

# Recent advances in the diagnosis and management of cluster headache

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## ABSTRACT

Cluster headache, a primary headache disorder, consists of short (15-180 minutes), frequent (up to eight a day), unilateral attacks of facial pain with associated ipsilateral autonomic features and restlessness. The attacks are suspected to be one of the most painful human experiences, and the disorder is associated with a high rate of suicidal ideation. Proper diagnosis is key, as some of the most effective treatments, such as high flow oxygen gas, are rarely used in other headache disorders. Yet diagnostic delay is typically years for this disorder, as it is often confused with migraine and trigeminal neuralgia, and secondary causes may be overlooked. This review covers the clinical, pathophysiologic, and therapeutic features of cluster headache. Recent updates in diagnosis include the redefinition of chronic cluster headache (remission periods lasting less than three months instead of the previous one month), and recent advances in management include new treatments for episodic cluster headache (galcanezumab and non-invasive vagus nerve stimulation).

## Introduction

Cluster headache is an uncommon headache disorder with unique features that provide valuable insight into the neurobiology of headache. As the origins of this severely painful disorder continue to be investigated and better understood, challenges in timely diagnosis and proper management of cluster headache persist. This review seeks to improve the recognition of cluster headache by describing not only classic characteristics but other features of the disorder (for example, aura) that might contribute to diagnostic delays. The various modes of treatment in cluster headache, including newly available therapies, are also described; the management of special populations is included. This review is the first to contain a video of a patient acutely treating a cluster attack. In it, we also seek to improve understanding of disease and treatment mechanisms by detailing relevant pathophysiology and neuropharmacology. Adding to advancements in headache medicine in recent years, cluster headache offers important insights into the biology of headache. Continued research is warranted, but it can occur only in conjunction with improved recognition of the disorder and treatment of patients.

## Sources and search criteria

We searched Medline for articles on cluster headache over the past five years (1 January 2016 to present) by using the following research string: (((“Cluster Headache”[Mesh])) OR (“cluster headache”[tiab] OR “cluster headaches”[tiab] OR “probable cluster

headache”[tiab] OR “Ciliary Neuralgia”[tiab] OR “Cluster Headache Syndrome”[tiab] OR “Histamine Cephalgia”[tiab] OR “Horton Syndrome”[tiab] OR “Horton’s Syndrome”[tiab] OR “Chronic Cluster Headache”[tiab] OR “Chronic Cluster Headaches”[tiab] OR “Episodic Cluster Headache”[tiab] OR “Atypical Cluster Headache”[tiab])) OR (“cluster headache”[ot] OR “cluster headaches”[ot] OR “Chronic Cluster Headache”[ot] OR “Episodic Cluster Headache”[ot])) AND 2016:2021[dp]. The two authors reviewed relevant titles, followed by relevant abstracts, and then relevant articles. We each did the entire process independently. We also added relevant references on the basis of our narrative reviews of the literature. For determination of articles to include in this review, we prioritized guideline recommendations, systematic reviews, and clinical trials. Data were lacking in some areas, so we next prioritized observational studies and case series (favoring studies with large population sizes). We excluded case studies. For basic science, we prioritized imaging and molecular data not already covered in guidelines or systematic reviews. Evidence for each section is as follows.

**Epidemiology section**—Data are based on systematic reviews and meta-analyses unless otherwise noted.

**Clinical manifestations section**—The diagnostic criteria are based on the official definition from the Classification Committee of the International Headache Society. The remainder of the information in this section is based on observational studies, primarily in Europe and the US.

*Pathophysiology section*—Data are based on primary studies from laboratory and imaging studies, as well as clinical trials, with relevant reviews provided for the hypothalamus section.

*Treatment section*—For acute, bridge, and preventive treatments, data are based on official recommendations from the American Headache Society (AHS) and European Federation of Neurological Societies (EFNS).<sup>1 2</sup> We also report individual data from clinical trials, observational studies, and surveys of patients, as noted in the text. For patient directed disease management, refractory patients, pregnant and lactating patients, and pediatric patients, data in the literature are quite limited. These are important aspects of cluster headache to discuss, however, so we present these topics primarily on the basis of expert opinion and patient reports.

## Epidemiology

### General features

The lifetime prevalence of cluster headache is 0.12% (95% confidence interval 0.10% to 0.15%) in 16 articles across four continents, although data on one year incidence are limited.<sup>3</sup> Onset can occur at any age but is typically between 20 and 40 years of age on the basis of large case series and questionnaires.<sup>4-7</sup> Men are more likely than women to have cluster headache, although the exact sex ratio is unclear (box 1). Little is known about race and cluster headache, but a recent review suggests that Asian countries have greater male predominance, lower prevalence of chronic cluster headache, less restlessness, and less circadian periodicity compared with European and North American populations.<sup>11</sup> However, whether these differences are due to race, location, cultural aspects, or other factors is unclear.

### Comorbidities

Cluster headache is associated with an increased risk of sleep apnea<sup>4 12</sup> and, interestingly, a potentially decreased risk of diabetes.<sup>9 13 14</sup> Psychological comorbidities are common in cluster headache, especially mood disorders as patients are at an increased risk of both anxiety and depression.<sup>15-17</sup> The rate of suicidal ideation is distressingly high, upwards of 55-64% of patients in studies from the US and South Korea.<sup>4 18</sup>

Although suicidal ideation may be the most notable comorbidity, the best established may be tobacco use. An increased prevalence of smoking has been reported in many studies.<sup>4 19 20</sup> Whether the relation between tobacco use and cluster headache is one of

correlation or causation is unclear, although a recent study suggests that smoking often starts before the onset of cluster headache.<sup>21</sup> Unfortunately, stopping tobacco and nicotine use does not seem to alter the disease once it starts.<sup>20</sup>

## Clinical manifestations

### Diagnostic criteria

The hallmark of cluster headache is the cluster attack, a severely painful unilateral (and typically exclusively one sided or side locked) headache focused behind or around the eye accompanied by ipsilateral autonomic symptoms and restlessness. Cluster attack pain is of a stabbing, searing quality, sometimes described as a knife in the eye or a meat grinder behind the eye. Duration, frequency, and particularly restlessness during attacks distinguish it from more common headache disorders (migraine or tension-type headache). Table 1 outlines the diagnostic features of cluster headache. The descriptions in the “Most common” column in table 1 are largely gathered from retrospective reports, which are recognized to overestimate the duration and severity of attacks.<sup>26</sup> With regard to attack duration, in addition to the biases involved with retrospective reports, patients in these studies might have included pre-ictal and post-ictal phases of attacks.

Approximately 80% of patients with cluster headache have the episodic subtype, wherein attacks occur only during a period of weeks to months, often occurring on an annual cycle. The remainder have the chronic subtype, wherein attacks occur regularly throughout the year without remission longer than three months.<sup>27</sup> The three month cut-off for remission has recently been updated from the former one month cut-off.<sup>28</sup> An estimated 15% of patients may transition from one subtype to another.<sup>23 24</sup>

### Characteristics and other clinical features

Although its attacks are quite distinct, cluster headache is often misdiagnosed,<sup>4 29 30</sup> resulting in diagnostic delays ranging from months to decades.<sup>4 24 29</sup> In addition to careful review of the diagnostic criteria, other features of the disease assist in making the correct diagnosis.

### Intensity of pain

The pain intensity in cluster headache is renowned, although it may be dismissed by people unfamiliar with the disease. In a retrospective online survey of 1604 patients with cluster headache, the average pain intensity of a cluster attack was 9.7 on the 0-10 numerical rating scale, whereas the next highest pain was childbirth at 7.2.<sup>4</sup> Intra-individual variability may be high; a single patient, who recorded 4600 attacks over six years, recorded attacks that ranged from 1 to 9 out of 10 in intensity.<sup>31</sup> Inter-individual variability may also be high; in a prospective clinic based study of 57 patients and 500 attacks, pain intensity of cluster headache was rated an average of 7.0 out of 10.<sup>32</sup> This lower pain intensity may highlight the differences between retrospective and

#### Box 1: Sex ratios and cluster headache

The true sex ratio is unclear, as the sex ratio decreased each decade from the 1960s to the 1990s at a single site,<sup>8</sup> and the male to female ratio was 4.3:1 in a 2008 meta-analysis<sup>3</sup> but 1.3-2.6 in large studies in the 2010s.<sup>4 5 9</sup> Previous misdiagnoses in women are one possible reason for the decreasing sex ratio.<sup>10</sup>

Table 1 | Criteria for cluster headache\*

Parameter	Most common	
<b>Attack characteristic</b>		
Pain intensity	Severe or very severe	Very severe (9.7/10) <sup>22</sup>
Laterality	Unilateral and typically side locked	Unilateral and side locked (right > left) <sup>4 23 24</sup>
Location	Orbital, supraorbital, and/or temporal	Orbital <sup>4 22 23</sup>
Associated features (either or both of 1 and 2)	1. At least one ipsilateral to pain: 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. Restlessness or agitation	Lacrimation, rhinorrhea, nasal congestion, ptosis <sup>4 10 22 23</sup> Restless, agitated
Duration (when untreated)	15 to 180 minutes	100 minutes <sup>4 5 10 24 25</sup>
Frequency	1 every other day to 8 daily	2 to 4 daily <sup>4 10 23</sup>
Number of attacks	A total of five attacks is required before the diagnosis can be made	
Other diagnoses ruled out	Not better accounted for by another headache or facial pain diagnosis	
<b>Subtype</b>		
Episodic	Periods of attacks lasting from 7 days to 1 year with pain-free remission $\geq 3$ months	Prevalence: 80%
Chronic	Attacks for >1 year with pain-free remission <3 months	Prevalence: 20%

\*Criteria based on International Classification of Headache Disorders, 3rd edition (ICHD-3).

†Subject to overestimation in retrospective reports<sup>26</sup>

prospective approaches, between online and clinic based populations, or between patients taking effective preventive treatments and those without effective prevention. However, it may also suggest that some patients have less severe attacks and that pain intensity alone is not a defining feature.

#### *Premonitory and inter-ictal symptoms*

Pain and associated symptoms are most severe ictally, but patients also report premonitory and inter-ictal symptoms. Most patients (approximately 83%) describe sensations before an attack, such as ipsilateral aching, lacrimation, or nasal congestion (minutes before), as well as generalized symptoms, such as difficulty concentrating and mood changes (one hour before).<sup>25</sup> Among patients with cluster headache, the localized sensations are commonly referred to as “shadows.” The literature on shadows is limited, but they may precede attacks or manifest in isolation, sometimes as the herald of a new cycle.<sup>33</sup> Mild symptoms may also remain between attacks, particularly if attacks occur multiple times daily. In this case, the pain may be nearly constant and can be confused with hemicrania continua.

#### *Migrainous symptoms*

Up to two thirds of patients with cluster headache report sensitivity to light and sound, and about a quarter report nausea/vomiting during attacks.<sup>4 10 23 34</sup> Some patients report auras that are quite similar to those described in migraine.<sup>4 23 34 35</sup> Cluster headache can thus be confused with migraine, especially as some patients with migraine show cranial autonomic features.<sup>36 37</sup> Cluster headache and migraine can best be differentiated by duration (shorter than three hours in cluster headache; longer than four hours in migraine) and restlessness (typically present in cluster headache as discussed below; typically absent in migraine as movement often worsens the headache).

#### *Restlessness and self-injury*

Attack related restlessness is one of the most distinctive features of cluster headache. During

attacks, patients may pace, rock, vocalize, and carry out other various activities, such as push-ups and running.<sup>38</sup> At times, patients may carry out self-injurious behaviors; importantly, these are usually unrelated to suicidal ideation (discussed below). Hitting or rubbing one’s head, punching the wall, and cutting or piercing the skin are some such self-injurious behaviors carried out during attacks.<sup>4 38 39</sup>

Video 1 shows a striking demonstration of attack related restlessness, as well as reflection on the attack.

**Video 1 | A 60 year old man with chronic cluster headache has an attack in the presence of family. The attack has been occurring for 14 minutes at the start of the video. Right sided retro-orbital pain, which the patient rates as 7/10, and rhinitis are evident. The patient’s son prevents him from striking his head as he is taking an anticoagulant, although he manages to rub his temple and press his eye. The patient inhales high flow oxygen (25 L/min) using a non-rebreather mask customized for cluster headache (ClusterO2 Kit). As the attack subsides, he continues to inhale oxygen to ensure complete termination. His attacks are typically right sided retro-orbital stabbing pain, which he rates at 5-6/10 in intensity, associated with ipsilateral lacrimation, rhinorrhea, nasal congestion, and restlessness**

sche059577-vid1The BMJ Video Player

#### *Dysautonomia*

Systemic and central changes in autonomic tone have been observed in patients with cluster headache, including bradycardia, altered tilt table testing, and nocturnal lipolysis.<sup>40-42</sup> Some authors have called cluster headache a “parasympathetic paroxysm,” given the many autonomic alterations.<sup>41</sup>

#### *Circadian and circannual patterns*

Cluster headache has several different names and eponyms, but “cluster” is a descriptive term highlighting the chronobiology of the disease. Approximately 80% of patients can predict the time of day when attacks occur, the most common being between 2 am and 3 am.<sup>4 43</sup> Attacks may arise during daytime naps but are more than twice as common

during nocturnal sleep, suggesting additional factors besides sleep alone.<sup>43 44</sup> Attacks may arise during any stage of sleep.<sup>45 46</sup>

Annual rhythmicity is reported in approximately two thirds of patients with episodic cluster headaches and one third of those with chronic cluster headaches.<sup>4 43</sup> Summer is reported as the least burdensome time of year; a strong negative association between daylight hours and attack burden has been identified.<sup>43</sup> Spring and fall were identified as the most common times of year for attacks,<sup>4 23</sup> which may reflect not only daylight changes but also weather fluctuations and other environmental triggers (see “Attack triggers”).<sup>4 43</sup>

#### Attack triggers

The most common trigger for cluster attacks is alcohol, present in 40-80% of patients.<sup>4 10 23 34 47</sup> Many other triggers, falling into several categories, have been reported (table 2). Although some of these stimuli are triggers for other types of headache attacks (such as migraine), asking about them in detail can assist in diagnosis. For instance, sublingual nitroglycerin provokes cluster attacks within an hour, whereas migraine attacks are delayed up to 12 hours.<sup>51-53</sup> Importantly, triggers in patients with episodic cluster headache are effective only when the patient is in a headache cycle; outside of the cycle, the triggers have no effect.

#### Differential diagnosis

Two considerations are important in the differential diagnosis of cluster headache: primary headache disorders with similar features and secondary headaches that present with cluster-like headaches.

For primary headaches, cluster headache is part of a group of five disorders called trigeminal autonomic cephalalgias; these all present quite similarly but differ in duration, frequency, and treatment. The other four trigeminal autonomic cephalalgias are hemicrania continua, paroxysmal hemicrania, short lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT), and short lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA). Like cluster headache, the other trigeminal autonomic cephalalgias present with ipsilateral autonomic features and, at least for hemicrania continua and paroxysmal hemicrania, restlessness. Cluster headache is sometimes confused with hemicrania continua (constant pain) and paroxysmal hemicrania (pain lasting two to 30 minutes occurring more than five times a day). However, both

hemicrania continua and paroxysmal hemicrania are treated completely with indomethacin whereas cluster headache is not. SUNCT and SUNA, with headaches lasting between one second and 10 minutes and with cutaneous triggers, are more often misdiagnosed as trigeminal neuralgia than cluster headache. However, in a meta-analysis of more than 4000 patients, the most common primary headaches and facial pain misdiagnoses of cluster headache were in fact trigeminal neuralgia and migraine.<sup>54</sup>

Secondary causes for cluster headache also exist, including pituitary adenomas, meningiomas, arteriovenous malformations, and other lesions (fig 1).<sup>55 59-61</sup> These lesions can present with attacks that are indistinguishable from primary cluster headache, but treatment of the lesions can be curative. For pituitary adenomas, prolactinomas seem to be the most common secondary cause, although some pituitary adenomas may be incidental and treatment may not relieve the headaches.<sup>62</sup> Other secondary headaches confused with cluster headache include acute angle glaucoma, impacted molar teeth, Tolosa-Hunt syndrome, and temporal arteritis. However, these disorders typically present similarly but not identically to primary cluster headache.

#### Pathophysiology

The mechanism of cluster headache has not been fully explained. No molecular blood tests, single gene polymorphisms, or imaging biosignatures are available to diagnose cluster headache. No animal models that recapitulate most of the features of cluster headache exist—only models that examine parts such as the pain component or the autonomic component.<sup>63 64</sup> Our current understanding is based on clinical observations, molecular changes, and imaging findings, which suggest that at least three systems are involved in cluster headache: the trigeminovascular system, the autonomic system, and the hypothalamus (fig 2). The most direct evidence that these systems are involved is that neuromodulation of all three systems—occipital nerve stimulation (trigeminovascular system), sphenopalatine ganglion stimulation (autonomic system), and hypothalamic deep brain stimulation—have all shown promise in treating cluster headache.

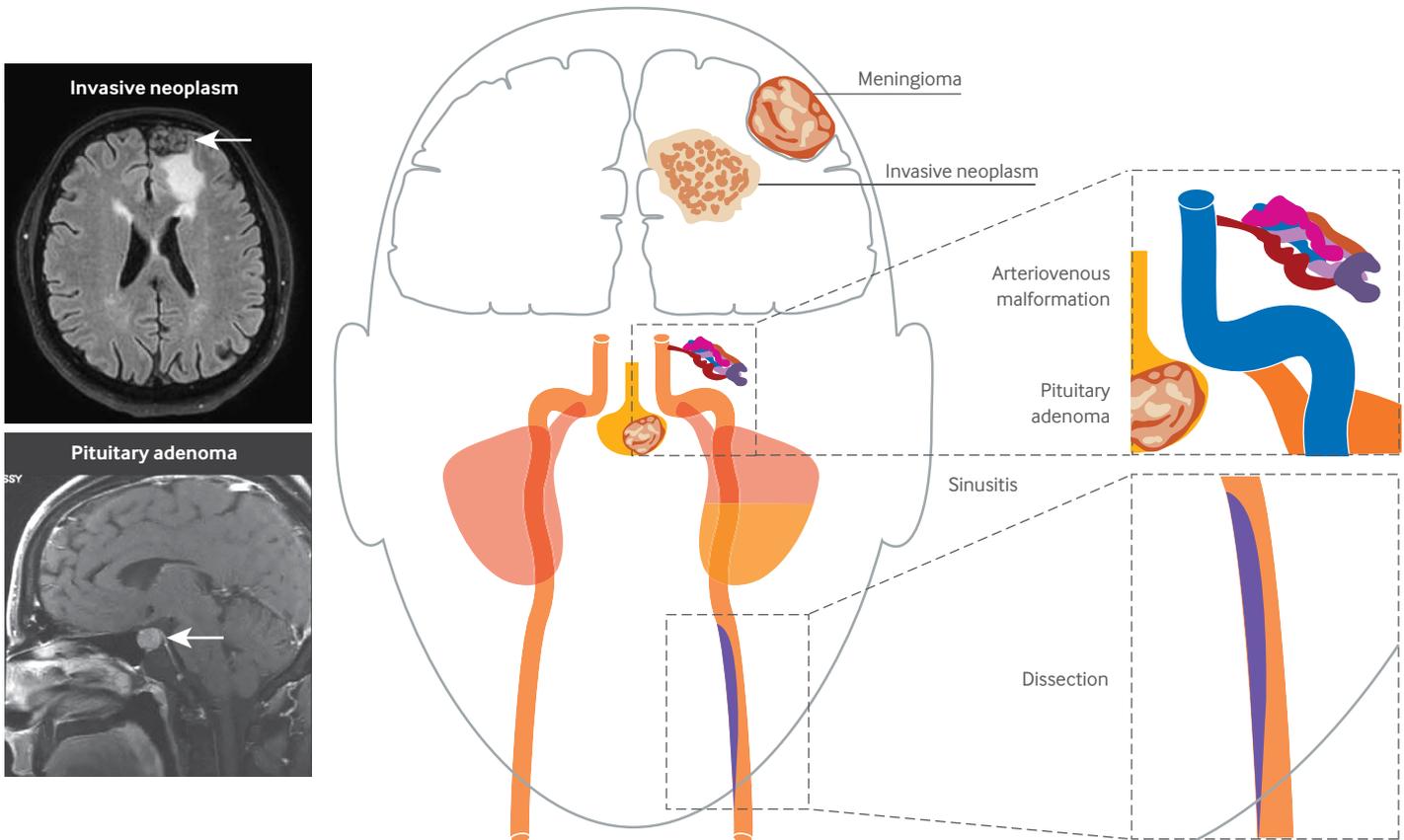
#### Trigeminovascular system

Anatomically, the trigeminovascular system receives extracranial inputs (skin, muscles, fascia, and blood vessels of the face, as well as the sinus mucosa and dental structures) from all divisions of the trigeminal nerve and intracranial inputs (dura, dural arteries,

**Table 2 | Triggers of cluster attacks**

Category	Attack trigger
Chemical <sup>4 10 23 34 47-49</sup>	Alcohol (usually within 1 hour); nitroglycerin, PDE5 inhibitors (eg, sildenafil); strong smells (eg, perfumes, cleaners)
Environmental <sup>4 10 50</sup>	High altitude (eg, flying, mountain climbing); weather changes (eg, temperature, barometer); bright sun (particularly reflecting off snow)
Physiologic <sup>10 48</sup>	Sleep (nocturnal sleep > daytime naps); circadian disruption (eg, shift work, jetlag, daylight savings); stress or relaxation (drop in hormones after stress); menstruation, menopause, post partum; low testosterone concentrations

PDE5=phosphodiesterase type 5.



**Fig 1 | Secondary causes of cluster-like headaches.** Cluster headache is a primary headache disorder with no known underlying lesions. However, in rare cases, secondary or “symptomatic” causes exist that are indistinguishable from primary cluster headache, and treatment of the lesion results in resolution of the headaches. On the left are two cases of secondary cluster-like headaches from the authors’ personal experiences: an invasive metastatic neuroendocrine tumor (the headaches resolved after resection of the left frontal tumor) and a pituitary tumor or more specifically a prolactinoma (the headaches completely remitted once cabergoline was started to correct the prolactinemia). On the right is a diagram of the more frequent causes of secondary cluster-like headaches from reviews of case reports.<sup>55-57</sup> The imaging for the pituitary tumor is reprinted with permission<sup>58</sup>

large venous sinuses, and larger arteries near the circle of Willis) via the ophthalmic or V1 division.<sup>66</sup> The pain component of these inputs is carried through the trigeminal ganglion to the inferior-most part of the trigeminal nucleus in the trigeminal nucleus caudalis. Here, the trigeminal nucleus caudalis is grouped with the adjacent dorsal horns of the upper cervical spinal cord (C1-3) to create a functional unit called the trigeminocervical complex. This trigeminocervical complex thus includes pain dermatomes of the entire head and neck, providing a possible explanation for why many patients with headache feel pain that extends beyond the trigeminal area to other parts of the head. The trigeminocervical complex then connects to thalamic, cortical, and other pain processing areas known to be abnormal in cluster headache on the basis of structural and functional imaging studies.<sup>67</sup>

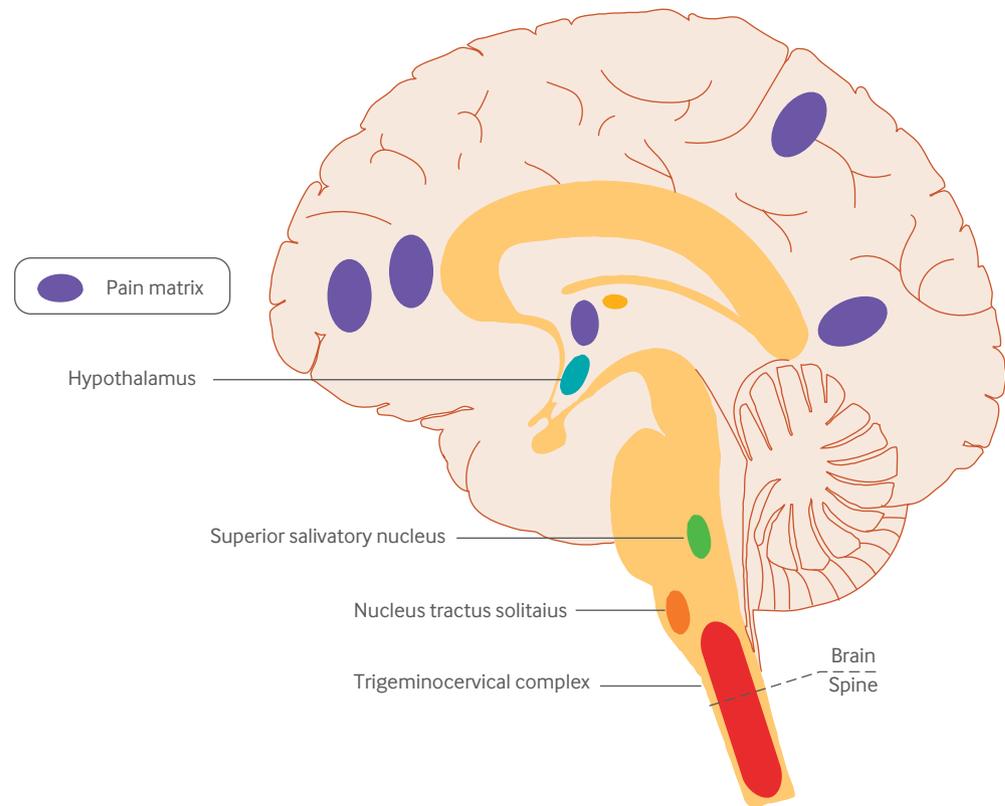
The location of pain in cluster headache is primarily the V1 distribution, but several clinical observations suggest that the entire trigeminocervical complex is involved. Firstly, many patients have reported pain of the upper teeth or V2 distribution,<sup>68</sup> with 18% of 230 British patients mistakenly having dental procedures in an effort to treat the attacks.<sup>30</sup> Despite patients rarely having occipital pain, suboccipital steroid

injections are effective in cluster headache, likely via actions on the trigeminocervical complex. Finally, many of the secondary causes of cluster headache are inputs into the trigeminocervical complex, including vascular malformations, arterial dissections, maxillary sinus infections, and meningiomas.<sup>60-61-69</sup>

Molecularly, the trigeminovascular system uses several pain signaling molecules, including calcitonin gene related peptide (CGRP) and pituitary adenylate cyclase activating peptide-38 (PACAP-38). Blood concentrations of CGRP and, in preliminary studies, PACAP-38 are increased during a cluster headache attack.<sup>70-71</sup> Moreover, infusions of both CGRP and PACAP-38 trigger cluster headache attacks in patients with cluster headache.<sup>72-73</sup>

#### Autonomic system

The cranial autonomic system in cluster headache includes both parasympathetic hyperactivity (such as lacrimation and conjunctival injection) and sympathetic inactivity (miosis and ptosis). The autonomic features of cluster headache include a parasympathetic circuit from the superior salivatory nucleus, to the sphenopalatine ganglion (via the facial nerve), to the lacrimal and other glands of the



**Fig 2 | Current understanding of the pathogenesis of cluster headache.** According to clinical, imaging, biomarker, and neuromodulation studies, several systems and multiple brain areas are involved in cluster headache. These ultimately lead to activation of the widely distributed pain matrix (purple). During a cluster headache attack, altered pain matrix areas include (from left to right in purple) the prefrontal cortex, anterior cingulate cortex, thalamus, primary somatosensory cortex, and insula<sup>65</sup>

face.<sup>74</sup> Evidence for the importance of the superior salivatory nucleus comes from basic science data, in which oxygen gas was found to have anti-nociceptive effects through modulation of the superior salivatory nucleus.<sup>64</sup> Evidence for the importance of the sphenopalatine ganglion pathway comes from clinical studies, in which low frequency stimulation of the sphenopalatine ganglion induces attacks whereas high frequency stimulation inhibits attacks in patients with cluster headache.<sup>75</sup> The role of the sympathetic pathway in cluster headache is less understood, although post-carotid endarterectomy headaches can present as cluster headache-like pain.<sup>27</sup> Carotid endarterectomies physiologically might include damage to both sympathetic and trigeminal fibers, and some authors have proposed that damage to both of these structures could indirectly lead to parasympathetic activation.<sup>76</sup>

At the molecular level, the autonomic system uses several signaling molecules: it shares PACAP-38 with the trigeminovascular system and also uses vasoactive intestinal peptide. Infusions of vasoactive intestinal peptide, like PACAP-38 and CGRP, trigger cluster headache attacks in patients with cluster headache.<sup>72</sup>

The cranial autonomic system connects with the trigeminovascular system through the trigeminal autonomic reflex, a physiologic response to facial pain that protects the eye (for example, lacrimation), nose (for example, rhinorrhea), and other facial structures.<sup>74</sup>

The trigeminal autonomic reflex is in fact bidirectional, as sphenopalatine ganglion stimulation dilates cranial arteries that activate the trigeminocervical complex.<sup>77</sup> This reflex has been recently studied clinically via irritation of the nose, which caused a statistically significant increase in lacrimation.<sup>78</sup> However, in patients with cluster headache, this nose irritation did not trigger an attack, suggesting that the trigeminal autonomic circuit alone is insufficient to trigger a headache and that a central input, such as the hypothalamus, may be necessary.<sup>78</sup> The hypothalamus, in particular the paraventricular nucleus,<sup>79</sup> not only connects to the autonomic system but is of crucial importance to the central autonomic network.<sup>80</sup>

### Hypothalamus

The posterior hypothalamus is one of the few areas activated at the beginning of a cluster headache attack.<sup>67 81 82</sup> This is a strong indication of hypothalamic involvement in cluster headache, but it is far from the only indication (table 3). The exact role of the hypothalamus is still unclear, but it may be involved in the initiation of attacks on the basis of three lines of evidence. The first is the functional imaging data noted above, showing that the posterior hypothalamus is active at the beginning of an attack. The second is hypothalamic deep brain stimulation: some stimulation parameters could activate an attack,<sup>93</sup> but no stimulation parameters were found

**Table 3 | Multiple lines of evidence for hypothalamic involvement in cluster headache**

Feature	Clinical data	Relevant hypothalamic area
Circadian periodicity <sup>83 84</sup>	Most patients have headaches at the same time each day. Across multiple time zones, the most common time for an attack is 2 am	Suprachiasmatic nucleus
Circannual periodicity <sup>65</sup>	In episodic CH, the most common seasons for a headache cycle are spring and fall. Patients with chronic CH may have yearly cycles in the frequency of attacks	Unknown, suspect suprachiasmatic nucleus
Restlessness/agitation <sup>85</sup>	Restlessness/agitation is a defining criterion of cluster headache	Ventromedial hypothalamus
Structural imaging <sup>67 81</sup>	VBM: enlargement of the anterior hypothalamus	Anterior hypothalamus (including suprachiasmatic nucleus)
Functional imaging <sup>67 81</sup>	PET: activation of the ipsilateral inferior posterior hypothalamus in nitroglycerin triggered CH attacks fMRI: activation of the ipsilateral hypothalamus in spontaneous CH attacks Resting state fMRI: abnormal functional connectivity of the hypothalamus; in patients with episodic CH, this connectively changes when in cycle versus out of cycle	Multiple
Biochemical imaging <sup>81</sup>	<sup>1</sup> H-MRS: altered hypothalamic ratios of choline/creatine and N-acetylaspartate/creatine	Unknown
Signaling molecules shared with other CH systems <sup>86 87</sup>	CGRP (shared with trigeminovascular system); VIP (shared with autonomic system); PACAP (shared with trigeminovascular and autonomic systems)	Multiple
Endocrine changes <sup>88 89</sup>	Alterations in follicle stimulating hormone, growth hormone, luteinizing hormone, prolactin, testosterone, and thyroid stimulating hormone	Multiple
Genetics <sup>90</sup>	Multiple studies have found mutations in the HCRTR2 gene	Multiple
CH treatments that act on hypothalamus <sup>91 92</sup>	Hypothalamic DBS, verapamil, corticosteroids, melatonin, lithium, valproic acid, baclofen	Posterior hypothalamus (for DBS); suprachiasmatic nucleus (for all drugs)

CGRP=calcitonin gene related peptide; CH=cluster headache; DBS=deep brain stimulation; fMRI=functional magnetic resonance imaging; <sup>1</sup>H-MRS=proton magnetic resonance spectroscopy; HCRTR2=hypocretin (orexin) receptor 2; PACAP=pituitary adenylate cyclase activating polypeptide-38; PET=positron emission tomography; VBM=voxel based morphometry; VIP=vasoactive intestinal peptide.

to terminate an ongoing attack.<sup>94</sup> The third is clinical observations suggesting that the autonomic and trigeminovascular systems are likely not involved in the initiation of attacks. Some patients with cluster headache do not have autonomic features,<sup>29</sup> suggesting that the autonomic system is not vital to attack initiation. Also, patients with cluster headache were treated in the past with complete trigeminal nerve section; afterwards, some patients had attacks with autonomic features but without pain.<sup>95</sup> This suggests that the trigeminovascular system, or at least the peripheral part of this system, is also not vital to attack initiation.

The hypothalamus has direct connections with the trigeminovascular and autonomic systems, as preclinical studies show direct connections to the trigeminal nucleus caudalis and superior salivatory nucleus, respectively.<sup>96 97</sup> The exact function of these connections has not been fully elucidated, however.

### Genetics

Two recent systematic reviews have found a rate of a family history of cluster headache between 6.3% and 8.2%.<sup>90 98</sup> Both autosomal dominant and recessive patterns of inheritance were found, suggesting that multiple genes may be involved. Unsurprisingly, several candidate genes with pathophysiologic relevance to cluster headache have been identified. A recent systematic review of studies of the genetics of cluster headache, which analyzed single nucleotide polymorphisms found in at least two study populations, found two promising single nucleotide polymorphisms on the orexin (hypocretin) 2 receptor gene mutation,<sup>99 100</sup> although these were not significant after correction for multiple testing.<sup>101</sup> Two recent genome-wide association studies identified the same four new genetic loci<sup>102</sup>; their functions need further investigation, as some are located near known genes or on introns of known genes. Smaller and less definitive studies

have also found associations with PACAP receptor type 1, membrane metalloendopeptidase,<sup>103</sup> alcohol dehydrogenase 4, and G protein  $\beta$  3.<sup>104</sup> Cluster headache may ultimately result from a combination of susceptibility genes and environmental factors.

### Investigation

The recommended investigations for cluster headache consider the differential diagnosis of cluster headache, including secondary causes of cluster headache as discussed above in the “Differential diagnosis” section. A consensus statement from the European Headache Federation recommends magnetic resonance imaging (MRI) of the brain in all patients with cluster headache (with detailed views of the cavernous sinus and pituitary area); in refractory patients, it recommends consideration of magnetic resonance angiography (MRA) of the head and neck, pituitary laboratory testing, a sleep study for obstructive sleep apnea, and, in patients with Horner syndrome, imaging of the lung apex.<sup>105</sup>

### Treatment

#### Guidelines

Treatments for cluster headache can be divided into acute or “as needed” therapies, bridge or “short term preventive” therapies that can be taken only for short courses, and preventive therapies. Below, we discuss acute, bridge, and preventive therapies listed by the AHS (published in 2016)<sup>106</sup> and EFNS (published in 2006),<sup>107</sup> as well as clinical trial data published since 2016. The AHS guidelines also used data from a 2010 systematic review of double blind, randomized controlled trials.<sup>108</sup> Both groups used systematic reviews of the existing literature, but the AHS criteria were stricter in two areas. Firstly, the AHS systematic review included only randomized controlled trials whereas the EFNS systematic review included controlled trials and case series of five or more patients. Secondly, the AHS recommendation

Table 4 | Acute therapies for cluster headache

Summary		Specific studies						
Treatment	Pharmacology / relevance to cluster headache	Adverse events	Other comments	Study design	No	Dose / regimen	Primary outcome	Results (95% CI or other specified)
Oxygen <sup>64, 110-112</sup>	100% at 6-12 L/min with NRB mask* Inactivation of autonomic systems governing pain	Minimal neck pain	Can be taken multiple times daily with minimal risk; requires NRB mask and regulator for high flow	Double blind, placebo controlled, crossover <sup>110</sup>	19	100% O <sub>2</sub> v air, 6 L/min, 15 min, NRB mask	Pain relief at 15 min (3=complete, 2=substantial, 1=slight, 0=none)	O <sub>2</sub> 1.93 (SE 0.22), air 0.77 (0.23), P<0.01
Sumatriptan <sup>65</sup>	6 mg SC, 20 mg nasal Serotonin 1B and 1D agonist; modulation of trigeminocervical complex	Chest discomfort; jaw/neck pain; anxiety	Contraindicated in patients with vascular disorders (history of stroke, myocardial infarction, Raynaud's)	Randomized, double blind, placebo controlled, crossover <sup>111</sup> Multicenter, randomized, double blind, placebo controlled, crossover <sup>113</sup>	109	100% O <sub>2</sub> v air, 12 L/min, 15 min, NRB mask	Percentage with pain relief (pain freedom or adequate relief) at 15 min	O <sub>2</sub> 7.8% (7.1% to 8.5%), air 20% (1.4% to 26%), P<0.001
Zolmitriptan	5-10 mg nasal or oral Same as sumatriptan	Same as sumatriptan	Same as sumatriptan	Multicenter, randomized, double blind, placebo controlled, crossover <sup>114</sup> Multicenter, randomized, double blind, placebo controlled, crossover <sup>115</sup>	39	Sumatriptan 6 mg v saline SC	Percentage with pain relief at 15 min	Sumatriptan 7.4%, placebo 2.6%, P<0.001
Octreotide <sup>119</sup>	100 µg SC Somatostatin analog with longer half life, may decrease CGRP and VIP concentrations	Abdominal pain; nausea and vomiting; diarrhea or constipation	Caution in patients with diabetes or cholelithiasis	Multicenter, randomized, double blind, placebo controlled, crossover <sup>116</sup> Multicenter, randomized, double blind, placebo controlled, crossover <sup>117</sup>	157	Sumatriptan 0, 6, 12 mg SC	Percentage with pain relief at 10 min	0 mg 25%, 6 mg 49% (P<0.001), 12 mg 63% (P<0.001) (P v placebo)
Lidocaine <sup>120</sup>	1 mL 10% solution Inactivation of nerve conduction at sphenopalatine ganglion	Lightheadedness; dizziness		Multicenter, randomized, double blind, placebo controlled, crossover <sup>118</sup>	77	Sumatriptan 20 mg v placebo nasal	Percentage with pain relief at 30 min	Sumatriptan 57%, placebo 2.6%, P=0.002
nVNS <sup>121-123</sup>	Three 2 min stimulations Modulation of trigeminal signaling through vagal stimulation	Dizziness; neck pain	Contraindicated in patients with metallic hardware in neck, carotid surgery, significant carotid disease, implanted electrical devices (eg, pacemaker)	Randomized, double blind, crossover <sup>119</sup> Double blind, placebo controlled, sublingual 0.9 mg NTG induced attack <sup>120</sup> Multicenter, randomized, double blind, sham controlled <sup>121</sup>	69	Zolmitriptan 0, 5, 10 mg nasal	Percentage with pain relief at 30 min	0 mg 23%, 5 mg 42% (P<0.002), 10 mg 61% (P<0.002) (P v placebo)
					52	Zolmitriptan 0, 5, 10 mg nasal	Percentage with pain relief at 30 min	0 mg 30%, 5 mg 50% (P<0.05), 10 mg 63.3% (P<0.01) (P v placebo)
					114	Zolmitriptan 0, 5, 10 mg oral	Percentage with pain relief at 30 min (2 point reduction on 5 point pain scale)	ECH: 0 mg 28.9%, 5 mg 39.8% (NS), 10 mg 46.8% (P=0.02); CCH: 0 mg 31.3%, 5 mg 16.1% (NS), 10 mg 25% (NS) (P v placebo)
					47	Octreotide 100 µg SC v placebo	Percentage with pain relief at 30 min	Octreotide 52%, placebo 36%, P=0.007
					15	Lidocaine 10% cocaine 10%, saline 1 mL applied to bilateral sphenopalatine fossae	Time to pain freedom (min)	Lidocaine 37.0 (SD 7.8, P<0.01), cocaine 31.3 (13.1, P<0.01), saline 59.3 (12.3, P v saline)
					133	nVNS v sham (low frequency)	Proportion with pain relief at 15 min	Total: nVNS 26.7%, sham 15.1%, P=0.1; ECH: nVNS 34.2%, sham 10.6%, P=0.008; CCH: nVNS 13.6%, sham 23.1%, P=0.48
					102	nVNS v sham (low frequency)	Proportion of attacks pain free at 15 min	Total: nVNS 14%, sham 12%, P=0.71; ECH: nVNS 48%, sham 6%, P<0.01; CCH: nVNS 5%, sham 13%, P=0.13

CCH=chronic cluster headache; CGRP=calcitonin gene related peptide; CI=confidence interval; ECH=episodic cluster headache; NRB=non-rebreather; NTG=nitroglycerin; nVNS=non-invasive vagus nerve stimulation; SC=subcutaneous; SD=standard deviation; SE=standard error; VIP=vasoactive intestinal peptide.  
 Pain relief=reduction from moderate-severe to none-mild pain (unless otherwise specified).  
 \*Effective dose based on published studies; although other doses may be used clinically. For example, oxygen prescribing instructions recommend that patients and oxygen suppliers should be prepared to use flow rates of at least 15 L/min. Oxygen doses of 15 L/min have been recommended in more recent literature on basis of expert opinion<sup>117</sup> and comparative mask trials,<sup>124</sup> although no clinical trials have been performed at 15 L/min.

levels (A, B, C, and U) were based on the level of evidence (for example, level A studies required two high level or “class I” trials), whereas the EFNS recommendation levels (A, B, and C) were based on a combination of level of evidence and effectiveness.

### Acute treatment

The first line acute treatments for cluster headache are subcutaneous sumatriptan and oxygen. Expert guidelines have given both of these treatments level A evidence,<sup>12</sup> and surveys of patients have generally found triptans and oxygen to be the most effective acute treatments.<sup>5 109</sup> Often, both treatments are prescribed: daily use of subcutaneous sumatriptan for weeks or more is not favored owing to its vasoconstrictive properties, and oxygen has logistical limitations such as portability (table 4).

#### Subcutaneous sumatriptan

Subcutaneous sumatriptan may be the single most effective acute treatment according to data from surveys of patients.<sup>109 113</sup> More rapid forms of administration of the triptans are preferred, starting with subcutaneous sumatriptan, followed by nasal zolmitriptan and nasal sumatriptan, followed by oral zolmitriptan. The triptans cause vasoconstriction via activation of the 5HT<sub>1B</sub> receptor and are not recommended in patients with vascular disorders such as myocardial infarctions, strokes, and uncontrolled hypertension.

#### Oxygen

Inhaled oxygen effectively treats attacks at flow rates of 6 L/min and 12 L/min.<sup>110 111</sup> Higher flow

rates are generally preferred, with a survey of patients suggesting that flow rates over 10 L/min were more efficacious than those under 10 L/min and as efficacious as injectable sumatriptan.<sup>47</sup> To achieve high flow rates, the prescription for oxygen requires not only an oxygen tank but also two accessories: a non-rebreather mask, or possibly a demand-valve mask,<sup>125</sup> and a regulator placed on the tank to increase the flow rate.<sup>112</sup> Oxygen has a high effectiveness and low side effects compared with other acute drug treatments.<sup>5</sup> Contraindications are rare but include the risk of fire: smoking and open flames are prohibited when using oxygen.<sup>126</sup> As the rate of smoking is high in patients with cluster headache, those who smoke should be made aware not to smoke or have other people nearby smoke when the oxygen is in use. Another risk is carbon dioxide retainers, such as patients with very severe chronic obstructive pulmonary disease. In carbon dioxide retainers, low oxygen concentrations drive the breathing reflex; supplementary oxygen would decrease this drive.<sup>127</sup>

#### Non-invasive vagus nerve stimulation

Non-invasive vagus nerve stimulation was recently shown in two clinical trials to be effective in aborting attacks in patients with episodic but not chronic cluster headache.<sup>121 122</sup> Like oxygen, non-invasive vagus nerve stimulation is a treatment that can be safely used on a regular basis. Contraindications include implanted medical devices (for example, pacemaker or hearing aid implants) and implanted metal near the neck (for example, carotid stent or cervical bone screw). The device has not been

Table 5 | Transitional therapies for cluster headache

Treatment	Summary				Specific studies				
	Effective dose*	Pharmacology / relevance to cluster headache	Adverse events	Other comments	Study design	No	Dose / regimen	Primary outcome	Results (95% CI or other specified)
SC occipital steroid injection (cortivazol, methylprednisolone, triamcinolone, betamethasone; +/- anesthetic) <sup>128-130</sup>	Not defined	Modulation of TCC; anti-inflammation; hypothalamic-pituitary-adrenal axis effects; circadian effects	Pain; bleeding; infection; localized hair loss	Less effective than systemic steroids; fewer side effects than systemic steroids	Randomized, double blind, placebo controlled <sup>129</sup>	43	Cortivazol 3.75 mg v. saline, 1.5 mL unilateral SC suboccipital injection, 3 injections 48-72 h apart, each adjunctive to prophylaxis	Reduction to ≤2 daily attacks in the 72 h period 2-4 days after third injection	Cortivazol 20/21, placebo 12/22, odds ratio 14.5 (1.8 to 116.9), P=0.012
					Randomized, double blind, placebo controlled <sup>131</sup>	23	Betamethasone dipropionate 12.46 mg + betamethasone disodium phosphate 5.26 mg + .5 mL xylocaine 2% v saline + 0.5 mL xylocaine 2%, 2.5 mL unilateral SC suboccipital injection	Proportion attack-free days 3-7; days 3-28	Days 3-7: betamethasone 11/13, placebo 0/10, P<0.001; days 3-28: betamethasone 10/13, placebo 0/10, P<0.003
Oral prednisone <sup>130 132 133</sup>	Not defined	Anti-inflammation; hypothalamic-pituitary-adrenal axis effects; circadian effects	Agitation; glucose intolerance; weight gain; bone density loss; avascular hip necrosis; immune suppression	Taper duration does not seem to predict attack recurrence. Attacks may return after tapering off steroids, even while on a preventive	Multicenter, randomized, double blind, placebo controlled, adjunct to verapamil uptitration <sup>132</sup>	109 ECH	Prednisone v placebo, 100 mg daily for 5 days, titrating down by 20 mg every 3 days until off; verapamil started in parallel	Mean number of attacks in first week of treatment	Prednisone 7.1 (SD 6.5), placebo 9.5 (6.0), P=0.002

CI=confidence interval; ECH=episodic cluster headache; SC=subcutaneous; SD=standard deviation; TCC=trigemino-cervical complex.

\*Effective doses are not clearly defined for these transitional treatments; a variety of doses/regimens are used clinically.

studied in patients with several conditions including carotid atherosclerosis, uncontrolled hypertension, abnormal electrocardiograms, or a history of seizures.

#### Transitional treatment

Transitional or bridge therapies are important tools in the management of cluster headache. Whereas preventive drugs are uptitrated during times of high headache burden, transitional treatments can provide relatively quick relief for a brief period. They may also be used to terminate periods in episodic cluster headache or induce a period of remission in chronic cluster headache (table 5).

#### Corticosteroids

Corticosteroids have been delivered via occipital nerve blocks and via oral tablets; both methods of delivery have shown benefit using a variety of corticosteroids types and dosages.<sup>134-138</sup> Occipital and suboccipital nerve blocks were investigated in a meta-analysis, showing a relative risk ratio of 4.86 for freedom from pain at one month compared with control (across two randomized controlled studies and 66 participants), as well as an overall 50% freedom from pain at one month (across five randomized studies and 156 participants with cluster headache).<sup>128</sup> The exact components of the blocks differed widely. The systematic review identified 12 observational and randomized studies that used a variety of steroids (betamethasone 18-21 mg, cortivazol 3.75 mg in three injections every 48-72 hours, methylprednisolone 32-160 mg, or triamcinolone 40 mg), usually combined with a local anesthetic (bupivacaine 0.5% 2-4 mL, lidocaine 1% 2-9 mL, lidocaine 2% 0.5-5 mL, or prilocaine 1%). For oral steroids, a recent randomized controlled trial showed significant improvement with a 17 day course of prednisone (starting at 100 mg daily for five days, then titrating down by 20 mg every three days).<sup>132</sup> Observational studies of various oral corticosteroid pulses, as well as intravenous methylprednisolone, have also been described.<sup>133-137</sup>

#### Dihydroergotamine

Dihydroergotamine is an ergot compound with clinical effects in cluster headache likely due to its serotonergic activity.<sup>139</sup> Although dihydroergotamine is not specifically recommended by current guidelines, several retrospective analyses support its use in cluster headache.<sup>138</sup> Variations on the dihydroergotamine pulse regimen lasting from three days to three weeks, involving combinations of intravenous, subcutaneous, and intranasal administrations in inpatient and/or outpatient settings have also been described.<sup>138 140</sup>

#### Preventive treatment

Generally, patients with chronic symptoms need continual preventive therapy, whereas patients with episodic symptoms need it only during their cluster period. Exceptions do exist; for instance, a patient with multiple annual cycles may choose to stay on

preventive therapy year-round. Some patients with episodic symptoms may start preventives before their anticipated period, during the prodromal stage. Preventive treatment usually does not eliminate attacks but reduces their frequency, intensity, or both, necessitating continued access to effective abortive therapy. More than one preventive may be used for more effective suppression, although evidence for combination treatment is limited. Table 6 shows the treatments for which good evidence in cluster prevention exists. These are discussed below in additional detail.

#### Verapamil

Verapamil is a calcium channel blocker and considered the first line preventive. Activity in several monoaminergic neurotransmitter systems and the hypothalamus may be relevant to verapamil's cluster suppressing effects.<sup>141</sup> In controlled trials, verapamil 120 mg immediate release three times daily reduced headache burden by at least 50% after one to two weeks of treatment in both episodic and chronic cluster headache.<sup>143 144</sup> Sustained release verapamil is available, although it is generally not thought to be as effective as the immediate release formulation. Constipation and prolongation of the cardiac P-R interval are of primary concern with the use of verapamil. Electrocardiographic monitoring is recommended before initiation, one to two weeks after an increase in dose, and every six months thereafter.<sup>159</sup>

#### Lithium carbonate

Lithium carbonate is an agent with a long medical history and primary clinical application in the management of mood disorders. Lithium interrupts G-protein signaling, implicating several neurotransmitter systems, and it also affects hypothalamic and sleep function.<sup>138</sup> Lithium is less commonly used than other modern preventives, given its narrow therapeutic range and undesirable side effect profile, including somnolence, thyroid dysfunction, and diabetes insipidus.

#### Melatonin

Melatonin is a circadian hormone produced by the pineal gland best known for its role in sleep. Nightly melatonin (10 mg orally) was reported to terminate cluster attacks in half of participants in a placebo controlled trial.<sup>146</sup>

#### Civamide

Civamide (zucapsaicin) is a synthetically produced *cis* isomer of capsaicin, the naturally occurring "active ingredient" of hot peppers. Civamide inhibits pain transmission by activating the vanilloid 1 receptor (or transient receptor potential cation channel subfamily V member 1 receptor) and by blocking calcium channels.<sup>151</sup> Nasal burning and lacrimation were commonly reported adverse events, resulting in 17% of participants withdrawing from the civamide group.<sup>151</sup>

### *Topiramate*

Topiramate is used widely in neurology to treat epilepsy, neuropathy, tremor, and migraine. In addition to its well known role as an inhibitor of carbonic anhydrase, topiramate has several other pharmacologic targets, including sodium and calcium channels and the  $\gamma$  aminobutyric acid (GABA)-A receptor. Open label trials of topiramate in cluster headache support clinical efficacy, although no controlled studies exist.<sup>160</sup> In the most recent prospective study investigating topiramate in cluster headache, the average dose of 273 (range 100-400) mg induced remission in nine of 12 patients with episodic cluster headache in an average of 10.7 (6-18) days, representing a 51% reduction in the duration of remaining cluster period.<sup>155</sup>

### *Baclofen*

Baclofen is a GABA-B receptor agonist. It is best known as a muscle relaxer, but clinical effects in pain conditions such as trigeminal neuralgia, glossopharyngeal neuralgia, and post-herpetic neuralgia support its consideration in headache disorders. In an open label study of baclofen in episodic cluster headache, 12 of 16 participants were attack-free after one week of treatment at a dose of 15-30 mg divided three times daily.<sup>158</sup>

### *Other oral agents*

The antiepileptics valproic acid and gabapentin have been studied in open label trials, showing some preventive effects.<sup>154 156 157</sup> One controlled trial of valproic acid in 96 patients with cluster headache showed no difference from placebo.<sup>153</sup> At international normalized ratio levels between 1.5 and 1.9, warfarin was shown to induce remission of four weeks or longer in half of the 34 patients with medically refractory chronic cluster headache during the 12 week treatment period in a placebo controlled, crossover pilot study.<sup>152</sup> The need for laboratory monitoring and the risk of bleeding in people who self-injure during attacks may preclude practical and safe use in cluster headache (see video 1 for a case of self-injury in a patient on anticoagulation), and this drug is not routinely used in cluster headache management.

### *Galcanezumab*

Galcanezumab, a humanized monoclonal antibody against CGRP, is the newest preventive drug available for episodic cluster headache. In weeks 1 through 3 after injection, 71% of patients with episodic cluster headache who received galcanezumab had a 50% or greater reduction in weekly attacks, compared with 53% who received placebo.<sup>148</sup> Importantly, the dose for cluster headache is 300 mg monthly, whereas the dose for migraine is only 120 mg. Galcanezumab was not as effective in a separate trial for chronic cluster headache.<sup>161</sup> However, given the refractory nature of chronic cluster headache in many patients, some authors advocate its use in chronic cluster headache given its effectiveness in isolated cases.<sup>162</sup>

### *Neuromodulation*

The non-invasive vagus nerve stimulation device was shown to significantly reduce attack frequency in cluster headache when used as adjunctive therapy compared with standard of care alone.<sup>149 150</sup> Invasive neuromodulation devices (occipital nerve stimulation, sphenopalatine ganglion stimulation, and deep brain stimulation) are discussed below in the “Refractory” section.

### **Patient directed disease management**

The diagnostic and treatment challenges endured by many patients with cluster headache has also led to several patient directed measures, including unconventional, and at times illicit, treatments.<sup>24</sup> Patients may or may not reveal these self-directed methods, although clinicians should be aware that the cluster headache community widely discusses these treatments.

Patients with cluster headache may consume coffee or energy drinks as an acute treatment; both of these contain caffeine, and the second one contains other compounds, such as vitamin B<sub>12</sub> and taurine.<sup>5 14 24 38</sup> Various vitamin regimens are taken by patients for disease prevention, high dose vitamin D (starting at 50 000 IU daily with a maintenance dose of 10 000 IU daily) being one of the more common ones. Vitamin D concentrations have been reported to be low in people with cluster headache,<sup>163</sup> although the role for supra-supplementary dosing in treatment needs further investigation. According to the Institute of Medicine, patients should avoid doses of vitamin D over 125-150 nmol (slightly above the normal range of 30-100 nmol), in part because of the risk of hypercalcemia.<sup>164</sup> A randomized, double blind, placebo controlled clinical trial investigating high dose vitamin D in cluster headache is in preparation (clinicaltrials.gov NCT04570475).

For more than two decades, patients with cluster headache have been using classic serotonergic psychedelics, such as lysergic acid diethylamide (LSD) and psilocybin (found in so called “magic mushrooms”), in disease management. Unlike conventional medications, this drug class is reported to induce long term (months or years) reduction of headache burden after limited administration (for example, three doses).<sup>24 165</sup> Importantly, sub-hallucinogenic doses and non-hallucinogenic congeners of these psychedelic drugs are also reported to have longlasting therapeutic effects.<sup>24 165 167</sup> The first clinical trials in cluster headache have begun with LSD (NCT03781128) and psilocybin (NCT02981173, NCT04280055). These studies all exclude patients with serious medical disease or psychotic or manic disorders, as psychedelics could lead to serious adverse events in these groups. As psilocybin and other classic psychedelics activate serotonin receptors, certain serotonergic drugs are excluded or limited in these studies. In patients using these substances as treatment, the use of other serotonergic drugs (for example, antidepressants, triptans, or ergotamines) is similarly discouraged.

Table 6 | Preventive therapies for cluster headache

Summary		Specific studies							
Treatment	Effective dose*	Pharmacology / relevance to cluster headache	Adverse events	Other comments	Study design	No	Dose / regimen	Primary outcome	Results (95% CI or other specified)
Verapamil <sup>141, 142</sup>	360 mg divided TID (immediate release)	Calcium channel blockade; affects hypothalamus	Constipation; hypotension; PR prolongation; heart block	Check ECG before starting and ~1 week after dose changes; evidence lacking for sustained release formulation	Multicenter, randomized, double dummy, double blind, crossover <sup>143</sup>	24 CCH	Verapamil 120 mg TID v lithium carbonate 300 mg TID	Improved Headache Index (not defined) from baseline or washout	Week 1: verapamil 50%, lithium 37%; over 8 weeks: both improved from baseline, P<0.01; no difference between drugs
Lithium carbonate <sup>138</sup>	900 mg divided TID	Interruption of G-protein signaling; affects several neurotransmitter systems; affects sleep cycle and hypothalamus	Somnolence; cognitive impairment; diabetes insipidus; hypothyroidism	Narrow therapeutic range: check lithium concentrations; check chemistry and thyroid function. Negative evidence for sustained release formulation	Multicenter, randomized, double dummy, double blind, crossover <sup>143</sup>	24 CCH	Lithium carbonate 300 mg TID v verapamil 120 mg TID	Improved Headache Index (not defined) from baseline or washout	Week 1: lithium 37%, verapamil 50%; over 8 weeks: both improved from baseline, P<0.01; no difference between drugs
Melatonin <sup>146, 147</sup>	10 mg nightly	Supplementation of endogenous pineal gland product	Somnolence (if so, may be taking too close to bedtime)	Should be taken a couple hours before bedtime.	Double blind, placebo controlled, matched parallel groups <sup>145</sup>	27 ECH	Lithium carbonate (slow release) 800 mg nightly v placebo	Percentage attack-free after 1 week	Lithium 15% (2% to 45%), placebo 14% (2% to 43%), P=NS
Galcanezumab <sup>148</sup>	300 mg SC monthly	Monoclonal antibody against CGRP	Local injection site reaction; constipation	Approved for ECH only	Randomized, double blind, placebo controlled <sup>146</sup>	20	Melatonin 10 mg nightly v placebo	Mean daily attacks over 2 weeks	Melatonin 3.3 (SD 1.12), 1.89 (1.51), 1.5 (1.7), P<0.03; placebo 2.39 (1.01), 2.7 (0.86), 2.5 (0.86), P=0.7 (baseline, week 1, week 2)
nVNS <sup>122, 123, 149, 150</sup>	Three 2 min stimulations BID	Modulation of trigeminocervical nociception	Redness at site; muscle soreness at site	US: (1) acute treatment in ECH; (2) adjunctive prevention in ECH and CCH; EU: acute and preventive treatment for CH	Multicenter, randomized, open label, adjunct v SoC <sup>150</sup>	106 ECH	Galcanezumab 300 mg SC v placebo	Change in weekly attacks through week 3	Galcanzumab -8.7 (SE 1.4), placebo -5.2 (1.3), P=0.04
Civamide <sup>151</sup>	100 µL into each nostril daily	Activation of vanilloid 1 receptor	Nasal burning; cranial autonomic symptoms (lacrimation, rhinorrhea)		Multicenter, randomized, double blind, placebo controlled <sup>151</sup>	24 ECH	Civamide 100 µL 0.025% solution v vehicle 100 µL into each nostril daily for 7 days	Change in attacks per week over 20 days after 7 day treatment	Civamide -61.4%, placebo -30.9%, P=0.054; week 1 only: civamide -5.5%, placebo -25.9%, P=0.03
Warfarin	Not defined	Inhibition of vitamin K dependent clotting factors	Bleeding	Contraindicated in patients with bleeding risk; caution in patients who self-injure during attacks	Randomized, placebo controlled, crossover <sup>152</sup>	34 CCH	Warfarin with INR 1.5-1.9 v placebo with sham INR and adjustments	Remission ≥4 weeks in duration	Warfarin 50%, placebo 11.8%, P=0.004
Sodium valproate	Not defined	Blockade of voltage gated sodium channels	Nausea; tremor; weight gain; alopecia		Multicenter, randomized, double blind, placebo controlled <sup>153</sup>	96	Sodium valproate 1000-2000 mg/day	Percentage with ≥50% reduction in weekly attacks in second (last) week	Sodium valproate 50%, placebo 62%, P=0.23
					Open label, prospective <sup>154</sup>	15	Sodium valproate 600-2000 mg/day divided BID	Not defined	Complete pain control in 9, partial effect in 2, no effect or loss of effect in 4

(Continued)

Table 6 | Continued

Summary		Specific studies							
Treatment	Effective dose*	Pharmacology / relevance to cluster headache	Adverse events	Other comments	Study design	No	Dose / regimen	Primary outcome	Results (95% CI or other specified)
Topiramate	Not defined	Inhibits carbonic anhydrase	Paresthesia; cognitive impairment; appetite suppression	Contraindicated in nephrolithiasis	Open label, prospective <sup>155</sup>	13	Topiramate 50 mg BID → max 400 mg/day divided BID	Not defined	9/12 ECH achieved remission (3 days without attacks) in 10.7 (SD 3.9) days, mean dose 273 (132) mg/day
Gabapentin	Not defined	Interrupts calcium channel function	Drowsiness; dizziness; slowness; constipation	Dose adjustments needed in kidney failure	Open label, prospective <sup>156</sup>	14 ECH	Gabapentin 900-2400 mg/day divided TID	Change in monthly days with attacks	-12 attack days/month (-44, 94%)
Baclofen	Not defined	Activation of GABA-B receptors	Sedation	-	Open label, prospective <sup>157</sup>	8 CCH	Gabapentin 800-3600 mg/day	≥50% reduction in attack frequency at month 4	6/8 participants
					Open label, prospective <sup>158</sup>	16 ECH	Baclofen 5-10 mg TID	Not defined	12/16 attack-free by end of week 1

BID=twice daily; CCH=chronic cluster headache; CGRP=calcitonin gene related peptide; CI=confidence interval; ECH=episodic cluster headache; ECG=electrocardiogram; GABA=γ aminobutyric acid; INR=international normalized ratio; nVNS=non-invasive vagus nerve stimulation; SC=subcutaneous; SD=standard deviation; SE=standard error; SoC=standard of care; TID=three times daily.  
\*Effective dose based on published studies, although other doses may be used clinically.

## Special populations

### Refractory cluster headaches

When patients' cluster headaches are refractory to treatment, additional investigation for secondary headaches is recommended, including MRA of the head and neck, pituitary hormone measurements, and a sleep study. This is particularly relevant in chronic cluster headaches, which anecdotally have been more refractory to treatments, a notion supported by recent trials of galcanezumab and non-invasive vagus nerve stimulation, which were effective in episodic but not chronic cluster headache.<sup>161 168</sup> Should extensive treatment trials be ineffective or intolerable and should additional investigations be unrevealing, invasive procedures can be explored. Suggested guidelines for proceeding to invasive procedures include chronic cluster headache for two years, management by a single provider for one year, extensive treatments trials, and a psychological evaluation.<sup>169</sup>

Although previous invasive procedures include destructive lesions such as trigeminal nerve sectioning,<sup>170</sup> these have largely been replaced by implantable neuromodulation devices. Occipital nerve stimulation was found to be effective in several open label studies of 44-105 patients,<sup>171-174</sup> and more recently in a randomized dose controlled trial of 131 participants with medically refractory chronic cluster headache (defined as non-response to, intolerance of, or a contraindication to verapamil, lithium, and one other preventative drug).<sup>174</sup> Greater occipital nerve blocks were not predictive of response to occipital nerve stimulation,<sup>175</sup> but occipital nerve stimulation likely has a similar mechanism of action via modulation of the trigeminocervical complex. Complications of occipital nerve stimulation included infection, stimulator lead problems such as migration and fracture, and pain at the lead or generator sites.<sup>172</sup>

Two other invasive devices are worth noting, even though they are not in common use. Firstly, sphenopalatine ganglion stimulation uses a newly created device placed into the pterygopalatine fossa that aborts attacks in patients with chronic cluster headache,<sup>176 177</sup> via a wireless charger placed over the cheek to activate the device. Complications in the trials were primarily swelling or sensory problems (for example, numbness, paresthesias, and pain). Unfortunately, owing to commercial problems, the device is currently unavailable. Secondly, deep brain stimulation of several brain areas has been proposed, and hypothalamic deep brain stimulation has been the best studied. However, the AHS guidelines recommended against its use, stating that the evidence suggested that it did not reduce attack frequency.<sup>2</sup> Newer deep brain stimulation techniques, including targeting other areas, are being investigated.

Of note, some neuromodulation devices are MRI compatible or MRI conditional, whereas others are not. Thus if MRI is anticipated in the future, this point should be discussed with the implanting surgeon.

*Pregnant and lactating patients*

Cluster headache may improve in up to half of women during pregnancy, including skipping anticipated cluster cycles.<sup>34 178 179</sup> Data for managing cluster headache during pregnancy and lactation are limited, and many risks are unknown. High flow oxygen, lidocaine nasal spray, and lidocaine nerve blocks (without steroid) seem to have the lowest risk.<sup>180 181</sup>

Although retrospective analysis and a manufacturer's registry have failed to show teratogenicity with sumatriptan use during pregnancy, pre-term birth and low birth weight were suggested in one investigation.<sup>182</sup> Importantly, these studies involved patients with migraine, who are expected to use sumatriptan less frequently than those with cluster headache. Sumatriptan use is probably safe during lactation, but insufficient safety data exist for this or other triptans.<sup>180</sup>

The safety of other consumable products used in the management of cluster headache must be considered during pregnancy and lactation. Caffeine is often used to assist in aborting attacks,<sup>5 24</sup> but it is typically used in high doses, and high doses of caffeine are not recommended during pregnancy. Findings for caffeine and breastfeeding are lacking, but some studies identified infant night time awakening, colic, and atopic dermatitis associated with maternal consumption of caffeinated products.<sup>183</sup>

*Pediatric patients*

Data for cluster headache specifically in children are sparse and focus primarily on case reports and case series, summarized in a narrative review.<sup>180</sup> For abortive drugs, oxygen is a reasonable first line option in children given its low side effects and suggested efficacy in small clinical reports.<sup>184 185</sup> Of the recommended triptans, only zolmitriptan nasal spray is approved by the US Food and Drug Administration for pediatric use, specifically for ages 12 and over. However, subcutaneous and nasal sumatriptan have been proposed in pediatrics for other indications such as migraine,<sup>186</sup> and nasal sumatriptan is approved for ages 12 and over in Europe. Of note, many case reports have suggested that indomethacin is effective in cluster headache in children<sup>180</sup>; whether this is truly cluster headache or misdiagnosis of paroxysmal hemicrania is unclear. Bridge therapy in pediatrics includes the use of steroids, which may be effective according to small clinical reports.<sup>187</sup> Limited data are available for preventives, although verapamil has been tried with positive effects.<sup>185</sup>

**Emerging treatments**

One acute treatment for cluster headache is under investigation: a microneedle system for intracutaneous delivery of zolmitriptan, currently in a phase II/III trial (NCT04066023). Faster delivery methods are preferred in cluster headache, and zolmitriptan is currently available in oral and nasal formulations only. Preventive treatments under investigation include those discussed above in the "Patient directed disease management" section:

vitamin D (phase III trial NCT04570475), LSD (phase II trial NCT03781128), and psilocybin (phase I trial NCT02981173 and phase I/II trial NCT04280055). In addition, several of the CGRP monoclonal antibodies have been investigated for cluster headache. Phase III trials of fremanezumab were terminated early for futility in both episodic and chronic cluster headache (NCT02945046, NCT02964338). Galcanezumab was found to be effective in episodic but not chronic cluster headache, as discussed above in the "Preventive treatment" section. Eptinezumab, the only CGRP monoclonal antibody administered as an infusion, is being investigated as a preventive for episodic cluster headache in a phase III trial (NCT04688775).

**Conclusions**

Cluster headache is a primary headache disorder notable for a male preponderance, an increased risk of smoking, and attacks with an exceptionally high pain intensity that often occur with a daily rhythmicity. Despite many distinguishing features, cluster headache is often misdiagnosed, most commonly as migraine or trigeminal neuralgia. Cluster headache can be differentiated from these and other mimics by its attack duration and associated restlessness, and it can be differentiated from secondary causes of cluster-like headaches by MRI of the brain and, if refractory to treatment, by MRA of the head and neck, pituitary laboratory testing, lung apex imaging, and polysomnography. Although the exact mechanism of cluster headache is not understood, it is known to involve the trigeminovascular pain system, the autonomic system, and the hypothalamus. Treatments

**RESEARCH QUESTIONS****Epidemiology**

- Why is the disorder more prevalent in men?
- Why do clinical features so commonly begin between 20 and 40 years of age?
- What is the relation between cluster headache and cigarette smoking?

**Timing**

- What is the basis for the predictable daily and yearly periodicity?
- How does alcohol trigger an extra attack, often within minutes?
- Why does an individual attack stop after three hours?

**Pain**

- What is the basis for the extreme intensity of the pain?
- Why is the pain unilateral and sometimes side locked (that is, occurs on one side of the face, without exception, a patient's entire life)?

**Drug treatments**

- How does high flow oxygen work?
- How do we explain the very rapid time to onset of subcutaneous sumatriptan?
- Why does subcutaneous sumatriptan seem to work in the vast majority of, but not all, patients?
- Why does indomethacin not work?

include the first line acute therapies oxygen and sumatriptan, the first line transitional treatment corticosteroids, and the first line preventive treatment verapamil. However, new treatments are emerging, such as non-invasive vagus nerve stimulation and galcanezumab, and several clinical trials are ongoing, which will hopefully lead to more effective treatments for this severely disabling disease.

EADS is an employee of the US Department of Veterans Affairs. Any opinions, findings, and conclusions or recommendations expressed in this material are those of the authors and do not necessarily reflect the views of the US Department of Veterans Affairs.

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