCT, randomized controlled trial.

Assessment of the risk of bias

For each of the studies included, risk of bias assessment was performed using the ROB2 (Cochrane's Risk of Bias) assessment tool for RCTs [17] and ROBINS-I (Risk of Bias in Non-Randomized Studies of Interventions) assessment tool for observational studies [18]. A second reviewer (K.A.) cross-checked the assessment and any disagreements were resolved through discussion.

Data synthesis

If more than one relevant study was identified for a question, and pooling was considered appropriate, a meta-analysis was conducted using RevMan 5.4 software.

Dichotomous outcomes (e.g., achievement of pain-free status) were summarized by calculating the risk ratio, and continuous outcomes (e.g., attack reduction/week) via mean difference between groups. Uncertainty in each pooled outcome is reported with 95% confidence intervals (CIs). Heterogeneity was measured with I^2.

Evidence evaluation

For each individual PICO, the publications were assessed for the overall level of evidence using the GRADE system [16]. GRADE profiler (https://gradepro.org/) was used to create "summary of findings" tables.

"Summary of findings tables" were used to provide information concerning the overall certainty of evidence, the magnitude of effect of the interventions examined, and the sum of available data on all outcomes rated as important to patient care and decision-making. For each outcome, the certainty of evidence was rated as high certainty, moderate certainty, low certainty, or very low certainty.

An evidence report was written for each PICO question and circulated among the guideline panel before the final recommendations were agreed upon.

In addition to the GRADE assessment of the efficacy data, we reported the adverse effects in the tables descriptively, summarizing the most frequent ones as reported in the studies, and noted those that are important to be taken into consideration according to the opinion of the authors of the guidelines.

SEARCH STRATEGY

A literature search (last update July 2022) was performed independently by all task force members using the reference databases PubMed (Medline), Web of Science, and Cochrane Library; the keywords used were "trigeminal autonomic cephalalgia", "cluster headache", "treatment", and "therapy", as well as combinations of the headache type and a specific treatment (e.g., "cluster headache" AND "oxygen"). During an initial search step, available systematic reviews on specific treatments were evaluated for methodological quality using R-AMSTAR [19]. In a second step, all papers that were published in English were considered, if they reported on the effect of an intervention to improve the symptoms of cluster headache. Surveys and basic science studies were excluded. If a high-quality systematic review was available on one of the topics, only additional studies that were published after the cutoff date for the literature search of the systematic review were included in the evaluation of the overall level of evidence. Risk of bias was evaluated for all controlled trials published after the cutoff date of high-quality systematic reviews using tools recommended by the Cochrane Handbook [20], Cochrane Risk of Bias tool for randomized controlled trials, and the Downs and Black Scale [21] for observational studies. Flowcharts for search strategy and outcome of medications are in the supplemental material.

METHODS FOR REACHING A CONSENSUS

Based on the scientific level of evidence and on the expertise of this task force of the EAN, recommendations are provided. The recommendation levels employed here follow the previous EFNS and now EAN criteria [15, 22], which are based on the guidance from the GRADE Working Group [23] and are expressed as either "strong" or "weak" following all considerations of the GRADE Working Group [24]. These indicate the trade-off between desirable and undesirable consequences of an intervention but may also include other factors, such as confidence in the effect estimates [24]. All recommendations had to be agreed on by all members of the task force unanimously.

CLINICAL SYNDROME

The ICHD-3 [8] and its predecessors use explicit diagnostic criteria. Of note, no single technical or laboratory examination (e.g., imaging) is able to define, ensure, or differentiate primary headache disorders [25]. Nevertheless, in the clinical setting, the use of neuroimaging techniques, such as cranial computed tomography (CCT), magnetic resonance imaging (MRI), or magnetic resonance angiography, for headache patients varies widely. Electrophysiological and laboratory examinations including examination of the cerebrospinal fluid (CSF) are not helpful. For the initial diagnosis and in the case of an abnormal neurological examination and/or "red flags" in the history, cranial imaging (preferably a cranial MRI) is recommended to exclude cluster headache due to a neoplasm [26].

Episodic and chronic cluster headache (ICHD-3 codes 3.1.1 and 3.1.2)

The prevalence of cluster headache has been reported as 0.1%–0.2% [27, 28]. The gender proportion (male vs. female patients) is estimated at between 3 and 4:1 [27, 29] and 2:1 [30, 31]. Genetic factors are unknown, but observed prevalence within families indicates a 2%–7% genetic component [28]. The diagnostic criteria of cluster headache are presented in Table 2. Cluster headache is often easier to diagnose than any other headache types. However, the diagnosis of cluster headache is commonly delayed and treatment insufficient [2, 4, 31]. The term "cluster" [32] describes the typical characteristics of the syndrome; the majority of patients experience an episodic pattern (80%, ICHD-3 3.1.1) [33], with symptomatic periods (7 days to several months, most commonly 4–12 weeks) and symptom-free periods of variable duration (minimum of 3 months) [8]. During the symptomatic period, short and clustered attacks are typical (1–8 per day) and can be triggered by alcohol, nitroglycerin, or histamine. During the symptom-free period, the patient has no cluster-type headaches and otherwise triggering substances show no effect. In patients suffering from the less common chronic presentation (<20% of cluster headaches, ICHD-3 3.1.2) [33], attacks often occur on a daily basis; if symptom-free periods are experienced, these last <3 months, for at least 1 year [8]. Akin to other primary headaches, the natural history of cluster headache may also be characterized by spontaneous increases or improvements of headache severity. Up to 12% of episodic cluster headache patients progress to a chronic presentation [34]. Primary chronic presentations make up 15% of all cluster headache types. Conversely, reversion from a chronic to an episodic form can also be seen, although rarely, in some patients. Late onset, male gender, and episodic cluster headaches for >20 years indicate a poor prognosis [12].

TABLE 2 ICHD-3 criteria for cluster headache [8].

A. At least 5 attacks fulfilling criteria B–D
B. Severe or very severe unilateral orbital, supraorbital, and/or temporal pain lasting 15–180 min if untreated
C. Either or both of the following:
1. At least one of the following symptoms or signs, ipsilateral to the headache:
a. Conjunctival injection and/or lacrimation
b. Nasal congestion and/or rhinorrhea
c. Eyelid edema
d. Forehead and facial sweating
e. Miosis and/or ptosis
2. A sense of restlessness or agitation (akathisia)
D. Occurring with a frequency between one every other day and eight per day
E. Not better accounted for by another ICHD-3 diagnosis

Abbreviation: ICHD-3, International Classification of Headache Disorders, third edition.

Headaches are strictly unilateral and side-locked (78%), and rarely (12%) change sides between bouts [9, 31, 35–37]. The location is typically orbitofrontal, with referred pain to the forehead, jaw, throat, ear, neck, or shoulder. Patients frequently describe the pain quality as a "hot knife stabbing the eye" or as a "burning thorn in the temple"; the pain intensity is severe, with visual analog scale values up to 10/10 [37, 38]. A single attack can last between 15 and 180 min when untreated and, in the episodic form, often occurs 1–2 h after going to sleep and in the early morning [39]. In contrast to migraine patients, cluster patients during an attack have a strong urge to move; their behavior during attacks has been described as "pacing" or "rocking." This movement compulsion is very characteristic for cluster headache [35] and has therefore been included as a diagnostic criteria in the ICHD-3 as "a sense of restlessness or agitation" [8]. A proportion of patients report a constant but mild background pain between attacks during the symptomatic period [35, 40]. Some reports described a visual aura experienced by some patients prior to an attack [35, 41] and also prodromes/premonitory symptoms (such as yawning, coughing, polyuria) [42–44]. Other symptoms, known as typical for migraines, such as nausea, phonophobia, or photophobia have also been associated with cluster headaches [45], with photophobia and phonophobia tending to be lateralized to the side of pain [46].

The headache is almost always associated with cranial autonomic symptoms such as lacrimation, chemosis, rhinorrhea, incomplete Horner syndrome with miosis and ptosis, conjunctival injection, and facial or forehead sweating. The ICHD-3 includes a comment that cluster headaches can have a period (but less than half of the

duration since diagnosis) of reduced-intensity attacks associated with an alteration of the duration of each attack. In some patients, more than one headache type exists, and coexistence with migraine, tension-type headache and trigeminal neuralgia but also other forms of TAC have been described [38].

Diagnosis

The diagnosis of cluster headache is based on a thorough patient interview and a clinical neurological examination. Electrophysiological, laboratory, and CSF tests add nothing to the diagnosis. For the initial diagnosis, and in the case of associated neurological symptoms, a cerebral MRI including the craniocervical junction (in the case MRI is not available: CCT including the base of the skull) should be performed [47] (Table 3), because cluster-type headaches, especially with increased age, might have an underlying secondary cause. Interestingly the literature describes primarily intracranial tumors located near the midline (frontal or occipital or even in the cerebellum). These include malignant tumors and arteriovenous malformation, as well as brain infarction or inflammatory plaques [48]. Particularly in older patients, mass lesions or malformations in the midline have been described to be associated with symptomatic cluster headache [48], where lesions involving the posterior fossa or region of the pituitary gland need to be considered [49].

TABLE 3 Diagnosis of cluster headache [47].

Required

- Complete neurological examination including careful examination of the cranial nerves (especially trigeminal nerve)
- Brain and craniocervical junction MRI (ruling out cerebral pathologies located near midline)

In individual cases

Initial diagnosis, neurological symptoms, first diagnosed at >60 years of age, atypical presentation:

- CT of base of the skull (ruling out bone destructive processes) if MRI is not available
- CSF test (ruling out inflammatory disease)
- Occasionally: Doppler/duplex and MRI for DD dissection
- Occasionally: MR angiography (ruling out AVM and artery dissection)

Hospitalization may be required if

- Intravenous treatments, such as corticosteroids or dihydroergotamine
- Initial diagnosis of atypical presentation
- Unsuccessful treatment attempt with two preventative medications
- Psychophysical distress due to drug-refractory forms or persistent daily attacks (treatment and support)

Abbreviations: AVM, arteriovenous malformation; CSF, cerebrospinal fluid; CT, computed tomography; DD, differential diagnosis; MR, magnetic resonance; MRI, MR imaging.

Differential diagnosis

Differential diagnoses include secondary causes of TAC-like presentations, the other TACs and migraine. The most phenotypically similar is paroxysmal hemicrania.

Paroxysmal hemicrania (ICHD-3 code 3.2) is clinically similar, but attacks occur more frequently (at least five attacks per 24 h), are shorter (2–30 min), and show an obligatory response to indomethacin. Patients are more often female than male.

Cluster tic syndrome

Case studies reported patients with cluster headache symptoms and symptoms normally associated with trigeminal neuralgia. These patients receive both diagnoses. It is important to provide treatment for both pathologies to achieve pain reduction [50].

Cluster and migraine

Both headache types can occur in the same patients, and this has been reported to be an important reason for the marked diagnostic delay, especially in women [3]. Cluster headache attacks can occur with the typical migraine frequency (1–2 per week), and migraine attacks can be lateralized and associated with typical cluster symptoms such as ipsilateral miosis, orbital edema, and lacrimation and might even show a cyclical behavior [51]. The acute treatment should be individualized and include oxygen and injectable sumatriptan for the short cluster attacks; appropriate antimigraine drugs can be applied for the longer lasting migraine attacks. The preventive treatment should be directed against the dominant (more bothersome) component. If this is not clear, a pragmatic approach can be adopted; beta-blockers do not influence cluster headaches, whereas verapamil does not reduce migraine frequency.

Treatment of cluster headache

The treatment of cluster headache is mainly based on empirical data and not on a pathophysiological concept of the disease [6, 52]. Cluster headache attacks are usually excruciating; however, drug treatment trials in cluster headache have shown a placebo rate of 14%–43% [53]. Some of the response is natural history and attacks of cluster headache end, as do bouts of the episodic cluster headache, regardless of therapy, which undoubtedly demands the presence of a control arm in future studies to understand better potential therapeutic benefits. The treatment combines acute medication for the individual attack (Tables 4–8 and Tables S4–S8) and preventive medication to reduce the number of attacks (Tables 9 and 10 and Tables S9 and S10). In addition to pharmacological treatments, some neurostimulation procedures are efficacious (Tables 11–14 and Tables S11–S14). Physiotherapy and similar techniques, as well as different types of psychotherapy, are inefficacious in nearly all patients. Because such cases are very rare and no data exist for a differentiated treatment of cluster headache in pregnancy or breast feeding, pediatric age group, or cluster headache with comorbid conditions, we refer to the current guideline in combination with related guidelines of best practice in these patient groups.

TABLE 4 GRADE profile and summary of findings table for the efficacy of oxygen to terminate acute cluster headache attacks (chronic and episodic cluster patients).

Comparison: normobaric or hyperbaric oxygen vs. placebo (or ergotamine)								
Outcome: pain relief								
Certainty assessment						**Summary of findings**		
No. of participants (studies)	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Effect**	**Certainty**	**Importance of outcome**
253 participants (5 RCTs)	Serious[a]	Serious[b,c]	Not serious	Very serious[d]	None	Two studies (Cohen and Fogan) reported significant difference in favor of oxygen (chronic and episodic CH not stratified). No differences between groups were found in the remaining three studies.	Very low	Critical
Adverse effects	No important adverse effects reported							

Note: Strong recommendation for NBOT based on five RCTs (very low level of evidence). Reasons for the discrepancy between level of evidence and recommendation are the low adverse event profile with no contraindications, no interactions with other medications, and that this medication is well accepted by patients.

Abbreviations: CH, cluster headache; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; NBOT, normobaric oxygen therapy; RCT, randomized controlled trial.

[a]Some of the studies presented important risk of bias.

[b]Not clearly better than placebo across studies.

[c]The studies had different outcomes, different measurements, different flows of oxygen, different mask types, and different populations (some studies only included male patients).

[d]Meta-analysis is not possible due to high heterogeneity, individual studies with low number of patients.

TABLE 5 GRADE profile and summary of findings table for the efficacy of subcutaneous sumatriptan to terminate acute cluster headache attacks.

Comparison: subcutaneous sumatriptan vs. placebo								
Outcome: pain relief at 15 min								
Certainty assessment						**Summary of findings**		
No. of participants (studies)	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Effect**	**Certainty**	**Importance of outcome**
Subcutaneous sumatriptan 6 mg, 173 participants (2 studies)	Not serious	Not serious	Serious[a,b]	Serious[c]		RR = 2.77 [1.82–4.21]	Low	Critical
Subcutaneous sumatriptan 12 mg, 134 participants (1 study)	Not serious	N.A.[d]	Serious[a]	Serious[e]		RR = 3.00 [1.92–4.68]	Low	Critical
AEs	AE intervention: injection site reaction; flushing; sweating; warm sensation; malaise/fatigue; and prickling sensation, tightness/pressure AE comparators: injection site reaction, nausea, pressure sensation Important for consideration; injection site reaction, flushing, tightness/pressure							

Note: Strong recommendation based on a low level of evidence for subcutaneous sumatriptan. Reasons for the discrepancy between level of evidence and recommendation are the parenteral application form and fast onset.

Abbreviations: AE, adverse effect; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; N.A., not applicable; RR, risk ratio.

[a]Heterogeneous population; chronic and episodic cluster.

[b]Different definition of outcomes.

[c]Different dosages.

[d]Only one study.

[e]Low sample-size.

Attack treatment

Oxygen

The recommended dosage is inhalation of at least 12 L/min of 100% oxygen [54, 55] (in some cases up to 15 L/min) for a duration of 20 min using a nonrebreather mask; nasal cannulae are not sufficient. Different protocols and mask types are available [56]. Petersen and colleagues compared different types of masks and reported no significant difference between placebo and oxygen inhalation but a clear preference for the demand valve oxygen mask [57], which offers a higher flow rate.

Importantly, there are no cardiovascular limitations when ergotamine and triptans are contraindicated, as well as it being useful to avoid secondary medication overuse headache. Portable devices are available. In some settings, if the efficacy of oxygen is unknown, the treatment can be tested by hospitalizing a patient for 1–2 days prior to the prescription of the home device. The best approach should be determined in the context of the health care system in which the patient is being managed [58].

A high methodological quality (R-AMSTAR score 44/44) systematic review and meta-analysis published by the Cochrane Collaboration in 2015 [59] included three trials on normobaric oxygen therapy compared to sham or ergotamine tartrate (178 patients) [54, 60, 61] and three additional trials including cluster headache populations. The authors found a statistically significant effect for the termination of the attack and a 75% responder rate after 15 min. After the cutoff date for the literature search for this Cochrane review (15 June 2015), one trial compared oxygen 7 L/min with oxygen 12 L/min with no clinically relevant differences between the two dosages [62]. In this study, it is noteworthy that only five of 56 subjects contributed data to the primary endpoint, the odds ratio in favor of 12 L/min (3.75, 95% CI = 0.58–24.28) was quite high, and patients preferred the 12 L/min option. Given the flow rate was carefully blinded, and there is no safety issue, the higher flow rate seems better (Table 4 and Tables S1 and S2). When low-flow oxygen is sufficient, no change is necessary, but if it is not efficient, increased flow rates should be tried before declaring patients to be oxygen nonresponders [55]. One additional trial evaluated the effect of different types of mask and reported no statistically significant effect between groups [57].

Triptans

Several triptans with different application routes are available and have been investigated in the treatment of acute cluster headache

TABLE 6 GRADE profile and summary of findings table for the efficacy of intranasal sumatriptan to terminate acute cluster headache attacks.

Comparison: intranasal sumatriptan vs. placebo								
Outcome: pain relief at 30 min								
Certainty assessment						**Summary of findings**		
No. of participants (studies)	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Effect**	**Certainty**	**Importance of outcome**
Intranasal sumatriptan 20 mg 85 participants (1 study)	Not serious	N.A.[a]	Serious[b]	Serious[c]		RR = 2.2 [1.44–3.36]	Low	Critical
AEs	AE intervention: chest pressure, bitter taste AE comparators: bitter taste Important for consideration: chest pressure							

Note: Strong recommendation based on a moderate level of evidence for 20 mg intranasal sumatriptan.

Abbreviations: AE, adverse effect; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; N.A., not applicable; RR, risk ratio.

[a]One study only.

[b]Heterogeneous population; chronic and episodic cluster.

[c]Small sample-size.

TABLE 7 GRADE profile and summary of findings table for the efficacy of oral zolmitriptan to terminate acute cluster headache attacks.

Comparison: oral zolmitriptan vs. placebo								
Outcome: pain relief at 30 min								
Certainty assessment						**Summary of findings**		
No. of participants (studies)	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Effect**	**Certainty**	**Importance of outcome**
Oral zolmitriptan 5 mg 114 participants (1 study)	Not serious	N.A.[a]	Serious[b]	Serious[c]		RR = 1.18 [0.91–1.54]	Low	Critical
Oral zolmitriptan 10 mg 114 participants (1 study)	Not serious	N.A.[a]	Serious[b]	Serious[c]		RR = 1.20 [1.00–1.58]	Low	Critical
AEs	AE intervention: paresthesia, heaviness, asthenia, nausea, dizziness, and (nonchest) tightness AE comparators: paresthesia Important for consideration: chest tightness							

Note: Weak recommendation based on a very low level of evidence for oral zolmitriptan (5 or 10 mg).

Abbreviations: AE, adverse effect; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; N.A., not applicable; RR, risk ratio.

[a]Only one study.

[b]Heterogeneous population; chronic and episodic cluster.

[c]Low sample size, RR includes (1).

attacks (Tables 5–8 and Tables S3 and S4). A systematic review published by the Cochrane Collaboration in 2013 [63] included six studies evaluating the use of 6 or 12 mg sumatriptan subcutaneously [64, 65], of sumatriptan 20 mg intranasally [66], of 5 or 10 mg zolmitriptan orally [67] and of 5 or 10 mg zolmitriptan intranasally [68, 69]. When pooling the 6 mg [65] and 12 mg studies [64] of sumatriptan, 15 min after treatment, 48% of the patients were pain-free and 75% had no pain or mild pain after sumatriptan injection of 6 mg [63]. Intranasal zolmitriptan at doses of 5 and 10 mg was studied in two randomized placebo-controlled trials [68, 69]. A meta-analysis of these two

TABLE 8 GRADE profile and summary of findings table for the efficacy of nasal zolmitriptan to terminate acute cluster headache attacks.

Comparison: intranasal zolmitriptan vs. placebo								
Outcome: pain relief at 30 min								
Certainty assessment						**Summary of findings**		
No. of participants (studies)	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Effect**	**Certainty**	**Importance of outcome**
Intranasal zolmitriptan 5 mg 173 participants (2 studies)	Not serious	Not serious	Serious[a]	Serious[b]		RR = 1.74 [1.20–2.51]; NNT = 5 [2.5–100]	Low	Critical
Intranasal zolmitriptan 10 mg 173 participants (2 studies)	Not serious	Not serious	Serious[a]	Serious[b]		RR = 2.36 [1.62–3.34]	Low	Critical
AEs	AE intervention: chest tightness, paresthesia, shortness of breath AE comparators: no serious side effects Important for consideration: chest tightness							

Note: Strong recommendation based on a low level of evidence for intranasal zolmitriptan (5 mg). Reasons for the discrepancy between level of evidence and recommendation are the parenteral application form and fast onset.

Abbreviations: AE, adverse effect; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; NNT, number needed to treat; RR, risk ratio.

[a]Heterogeneous population – chronic and episodic cluster.

[b]Low sample size.

studies included 121 patients [70]. Headache relief at 30 min was observed in 63% of patients treated with 10 mg of zolmitriptan (application into the contralateral nostril is recommended) compared with 48% treated with 5 mg of zolmitriptan and 30% treated with placebo. In summary, zolmitriptan nasal spray at a preferred dose of 10 mg is efficacious in the treatment of cluster attacks [71]. In indirect comparisons, the efficacy is inferior to that of the subcutaneous application of sumatriptan [55]. Zolmitriptan nasal spray is only available in a 5-mg dose.

The effect after subcutaneous sumatriptan occurs much quicker than the effect of the intranasal formulation [13, 71], which is particularly important considering that attacks only last for approximately 15–180 min. The recommended (and available) dose is 6 mg, although lower doses studied in an open label noncontrolled fashion might be equally efficacious [72], and a 3-mg dose of sumatriptan is also available in some countries and sufficient for some patients with migraine [73]. It is safe, with no evidence of tachyphylaxis or rebound in most of the patients, even after frequent use [74, 75], although cluster headache patients with migraine may experience medication overuse headache [76]. Contraindications are cardio- and cerebrovascular disorders and untreated arterial hypertension.

Ergotamine derivatives

Due to poor oral absorption and the need for a rapid increase in plasma levels, dihydroergotamine (DHE) is best applied as aerosol spray, as suppository (no first path effect), or as subcutaneous injection [77–79]. One publication reported the use of 2–3 aerosol doses (0.35 mg each) with deep inhalation at the onset of an attack. The treatment did not significantly shorten the duration of the individual attack, nor did it reduce the frequency of attacks, but it significantly reduced the intensity of the individual attack [77] (Table S15). Ergotamine tartrate suppositories are not able to abort attacks because of the slow onset of action but may be used as short-term prophylaxis (see preventative drug treatment). Evidence for intravenous DHE is based on studies retrospectively evaluating medical records or on patient interviews where the treatment is used for short-term prevention [80–83]. Although these studies suggest efficacy, no prospective randomized controlled trial has confirmed this hypothesis. Although the published studies reported no adverse events for DHE in cluster headache, DHE might lead to nausea, muscle pain, and Raynaud syndrome.

Lidocaine

Nasal instillation into the ipsilateral nostril of 1 mL 4%–10% lidocaine solution with the patient positioned reclining 45° and 30–40° rotation toward the symptomatic side has been recommended for the reduction of acute symptoms [84]. It is thought to block the sphenopalatine ganglion in the pterygopalatine fossa. However, the topical use of local anesthetics is only beneficial in a minority of patients and not always consistent. All available evidence is based on case reports or case series [85, 86], on experimentally induced attacks [87], on studies including mixed primary headache groups [88], and on an uncontrolled study [89] (Table S16). It can be used as an initial

TABLE 9 GRADE profile and summary of findings table for the efficacy of corticosteroids for the reduction of the frequency of cluster headache attacks.

Comparison: prednisone vs. placebo								
Certainty assessment						**Summary of findings**		
No. of participants (studies)	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Effect (95% CI)**	**Certainty**	**Importance of outcome**
Outcome: cluster headache attacks in the first treatment week, baseline to Day 7 (follow-up: range = 7 days to 0)								
109 patients (1 study)	Not serious	N.A.[a]	Serious[b,c]	Serious[d]	None	MD = 2.4 prednisone lower (4.8 lower to 0)	Low	Critical
Outcome: cluster headache attacks, baseline to day 28 (follow-up: range = 28 days to 0)								
109 patients (1 study)	Not serious	N.A.[a]	Serious[b,e]	Serious[d]	None	MD = 4.7 prednisone lower (11 lower to 1.7 lower)	Low	Critical
AEs	AE intervention: headache, palpitations, dizziness AE comparators: headache, palpitations, dizziness, and nausea Important for consideration: none							

Note: Weak recommendation for prednisone in episodic cluster headache based on a low level of evidence.

Abbreviations: AE, adverse effect; CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; MD, mean difference; N.A., not applicable.

[a]Only one study.

[b]Included patients with a mean duration of previous episodes of at least 30 days, but the treatment may be applicable for patients with shorter duration of attacks.

[c]Seven-day follow-up.

[d]One study, did not reach the planned sample size.

[e]Secondary end point.

TABLE 10 GRADE profile and summary of findings table for the efficacy of galcanezumab for the reduction of the frequency of cluster headache attacks.

Comparison: galcanezumab vs. placebo								
Outcome: Decrease in the frequency of attacks in episodic cluster (mean change from baseline of the frequency of attacks)								
Certainty assessment						**Summary of findings**		
No. of participants (studies)	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Effect (95% CI)**	**Certainty**	**Importance of outcome**
Galcanezumab 106 patients (1 study)	Not serious	Not serious	Not serious	Very serious[a]	-	MD = 3.5 less in galcanezumab (0.2–6.7)	Low	Critical
AEs	AE intervention: injection site pain, nasopharyngitis, injection site erythema, and nausea AE comparators: injection site erythema Important for consideration: none							

Note: Weak recommendation for galcanezumab in episodic cluster headache based on a low level of evidence.

Abbreviations: AE, adverse effect; CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; MD, mean difference.

[a]Sample size not reached. Very wide confidence interval.

attempt, because it is almost free of side effects; however, the effect lasts only for approximately 2 h.

Octreotide

Octreotide, a somatostatin analog, has been tried in cluster headache and showed to be superior to placebo regarding pain-free rates [90]. However, octreotide can induce headache [91] and even cluster headache [92]. Further studies are necessary to evaluate its efficacy and clinical usefulness in cluster headache. Another somatostatin analog, pasireotide, has been reported in a case report to be efficacious in cluster headache [93]. A randomized, double-blind, placebo-controlled phase II trial (NCT02619617) was discontinued because of lack of efficacy.

Preventive drug treatment

The importance of an effective preventive regimen cannot be overstated. Because many patients have between one and eight short attacks per day, repeated attempts at abortive therapy may result in overmedication or toxicity. The primary goal of preventive therapy is to produce a suppression of attacks and to maintain remission over the expected duration of the cluster period.

Verapamil is the medication of choice for the prevention of episodic and chronic cluster headaches [38, 71]. The mechanism of action and efficacy have recently been summarized [94].

The efficacy was shown in a double-blind placebo-controlled trial including 30 patients (15 patients in each group). From the second week of the trial, the verapamil group (120 mg three times per day) showed a significantly higher reduction in attack frequency in episodic patients and thereby consumption of acute medication. The responder rate defined as 50% reduction in headache frequency was 80% [95]. The same group of authors published an earlier study comparing the effect of verapamil with the effect of lithium in chronic cluster headache patients, and found both drugs induced a statistically significant reduction in attack frequency with no difference between drugs, but verapamil caused fewer side effects [96] (Table S17). Another group reported an effect of verapamil in approximately 70% of the 48 included patients, but used an uncontrolled open label study design [97]. Verapamil dosages in both RCTs were 360 mg/day; however, in the open label studies, higher dosages are often needed to gain effect.

In clinical practice, most clinicians start up with 80 mg 3–4 times per day [6]. Electrocardiogram (ECG) is mandatory prior to the treatment. Dosages are increased by 80 mg every 3–4 days. Once a daily dosage of 480 mg is reached, ECGs should be repeated every 160 mg [98], optionally supported by exercise ECG before increasing by a further 80 mg. Again, depending on the efficacy and eventually side effects, the dosage may be increased further up to a maximum of 1000 mg under regular ECGs and eventually under cardiologist supervision. Verapamil is generally well tolerated and can therefore be used as a long-term medication. Both the regular and extended release preparations have been shown to be useful, but no direct comparative trials or documented regimes

TABLE 11 GRADE profile and summary of findings table for the efficacy of VNS for the reduction of the frequency of episodic cluster headache attacks and the pain intensity during attacks.

Comparison: VNS vs. sham treatment in episodic cluster headache								
Outcome: proportion of attacks reaching pain relief at 15 min								
Certainty assessment						**Summary of findings**		
No. of participants (studies)	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Effect (95% CI)**	**Certainty**	**Importance of outcome**
131 (1 meta-analysis, 2 RCTs)	Not serious[a]	Serious[b]	Not serious	Serious[c]		RR = 4.4 (2.7–7.2) for VNS vs. sham	Low	Critical
AEs	AE intervention: application site irritation and paresthesia, rash AE comparators: myalgia/myokymia, application site paresthesia, rash Important for consideration: application site irritation and paresthesia							

Note: Strong recommendation for noninvasive VNS based on low quality of evidence for treatment of attacks in episodic cluster headache. Reasons for the discrepancy between level of evidence and recommendation are the low adverse profile, noninvasiveness, and absent interactions with medications.

Abbreviations: AE, adverse effect; CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; RCT, randomized controlled trial; RR, risk ratio; VNS, vagus nerve stimulation.

[a]Blinding estimate after first treatment not met in ACT1 study, but then met after multiple stimulations; blinding estimate met in ACT2 study.

[b]Differences in number of stimulations allowed, rescue medications, and outcome definition across studies.

[c]Low sample size.

TABLE 12 GRADE profile and summary of findings table for the efficacy of VNS for the reduction of the frequency of chronic cluster headache attacks and the pain intensity during attacks.

Comparison: VNS vs. sham treatment in chronic cluster headache								
Outcome: Proportion of attacks reaching pain relief at 15 min								
Certainty assessment Summary of findings								
No. of participants (studies)	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Effect (95% CI)**	**Certainty**	**Importance of outcome**
122 (2 RCTs, 1 meta-analysis)	Not serious[a]	Serious[b]	Not serious	Serious[c]		RR = 0.4 (0.2–0.6) for VNS vs. sham	Low	Critical
AEs	AE intervention: headache, nasopharyngitis, dizziness, oropharyngeal pain, and neck pain AE comparators: headache, nasopharyngitis, dizziness, oropharyngeal pain, and neck pain Important for consideration: none							

Note: Weak recommendation for noninvasive VNS based on low quality of evidence for treatment of attacks in chronic cluster headache.

Abbreviations: AE, adverse effect; CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; RCT, randomized controlled trial; RR, risk ratio; VNS, vagus nerve stimulation.

[a]Blinding estimate after first treatment not met in ACT1 study, but then met after multiple stimulations; blinding estimate met in ACT2 study.

[b]Differences in number of stimulations allowed, rescue medications, and outcome definition across studies.

[c]Low sample size.

TABLE 13 GRADE profile and summary of findings table for the efficacy of VNS for the reduction of the frequency of episodic and chronic cluster headache attacks and the pain intensity during attacks.

Comparison: VNS vs. standard of care (any headache drug)								
Outcome: reduction in frequency of attacks per week								
Certainty assessment						**Summary of findings**		
No. of participants (studies)	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Effect (95% CI)**	**Certainty**	**Importance of outcome**
93 (1 RCT)	Serious[a]	N.A.[b]	Not serious	Very serious[c]		Mean = 3.9 attacks reduction per week (0.5–7.2) for VNS vs. standard of care	Very low	Critical
AEs	AE intervention: headache, nasopharyngitis, dizziness, oropharyngeal pain, and neck pain AE comparators: headache, nasopharyngitis, dizziness, oropharyngeal pain, and neck pain Important for consideration: none							

Note: Weak recommendation for noninvasive VNS for the prevention of attacks in chronic cluster headache based on a low quality of evidence from a single randomized controlled trial.

Abbreviations: AE, adverse effect; CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; N.A., not applicable; RCT, randomized controlled trial; VNS, vagus nerve stimulation.

[a]Bias in blinding.

[b]Only one study.

[c]Low sample size and wide CI.

TABLE 14 GRADE profile and summary of findings table for the efficacy of SPG stimulators for the reduction of the frequency of cluster headache attacks.

Comparison: SPG vs. placebo								
Outcome: frequency of attacks								
Certainty assessment						**Summary of findings**		
No. of participants (studies)	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Effect**	**Certainty**	**Importance of outcome**
73 (2 studies)	Not serious	Not serious	Not serious	Not serious	None	Pain relief in ~65% of attacks	Moderate	Critical
AEs	AE intervention: SPG neurostimulator lead revisions and SPG neurostimulator explant procedures, sensory disturbance, localized loss of sensation, local infections, and mild facial paresis AE comparators: SPG neurostimulator lead revisions and SPG neurostimulator explant procedures, sensory disturbance, localized loss of sensation, local infections, and mild facial paresis Important for consideration: sensory disturbance, localized loss of sensation, and mild facial paresis							

Note: Strong recommendation for SPG stimulation based on a moderate level of evidence from two randomized controlled trials.
Abbreviations: AE, adverse effect; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; SPG, sphenopalatine ganglion.

are available. Because high dosages might be required, the therapeutic potential might take 14–21 days to develop. In experienced patients, dosages can be increased faster. Hence, it is debatable to use verapamil in episodic cluster headaches when episodes are short-lasting (1–3 months). In these cases, systemic or local corticosteroids may be more applicable due to the rapid efficacy. When the bout is ended, verapamil must not be ended abruptly, but should be gradually reduced over 2–4 weeks depending on the dose and finally stopped. Corticosteroids can be used in cases of frequent attacks to bridge the gap between the onset of verapamil medication and its effect. A further option is ergotamine tartrate (2 mg oral or suppository), if available. Triptans (such as frovatriptan) are possibly a better option, with a long half-life, if attacks occur primarily at night [99]. Very rarely, ergotamine is used as a long-term medication (1–2 months in episodic cluster headaches with short bouts).

Verapamil is generally well tolerated and may therefore be used as a long-term medication. However, side effects occur in 35% [98]; the most common are tiredness, constipation, and ankle swelling. Gingival hyperplasia can be a concern [100, 101]. A major concern is cardiac side effects due to the negative inotropic and chronotropic effects of verapamil. Approximately one third will develop bradycardia (hazard ratio < 60), and one fifth will develop atrioventricular conduction abnormalities [98]. Serious ECG changes can also develop during a stable dosage, so regular follow-ups with ECG are required [98, 102]. Verapamil may enhance lithium excretion.

Corticosteroids are only used as a transitional therapy or an additive, for example, while waiting for the effect of verapamil or other preventives to take effect [6]. When active periods are shorter than 8 weeks and occur only once per year, verapamil may be too slow to be efficacious (see above under verapamil). In these cases, corticosteroid treatment as a transitional therapy can be considered. There is one adequate randomized, placebo-controlled trial in episodic cluster headache [103], and a range of open label studies report the efficacy of corticosteroid infusions [104–109] (Table 9 and Tables S7 and S8). There is no specific evidence on whether corticosteroids are efficacious in chronic cluster headache. However, clinical experience suggests that there is no major difference to episodic cluster headache with respect to efficacy. The use of corticosteroids in chronic cluster headache is limited by the development of severe side effects, including Cushing syndrome; therefore, no recommendation can be given for this situation.

Steroids can be administered orally or as infusion. Another approach is local nerve blocks, mainly of the greater occipital nerve (GON), where cortisone is added. Oral medication has been recommended, applying the following dosages: prednisone (60–100 mg) taken as a single dose in the morning for 5 days and subsequently reducing the daily dose every 4–5 days by 10 mg. Once 10–20 mg is reached, cluster headache attacks can recur, and the dosage has to be increased again [110]. There is no methodologically sound evidence supporting this recommendation except a study from 1975, which compared oral prednisone with placebo in a double-blind crossover study ($n = 19$) [111]. Because of its side effects, prednisone should not be used as a long-term medication.

Lithium carbonate is used in dosages of 600–1500 mg. A plasma level of 1.2 mmol/L should not be exceeded; a serum level of a minimum of 0.4 mmol/L seems to be required for the medication to be efficacious; ideal is 0.6–0.8 mmol/L, but it has been suggested that there is no correlation between lithium plasma levels and efficacy [96]. Measuring plasma levels is useful to prevent side effects. Clinical efficacy is reached within 1 week [112]. Efficacy was evaluated by two controlled trials [113, 114] and several open label

studies [115–117]. Prior to the treatment onset, electrolyte tests, renal tests, thyroid tests, urine analysis, and ECG are required. Side effects are common. Regular control of renal and thyroid function and of electrolytes is required. The wide usage of lithium is based on small-scale, relatively old studies, on open label studies, and on case reports [96, 118, 119]. As lithium in general has a narrow therapeutic window, and the risk of bias across studies is serious (Table S18), it should only be used in cluster patients who do not respond to verapamil. Physicians are reminded of an interaction between lithium and indomethacin that increases lithium levels and can lead to lithium toxicity [120]. If paroxysmal hemicrania is considered, lithium must be stopped before indomethacin dosing.

Topiramate showed some effect in open label and case studies [121–126] (Table S19). Large-scale studies providing valid data have not been conducted. Clinical experience has shown promising results, if the medication is well tolerated. The published studies used topiramate as monotherapy. The most common side effects are cognitive disturbances, paresthesias, and weight loss. It is contraindicated in nephrolithiasis and glaucoma. The rate of side effects can be reduced by slowly increasing the dosage by 25 mg/week.

Ergotamine and triptans can be used in addition to other medication and thereby increase the clinical efficacy. In the past, ergotamine (without additional caffeine) was given at night to prevent nightly attacks (1–2 mg) [127]. DHE can quickly reduce symptoms if injected intramuscularly with a dosage of 1 mg; it is often associated with nausea, so almost invariably given with an antiemetic such as prochlorperazine or ondansetron. More interesting is the use of intravenous DHE [83] via infusion during 3–5 days in a hospital setting. This might reduce symptoms effectively in otherwise refractory patients [82]. However, ergotamine and DHE are not available in many European countries.

The pre-emptive use of 5-$HT_{1B/1D}$ receptor agonists (triptans) for cluster headache remains controversial. In case studies [128, 129], a case series [130], and a retrospective analysis of medical records [131], naratriptan reduced the number of attacks. However, the attempt to conduct a double-blind RCT on frovatriptan was discontinued early (after 11 of 80 initially planned patients) due to recruitment difficulties [99] (Table S20). In clinical practice, oral triptans are used as short-term preventives for the nocturnal attacks [132], although this approach is not supported by good evidence.

Melatonin

Ten milligrams of oral melatonin was associated with a reduction of the frequency of headache and in the consumption of analgesic medication at 1 and 2 weeks compared to baseline, in a randomized double-blind, placebo-controlled study [133] (Table S21). In a small case–control study in otherwise refractory cluster headache, melatonin did not produce any additional efficacy [134].

OnabotulinumtoxinA and other observational reports

Some case reports and small case series have evaluated the efficacy and tolerability of botulinum-neurotoxin-A as add-on therapy in refractory chronic cluster headache (rCCH) patients and showed some benefit when using the PREEMPT study protocol for the injection procedure [135]. However, the mechanism of how such treatment would exert effects is not clear given the pathophysiological background of TACs, and valid double-blind studies are missing. The same holds true for ketogenic diet [136], clomiphene [137], and ketamine [138, 139].

Calcitonin gene-related peptide pathway antagonists

Calcitonin gene-related peptide (CGRP) is elevated in spontaneous and triggered cluster headache, is normalized by treatment, and can itself trigger attacks when episodic cluster headache patients are in bout [140, 141]. Monoclonal antibodies to CGRP, the ones relevant here being fremanezumab and galcanezumab, have been developed and are efficacious in the preventive treatment of migraine [142, 143]. In a randomized placebo-controlled double-blind trial in episodic cluster headache, galcanezumab 300 mg sc was more efficacious than placebo in reducing weekly attack frequency at the primary endpoint of 3 weeks [144, 145] (see Table 10 and Tables S5 and S6). In a double-blind randomized placebo-controlled trial in episodic and chronic cluster headache, fremanezumab (NCT03107052) was not more efficacious than placebo in reducing attack frequency at the 4-week endpoint (data only published as a poster). Galcanezumab (NCT02797951) was not more efficacious than placebo at reducing attack frequency in chronic cluster headache [146] but was efficacious in episodic cluster headache [144] and well tolerated in the open label follow-up study including episodic and chronic cluster headache patients [147]. Galcanezumab is now licensed for the treatment of episodic cluster headache by the US Food and Drug Administration, whereas the European Medicines Agency has not approved this indication.

Combination of preventive medications

Although there is no valid evidence for the superiority of combining various preventative drug treatments in cluster headache, it is important to realize that some patients may do better with a combination rather than with extensively high doses of a single therapy [148]. In clinical practice, a combination of drugs may be required, generally using verapamil at the dose best combining efficacy and tolerability in the individual patient as the standard medication and any of the abovementioned preventive medications as add-on therapy. Some case reports or open case series report some effect of valproic acid [149]. The dosage starts with an initial 5–10 mg/kg body weight and can be increased to 20 mg/kg body weight. It can take up to 4 weeks for the treatment effect to develop. For the intranasal application of capsaicin as short-term prevention, an RCT evaluating the application to the ipsilateral versus contralateral side showed an efficacy for ipsilateral application [150], confirmed by an open label study [151]. A placebo-controlled double-blind RCT using local capsaicin showed a better effect in episodic compared to chronic cluster headache patients [152]. Intranasal application of civamide for short-term prevention showed modest efficacy in a recent double-blind, placebo-controlled study [153]. Capsaicin blinding is a very significant limitation for study result interpretation. There is no evidence

that baclofen 15–30 mg [154] or transdermal clonidine [155] have any preventive effect in cluster headache.

In summary, no recommendation on the combination of preventive medications can be given.

Noninvasive and invasive procedures

Noninvasive vagus nerve stimulation

Acute attack treatment

Two double-blind sham-controlled randomized trials (ACT1 and ACT2) evaluated the efficacy of noninvasive vagus nerve stimulation (nVNS) in treating the acute attacks in both episodic and chronic cluster headache [156, 157]. Pooled analysis of ACT1 and ACTS trials demonstrated that, compared to sham treatment, nVNS was associated with (i) 27% higher proportion of people responding to treatment at first attack and (ii) 22% higher proportion of attacks responding to treatment [158] (Table S22).

These effects were not replicated for chronic cluster headache [158].

Preventive treatment

nVNS plus standard of care was significantly better than standard of care alone in preventing cluster headache attack recurrence in an RCT including people with chronic cluster headache (PREVA study) [159]. The duration of follow-up was 4 weeks for the double-blind phase, and 4 weeks for an extension open label phase [159] (Tables 11–13 and Tables S9 and S10).

Interventional injection involving peripheral nerves

GON block has been investigated in two RCTs [160, 161] against placebo (both with a low number of patients). Unilateral GON block was reported to have a preventive effect in episodic and chronic cluster headache (Table S24). No data exist to indicate whether unilateral or bilateral block of the GON is more efficient, and the same holds true regarding performing a dual block of both the lesser occipital nerve and the GON or the GON alone.

Surgical procedures

Invasive neuromodulation

Sphenopalatine ganglion stimulation: Neurostimulation of the sphenopalatine ganglion (SPG) has been studied in two randomized sham-controlled studies. SPG stimulation was efficacious in treating attacks and in reducing attack frequency in patients with chronic cluster headache. In a multicenter randomized trial (28 participants), >70% were pain-free, had a significant reduction of attacks, or both. Most patients experienced side effects due to the surgery (mild to moderate hypesthesia of the maxillary nerve of up to 3-month duration) [162] (Table 14 and Tables S11 and S12). In a randomized, sham-controlled trial ($n = 93$), the odds ratio (responders) for pain relief at 15 min after onset of SPG stimulation in an acute attack was 2.62 ($p = 0.008$), and weekly cluster headache frequency was shown to be reduced (although this study was designed for acute treatment only). These effects were recently confirmed in another large RCT [145]. Adverse events were surgery-related, and all resolved. Long-term results after 18 months confirm these results in the majority of participants and indicate that pain reduction can be expected to last in the long term [163]. However, it is important to point out that for this treatment to be successful, surgeons with experience in this technique should be the ones to implant the stimulator. The method is not available at the time of writing, because the original manufacturer of the stimulation device and sponsor of all abovenamed studies went out of business in 2018, although a new company (https://realeve.net/) has been formed to provide the therapy [164].

Occipital nerve stimulation: Case series and uncontrolled studies have evaluated the effect of GON stimulation (ONS) [165–173]. In an uncontrolled study, 35 drug-resistant chronic cluster headache patients received invasive occipital nerve stimulation. After 48.8 months mean follow-up, 59% of the patients were responders (≥50% headache frequency reduction) [169]. The randomized double-blind ICON study compared 100% ONS intensity and 30% ONS intensity and reported for both intensities a substantially reduced cluster attack frequency [174]. Summarizing the results, both interventions have a 50% chance of significant improvement (Table 15). Deep brain stimulation (DBS) has more associated risks; hence, ONS should be attempted first, although side effects such as lead migration, cable break, battery depletion, and infection are quite common (Table 15 and Tables S13 and S14).

Deep brain stimulation: Based on the results from positron emission tomography and morphometric studies, DBS of the posterior inferior hypothalamus has been considered as an option for refractory cases. Positive results for the long-term effects have been reported [175–177] (Table S23). However, secondary worsening of the symptoms after initial improvements have also been reported, as has death [178]. Overall, the risk of bleeding with DBS is estimated at approximately 2%. Therefore, new surgical and perhaps less risky approaches have been developed, such as endoventricular tegmental stimulation [179]. An RCT was negative [180], although the observation was probably not timed well.

Destructive procedures

If all medications, noninvasive neuromodulation, and peripheral nerve blocks have failed to achieve pain reduction, and no other pathology might explain the headaches, more invasive approaches had been the only option in the past. These approaches are only reported in small case series or have only rarely resulted in positive outcome, or the effect might not be sustaining. Furthermore, surgery induces the risk of neuropathic pain and anesthesia dolorosa. Single case studies report a positive effect following the application of glycerol [181] or local anesthetics to the trigeminal cistern or the trigeminal ganglion [182], high-frequency rhizotomy of the trigeminal ganglion [183, 184], vascular decompression, or resection of the greater superficial petrosal nerve or the sphenopalatine ganglion [185, 186]. Other case studies, such as radiation of the entry zone for the trigeminal nerve (gamma knife) [187], report a neutral result or a worsening of symptoms [188].

TABLE 15 GRADE profile and summary of findings table for the efficacy of ONS for the reduction of the frequency of cluster headache attacks.

Comparison: ONS cohorts								
Outcome: frequency of attacks (follow-up: range = 39.7 months to 6 months)								
Certainty assessment						**Summary of findings**		
No. of participants (studies)	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Effect**	**Certainty**	**Importance of outcome**
181 (2 cohort)	Serious[a]	Serious[b]	Not serious	Serious[c]	None	Miller, 2016: 51 patients; baseline mean = 3.73, baseline SD = 1.83, follow-up mean = 2.12, follow-up SD = 2.28 Wilbrink, 2021: 130 patients; baseline mean = 15.75, baseline SD = 36.36, follow-up mean = 7.38, follow-up SD = 28.12	Very low	Critical
AEs	AE intervention: local pain, impaired wound healing, neck stiffness, and hardware damage AE comparators: local pain, impaired wound healing, neck stiffness, and hardware damage Important for consideration: impaired wound healing and hardware damage							

Note: No recommendation for greater ONS based on a very low level of evidence.Abbreviations: AE, adverse effect; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; ONS, occipital nerve stimulation.

[a]Single-arm studies, no comparator.

[b]Different follow-up times between studies.

[c]Wide confidence intervals in one of the studies.

Summary of recommendations for cluster headache

Attack treatment

The first option for the treatment of acute attacks of cluster headache should be subcutaneous injection of sumatriptan 6 mg or the inhalation of 100% oxygen with at least 12 L/min over 15 min. An alternative would be zolmitriptan (5 mg) or sumatriptan (20 mg) nasal spray, with the disadvantage of a slower onset than with injected sumatriptan. nVNS is recommended for the treatment of acute attacks in episodic but not chronic cluster headache. Weak recommendations based on consensus further include DHE nasal spray and lidocaine (Table 16).

Preventive treatment

Initial preventive treatment of cluster headache is usually verapamil at a daily dose of at least 240 mg. The maximum dose depends on efficacy or tolerability, and ECG monitoring is obligatory with increasing doses. Lithium is a drug of second choice if verapamil is inefficacious or contraindicated. Lithium dosing is monitored according to blood levels of lithium, whereas for other preventives, the maximum dose depends on efficacy and tolerability. Topiramate at least 100 mg per day with a starting dose of 25 mg is promising, but only open trials with topiramate as monotherapy exist at this point. Corticosteroids can be used for short periods where bouts are short or to help establish another medication. Clinically, the use of at least 100 mg oral or up to 500 mg iv per day methylprednisolone (or equivalent corticosteroid) over 5 days (then tapering down) can be an option. Based on consensus, ergotamine tartrate or frovatriptan are also recommended for short-term prevention. Despite some positive case reports, local civamide and/or intranasal capsaicin should only be used as short-term prevention in rare cases, due to side effects. If one medication does not achieve sufficient symptom reduction, a combination might be beneficial (Table 17). Because preventative treatment needs time for dose escalation, the question arises as to when to start preventative treatment in episodic cluster headache. No sufficient data exist, but depending on the length of the active period, the above-named preventatives or short-term treatment with prednisolone, frovatriptan, or naratriptan may be considered.

Pharmacological nerve block of the GON is recommended and can be repeated if efficacious. Galcanezumab 300 mg sc every month is recommended in otherwise intractable patients based on one RCT despite missing labeling by the European authorities.

TABLE 16 Summary of recommendations for acute medication for cluster headache.

Substance	Evidence	Recommendation for usage	Effect/comments	Dosage
Oxygen	Very low level of evidence	Strong Low adverse event profile[a] No contraindications[a] No interactions with other medications[a] Accepted by patients[a] Can be used several times per day[a]	• If used early in the attack, efficacious and quick acute pain reduction • No preventive effect • Best effect at onset of attack • Efficacy depends on age of patient, mean effect approximately 60%–80% • No contraindications, especially no cardiovascular risks • Rebound effect • Portable oxygen containers available	• >12 L 100% O_2 for 15 min using a nonrebreather mask
Sumatriptan	Low level of evidence for subcutaneous Moderate level for 20 mg nasal	Strong Only available parenteral medication for the treatment of acute attacks[a] Fast onset[a] Very high efficacy[a]	• Method of choice in acute attack • >75% of patients are pain-free within 5–20 min • Long-term follow-ups indicated no loss of efficacy if taken frequently • Can be combined with lithium, corticosteroids, or Ca^{2+} antagonists	• 6 mg subcutaneously using self-injection device; in cases of needle phobia or side effects, 20 mg nostril spray can be used
Zolmitriptan	Very low level of evidence for oral Low level of evidence for intranasal	Weak for oral Strong for nasal In part absorbed through the nose; fast onset[a] Accepted by patients[a]	• Two RCTs indicated efficacy • Ideal for patients with moderate pain and long-lasting attacks	5 mg po; or better 5 mg as nasal spray
Octreotide	Consensus statement[b]	Consensus	• 1 RCT indicated efficacy	Subcutaneous octreotide 100 μg
Lidocaine	Consensus statement[b]	Consensus	• Efficacious in ~25%–30% within minutes • Nerve block of the peripheral (parasympathetic) cluster headache symptoms • Approbatory treatment for patients with contraindications for triptans	• 1 mL 4%–10% lidocaine solution into ipsilateral nostril; sitting 45° reclination and 30–40° rotation to the ipsilateral side
Ergotamine	Consensus statement[b]	Consensus	• Very low evidence that DHE nasal spray may be efficacious	• 1 mg of DHE nasal spray

Abbreviations: DHE, dihydroergotamine; RCT, randomized controlled trial.

[a]Reasons for discrepancy between level of evidence and recommendation.

[b]In the absence of evidence/studies.

TABLE 17 Summary of recommendations for preventive medication for cluster headache.

Substance	Evidence	Recommendation	Effect/comments	Dosage
Verapamil	Consensus statement[a]	Consensus	• Preventive method of choice in episodic and chronic cluster • Efficacy reached depending on dosage after 2–3 weeks or prior experience • In most cases, no complete suspense of attacks • Prednisone to bridge time until efficacy reached	• 80 mg oral (1–1–1) daily, up to target dosage of 360 mg/day • Can be increased to 720 mg/day or higher • Monitoring for side effects (blood pressure and ECG)
Oral corticosteroids	Low level of evidence	Weak	• Additional to bridge time until verapamil is efficacious • Efficacious in 70%–80% of patients • Gastric protection required • Avoid prolonged treatment regimes	• Prednisolone initially 250 or 500 mg iv in the morning or 60–100 mg po for 5 days, followed by reductions of 10 mg every 4 days, or equivalent dosage of other corticosteroid • Threshold dosage 10-20 mg/day
Galcanezumab	Low level of evidence	Weak	One positive RCT for episodic but not chronic cluster headache	• 300 mg sc monthly • Low side effect profile
Lithium	Consensus statement[a]	Consensus	• Some studies indicate a similar efficacy to verapamil (70%) • Side effect, therefore only chosen if other medications are contraindicated or failed (chronic cluster) • Efficacy reached within 1–2 weeks	• 600–1500 mg po (initially 400 mg, representing 2 × 10.8 mmol/L) • After 4 days, increase to 2 × 400 mg • Regular check of lithium levels in the early morning 12 h after last dose • Narrow therapeutic window: lithium levels must not exceed 1.2 mmol/L; 0.4 mmol/L is probably sufficient; 0.6–0.8 mmol/L is ideal
Topiramate	Consensus statement[a]	Consensus	• No valid trials but open label case series indicating positive effect • Efficacious after 2–3 weeks	• Initially 25 mg/week, weekly 25 mg increase until efficacy is reached or side effects occur
Ergotamine-tartrate	Consensus statement[a]	Consensus	• Efficacious in 70% • In combination with antiemetic medication • Short-term prophylaxis and to bridge time until verapamil effect sets in • In patients with attacks during the night	• 2–4 mg/day • Ideal: 2 mg 1–0–1 • If attacks in the night: 2 mg oral in late evening
Frovatriptan	Consensus statement[a]	Consensus	Short-term prophylaxis and in patients with attacks during the night	• 2.5–5 mg/day, e.g., 1–0–1 • If attacks in the night: 2.5 mg oral in late evening
Valproic acid	Consensus statement[a]	Consensus	• Only one trial indicating preventative efficacy • Can be used if other medication has failed (method of third choice) • Influenced circadian rhythm in animal studies; reduces GABA activity • Reaching efficacy can take up to 4 weeks	• Initially 5–10 mg/kg body weight, increase every 4 days by 5 mg (up to 20 mg/kg body weight) • In adults ~1200 mg (3 × 400 mg) per day
Melatonin	Consensus statement[a]	Consensus	• Can be used if other medication has failed (method of third choice) • Can be tried in patients with sleep problems	• 10 mg orally • Not efficacious in refractory cluster headache

Abbreviations: ECG, electrocardiogram; GABA, γ-aminobutyric acid; RCT, randomized controlled trial.

[a]In the absence of evidence/studies.

(Continues)

TABLE 18 Summary of recommendations for invasive and noninvasive procedures for cluster headache.

Intervention	Evidence	Recommendation	Effect/comments	Procedure
nVNS	Low level of evidence for episodic cluster Low level of evidence for chronic cluster	Strong Low adverse event profile[a] Noninvasive[a] No interactions[a]	• Efficacious in aborting attacks in episodic cluster headache • Can be used as add-on treatment	• Three self-administered consecutive 2-min stimulations ipsilateral to the CH attack at the time of attack onset • Not efficacious in chronic cluster headache • Low side effect profile
GON block	Consensus statement[b]	Consensus	• Additional to bridge time until verapamil is efficacious • Efficacious in 70%–80% of patients	• 2.5 mL betamethasone (rapid and long acting) plus 0.5 mL Xylocaine 2% sc ipsilateral to the pain
GON stimulation	Consensus statement[b]	Consensus	• Can be used if all medication has failed (method of third choice)	• Unfavorable efficacy/side effect profile
SPG stimulation	Moderate level of evidence	Strong	• Efficacious in aborting attacks and reducing attack frequency • Efficacious in 60%–70% of patients • At the time of publishing, not available in Europe	• Long-term results after 18 months confirm efficacy • Adverse events were surgery-related and all resolved

Abbreviations: CH, cluster headache; GON, greater occipital nerve; nVNS, noninvasive vagus nerve stimulation; SPG, sphenopalatine ganglion.
[a]Reasons for discrepancy between level of evidence and recommendation.
[b]In the absence of evidence/studies.

Surgical procedures are not indicated in most of the patients with cluster headache. European consensus publications indicate whether and for which type of patient a neurostimulation can be recommended [189, 190]. Doctors should be guided by the diagnostic criteria for refractory patients [191] and based on consensus, nVNS and SPG stimulation are the most promising approaches and should be discussed with the individual patient (Table 18). ONS is not recommended due to side effect profile, but because it is moderately effective and DBS has potentially more side effects, it could be discussed with patients before DBS is planned.

Need of update

These recommendations should be updated within 4 years, in particular with respect to the efficacy of biologic treatments in the preventative treatment of cluster headache and with respect to the efficacy, tolerability, and long-term results of SPG stimulation and nVNS.

ACKNOWLEDGEMENTS

Open Access funding enabled and organized by Projekt DEAL.

CONFLICT OF INTEREST STATEMENT

The present guidelines were developed without external financial support. None of the authors declares a conflict of interest. The authors report the following financial support. A.M. (past 3 years): Salary from the University Hospital of Hamburg; unrestricted scientific support for the University Clinic of Hamburg from Novartis; Chief Editor for *Cephalalgia* and *Cephalalgia Reports*. S.E. (past 3 years): Salary from Verein zur Betreuung Schwerbehinderter; honoraria and research grants from Lilly, Lundbeck, Novartis, Perfood, and Teva. P.J.G. (past 3 years): Salary from King's College London; grants and personal fees from Eli Lilly; grant from Celgene; personal fees from Aeon Biopharma, Allergan/Abbvie, Amgen, Biodelivery Sciences International, Biohaven Pharmaceuticals, CoolTech, Dr Reddys, Epalex, GlaxoSmithKline, Impel Neuropharma, Lundbeck, Novartis, Praxis, Sanofi, Satsuma, and Teva Pharmaceuticals; personal fees for advice through Gerson Lehrman Group, Guidepoint, SAI Med Partners, and Vector Metric; fees for educational materials from CME Outfitters, Omnia Education, and WebMD; publishing royalties or fees from Massachusetts Medical Society, Oxford University Press, UptoDate, and Wolters Kluwer; fees for medicolegal advice in headache; a patent magnetic stimulation for headache (No. WO2016090333 A1) assigned to eNeura without fee. R.J. (past 3 years): Salary from the University of Copenhagen and Rigshospitalet, Denmark; honoraria for lectures from Allergan, Teva, Novartis, and Autonomic Technologies; conducted clinical trials for Eli Lilly, Electrocore, and Autonomic Technologies; research grants from Lundbeck Foundation, TRYG Foundation, University of Copenhagen, NovoNordisk, Capital Region, and the Medical Society of Copenhagen. G.C.M. (past 3 years): Honoraria as advisory board and consultant for Med-ex. J.P. (past 3 years): Salary from the University of Cantabria; honoraria and/or research grants from Allergan, Almirall, Biohaven, Instituto de Salud Carlos III, Eli Lilly, Novartis-Amgen, Stendhal, and Teva. M.L. (past 3 years): Salary from the Foundation of the Carlo Besta Neurological Institute, Milan. P.P.-R. (past 3 years): Salary from Vall d'Hebron University Hospital; honoraria as consultant and speaker for Allergan, Biohaven, Chiesi, Eli Lilly, Lundbeck, Medscape, Pfizer, Novartis, and Teva; research grants from AbbVie, AGAUR, la Caixa foundation, FEDER RIS3CAT, EraNet NEURON, International Headache Society, Instituto de Salud Carlos III, Novartis, and Teva.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: May A, Evers S, Goadsby PJ, et al. European Academy of Neurology guidelines on the treatment of cluster headache. *Eur J Neurol*. 2023;30:2955-2979. doi:10.1111/ene.15956

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