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CLUSTER HEADACHE: A NARRATIVE REVIEW OF EPIDEMIOLOGY, DIAGNOSIS CRITERIA, RISK FACTORS, PATHOPHYSIOLOGY AND THERAPEUTIC STRATEGIES

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ABSTRACT

Introduction: Cluster Headache (CH) is a rare but highly disabling primary headache disorder characterized by unilateral pain and cranial autonomic symptoms. It causes major personal and societal burden due to its impact on patients' quality of life.
Purpose of the study: The aim of this review is to provide a comprehensive analysis of CH, including its epidemiology, diagnostic criteria, risk factors, pathophysiology, and treatment. Recent advances in neurobiology and targeted therapies are highlighted.
Description of the state of knowledge: Recognized as the most severe of the trigeminal autonomic cephalalgias, CH combines intense head pain with autonomic dysfunction and a distinct circadian pattern. Epidemiological studies report variability in prevalence across regions and demographic groups, with evidence of late-onset and pediatric cases contributing to diagnostic delays.
Several risk factors have been identified, including smoking, alcohol consumption, and disturbances in circadian rhythms. Genetic studies reveal susceptibility loci associated with neurovascular regulation, inflammation, and circadian pathways, suggesting a complex genetic background. Functional and structural neuroimaging consistently implicate hypothalamic dysfunction, which interacts with trigeminovascular and parasympathetic systems. Standard treatment includes acute therapies such as subcutaneous triptans and high-flow oxygen, as well as preventive strategies with verapamil.
Recent advances have introduced CGRP monoclonal antibodies and neuromodulation, providing new options for refractory patients.
Conclusion: Advances in understanding the neurobiological basis and risk factors of CH have enabled more precise diagnostic and therapeutic approaches. However, further research is needed to optimize management and reduce disease burden.

KEYWORDS

Cluster Headache, Trigeminal Autonomic Cephalalgia, Hypothalamus Dysfunction, CGRP, Neuromodulation

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Introduction

Cluster headaches (CH) belong to the subgroup of primary headaches known as trigeminal autonomic cephalalgias, characterized by intense unilateral head pain accompanied by cranial autonomic features. Although CH is relatively rare, it carries a disproportionate disease burden. The pain associated with cluster headache attacks is considered one of the most excruciating types of headaches, often described as even more severe than the pain experienced during childbirth (Burish et al., 2021; Sharaf & Ali, 2025). Recent studies have also highlighted the significant psychosocial impact of CH. According to research, up to 64% of patients report passive suicidal ideation during cluster periods, with 2.3% attempting suicide during attacks (Ji Lee et al., 2019). These alarming figures underscore the critical need for timely diagnosis, effective treatment, and holistic management strategies addressing both somatic and psychological aspects of the disorder.

This review aims to provide a comprehensive overview of CH, focusing on its epidemiology, diagnostic challenges, pathophysiology, and therapeutic options, while emphasizing the urgency of mitigating its immense burden on patients and healthcare systems.

Methodology

The literature review was based on the literature published between 2015 and 2025. PubMed and Google Scholar open databases were utilized in this study to search by keyword like cluster headache, trigeminal autonomic cephalalgia, hypothalamus dysfunction, CGRP, neuromodulation. In the end, 60 sources were cited.

Description of the state of knowledge

Epidemiology

The prevalence of cluster headache varies depending on the study population and the methodology used. To date, there is only one comprehensive meta-analysis— based mainly on studies from Western countries and widely cited in recent systematic reviews— has estimated a lifetime prevalence of 124 per 100,000 individuals (95% CI: 101-151) and a one-year prevalence of 53 per 100,000 (95% CI: 26-95) (Kaddumukasa et al., 2016; Kim et al., 2023). More recent studies focusing on smaller populations have revealed differences across regions. For example, a nationwide, population-based study conducted in Norway found a significantly lower one-year prevalence of 14.6 per 100,000 adults (95% CI: 13.5-15.8) (Hagen, 2024).

In contrast, a cross-sectional study from Uganda conducted after 2015 reported a prevalence of cluster headache of 1.0% (95% CI: 0.1-7.2) among adult participants (Kaddumukasa et al., 2016).

These discrepancies may reflect actual epidemiological and genetic variation but may also be influenced by differences in diagnostic criteria, healthcare access, and study design. For this reason, up-to-date, standardised, global epidemiological studies are essential to determine the current prevalence and distribution of cluster headaches(Kim et al., 2023)

Diagnosis

The International Classification of Headache Disorders, 3rd edition, provides a standardized framework for diagnosing CH. Diagnostic criteria include at least five attacks of strictly unilateral, severe or very severe orbital, supraorbital or temporal pain, lasting 15 to 180 minutes when untreated. The attacks must be accompanied by at least one ipsilateral cranial autonomic symptom (e.g., conjunctival injection, lacrimation, nasal congestion, rhinorrhoea, ptosis, miosis, eyelid oedema) and/or a sense of restlessness or agitation. The frequency of attacks must range from one every other day to eight per day. CH is further divided into two clinical subtypes: episodic cluster headache (ECH), which features attack periods lasting from 7 days to 1 year with pain-free remission periods of at least 3 months, and chronic cluster headache (CCH), in which attacks occur for more than a year without remission, or with remissions shorter than 3 months (Olesen, 2018). ECH is the more prevalent form, representing majority of cases (Moon et al., 2019). Recent studies also highlight persistent variability in CH presentation, including interictal pain or shifting laterality, suggesting a degree of phenotypic heterogeneity that may not be fully captured by current diagnostic criteria (Göbel et al., 2021).

Although diagnosis is based on a patient interview and a neurological examination, recent advances in diagnostic strategies underscore the importance of neuroimaging and laboratory testing primarily to exclude secondary causes that may mimic cluster headache. Magnetic resonance imaging (MRI) of the brain, including the pituitary region - is recommended in all patients presenting with a first episode of CH or with atypical features, such as side-shifting pain, continuous background headache, or abnormal neurological examination. Recent studies indicate that structural anomalies such as pituitary adenomas, artery dissection, and inflammatory entities are important differential diagnoses and can be reliably identified using high-resolution MRI or magnetic resonance angiography (MRA) (May et al., 2023a; Tsai et al., 2020).

Functional imaging, such as positron emission tomography (PET) and functional MRI (fMRI), has further elucidated the role of hypothalamic activation during attacks, although these modalities remain reserved for research settings rather than routine clinical practice (Schulte et al., 2020). Additionally, recent evidence points to altered hypothalamic microstructure and connectivity patterns in CH patients even during remission phases, supporting a model of persistent central nervous system dysregulation underlying the disorder (Abagnale et al., 2025)

Laboratory investigations remain adjunctive and are tailored based on clinical suspicion. Routine inflammatory markers (e.g., C-reactive protein, procalcitonin, erythrocyte sedimentation rate) are recommended to rule out inflammatory or infectious etiologies in atypical presentations (De Pue et al., 2016). Hormonal assays, particularly evaluating pituitary function (e.g., prolactin, insulin-like growth factor-1), may be warranted if imaging suggests pituitary abnormalities (Pineyro et al., 2017)

Recent studies have explored the potential of serum and cerebrospinal fluid (CSF) biomarkers in the diagnosis of CH. Elevated levels of calcitonin gene-related peptide (CGRP) and vasoactive intestinal peptide (VIP) during attacks have been reported, reflecting activation of the trigeminovascular and parasympathetic system (Snoer et al., 2019). However, variability in sampling protocols and overlap with other headache disorders limit their current diagnostic utility (Ran et al., 2024).

Risk factors

1. Age

Age is a significant epidemiological factor influencing the occurrence of cluster headache. According to earlier clinical descriptions, CH was characterized as a disorder predominantly affecting young and middle-aged adults, with the peak age at presentation ranging between 20 and 40 years (Kim et al., 2023; May et al., 2018). However, more recent data indicate that CH can also occur later in life. Manzoni et al. reported that whereas the highest incidence remains in early adulthood, there is a notable rise in new-onset CH among individuals aged 50 to 69, suggesting that the disorder may be underdiagnosed in older populations due to overlapping comorbidities and atypical clinical presentations (Manzoni et al., 2019). Furthermore, their findings highlighted a notable shift in sex distribution in this age group: while CH is generally more prevalent among males, late-onset CH shows a higher incidence in females, and late onset has been identified as a negative prognostic factor in women (Schor et al., 2021).

In addition to late-onset cases, paediatric CH is increasingly recognised, although often underdiagnosed. A large international survey found that 27.5% of respondents experienced CH onset before the age of 18, however only 15.2% received a diagnosis during childhood or adolescence. The mean diagnostic delay in paediatric cases was 11.1 years (Schor et al., 2021)

Collectively, these findings emphasise the broad age range over which CH can manifest. An atypical age at onset is associated with prolonged diagnostic delays, which may adversely affect patient outcomes. Therefore, increased clinical awareness is essential to facilitate timely and accurate diagnosis irrespective of patient age.

2. Sex

Sex-related differences constitute another important dimension in the epidemiology and clinical profile of cluster headache. Past research has shown a marked male predominance in CH, with male-to-female ratios reported as high as 6.2:1. However, recent data indicate a decline in this ratio to as low as 1.3:1 in Western countries, suggesting increasing recognition and diagnosis in women. Despite the global trend of decreasing M:F ratios in CH, studies from Asian countries continue to report higher male predominance, with ratios ranging from 3.8:1 to 7:1, potentially reflecting regional or cultural differences in diagnosis or disease expression (Fourier et al., 2023)

Importantly, emerging evidence indicates that not only the prevalence but also the underlying aetiological factors and clinical characteristics of CH differ by sex. Women are more likely to exhibit familial forms of CH, with a higher prevalence of first-degree relatives also affected, suggesting a stronger contribution of genetic predisposition in female patients(Fourier et al., 2023).

Beyond aetiological differences, sex may also influence the clinical phenotype of CH. Women with CH tend to report a higher frequency of eyelid oedema, vomiting, and nasal congestion. Additionally, women are more likely to experience chronic CH subtypes and often report longer attack durations and more prominent migraine-like symptoms compared to men (Allena et al., 2019; Fourier et al., 2023; Liaw et al., 2022).

Furthermore, differences have been reported in biological rhythms, with the average timing of nocturnal attacks occurring approximately one hour earlier in men than in women (N. Lund et al., 2017). These observations suggest that sex hormones, chronobiological regulation, and potentially genetic or epigenetic factors may contribute to the sex-specific expression and course of cluster headache.

3. Genetic

Genetic susceptibility plays an important role in the pathophysiology of cluster headache. A systematic review of large cohort studies reported positive family history rates ranging from 0% to 22%, with a median of 8.2%, supporting a heritable component in a subset of patients. Pedigree analyses further suggest diverse inheritance patterns, most commonly autosomal dominant or recessive, pointing to a complex genetic architecture potentially involving multiple susceptibility genes and gene-environment interactions (Waung et al., 2020).

Recent genome-wide association studies (GWAS) have provided novel insights into the genetic basis of CH. Winsvold et al. identified nine independent risk signals across eight genomic loci in a large meta-analysis comprising over 4,700 CH cases and 31,000 controls from European and East Asian populations. These loci are located near or within protein-coding genes such as DUSP10, MERTK, FTCDNL1, FHL5, WNT2, PLCE1, LRP1 and CAPN2. These genes are involved in diverse biological processes such as neurovascular regulation, inflammatory signalling and circadian processes, all of which have been implicated in the pathogenesis of CH. Importantly, three loci- FHL5, PLCE1, and LRP1 – overlap with those previously associated with migraine, suggesting a partially shared genetic architecture between the two primary headache disorders. However, the effect sizes at these loci were consistently higher in CH than in migraine, indicating their stronger role in CH susceptibility (Winsvold et al., 2023).

Moreover, certain phenotypic features may correlate with genetic load. For instance, patients with a familial form of CH have been shown to present more frequently with pronounced cranial autonomic symptoms, such as conjunctival injection and nasal congestion, compared to sporadic cases. These findings support the hypothesis that genetic variants may not only increase disease susceptibility but also influence clinical expression and severity. Future research focusing on the functional characterization of these loci and gene-environment interactions may facilitate the development of predictive genetic markers and targeted therapies for CH (O'Connor et al., 2022).

4. Environmental and lifestyle factors

Environmental and lifestyle-related factors are increasingly recognized as modulators of cluster headache susceptibility and attack frequency. Among these, cigarette smoking remains the most consistently associated behavioural risk factor. A recent genome-wide association study and meta-analysis including 4,777 clinically diagnosed CH patients and 31,575 controls from 11 European and East Asian cohorts reported that 74.3% of CH patients were current or former smokers – compared to notably lower rates in the general population – with the highest prevalence observed among individuals of European ancestry (77.3%). In addition to strong genetic correlation between CH and smoking-related traits such as cigarettes per day ($rg = 0.36$, $p = 6{,}32 \times 10^{-18}$), Mendelian randomization using 40 genetic variants associated with smoking intensity showed a significant causal effect on CH risk ($\beta = 1.11$, $SE = 0.43$, $p = 6.3 \times 10^{-6}$), which was further supported by a latent causal variable model indicating a high genetic causality proportion ($GCP = 0.74 \pm 0.18$, $p < 10^{-9}$). These findings underscore the potential importance of smoking cessation strategies in CH prevention and management particularly considering epigenetic evidence linking tobacco exposure to persistent DNA methylation changes in genes such as FBLN7, SLC20A1, and KDM4B, several of which were identified as candidate contributors to CH pathophysiology in this study (Winsvold et al., 2023).

Alcohol is another well-established environmental trigger, particularly during active cluster periods. In a Swedish case-control study, 56.2% of CH patients reported alcohol as a reliable trigger, with similar proportions among episodic and chronic subtypes, and across genders. Interestingly, no association was found between Ch and two specific polymorphisms in the ADH4 gene, which plays a role in alcohol metabolism, suggesting that environmental rather than genetic factors may underlie this response (Fourier et al., 2016). A 2019 Japanese cross-sectional study further revealed that habitual drinkers with CH exhibited significantly more pronounced conjunctival injection during attacks that non-drinkers, providing evidence to support alcohol's role in modulating cranial autonomic responses (Imai & Kitamura, 2019). Given the reproducibility and intensity of alcohol-induced attacks, clinical practice guidelines consistently advise patients to avoid alcohol entirely during active CH periods (May et al., 2023a).

Disruptions in circadian rhythm and sleep architecture constitute significant risk factors in the pathophysiology of cluster headache. The disorder is characterized by highly predictable attack patterns, with a prominent nocturnal peak between 1:00 and 2:00 a.m., implicating circadian dysregulation as a fundamental feature (Barloese, 2021). Seasonal clustering – particularly during periods of abrupt change in daylight duration, such as in spring and autumn – further supports the role of environmental entrainment failures in triggering attacks(Pilati et al., 2023).

Robust evidence supports the hypothesis that these temporal patterns are underpinned by impaired melatonin signalling. Both serum melatonin and its urinary metabolite, 6-sulfatoxymelatonin are significantly reduced during active cluster periods and remain abnormally low even in remission, indicating persistent chronobiological dysfunction (Liampas et al., 2020).

This dysfunction is likely mediated by disrupted hypothalamic regulation, particularly involving the suprachiasmatic nucleus, which regulates circadian timing via melatonin secretion (Barloese, 2021). Genetic investigations have further substantiated this association, identifying polymorphisms in key circadian genes such as CLOCK and altered expression of regulators like REV-ERBα in individuals with CH (Pilati et al., 2023).

Collectively, these findings suggest that sleep dysregulation and circadian misalignment function as modifiable risk factors in the onset and chronification of CH and may represent viable targets for preventive interventions.

Pathophysiology

The pathophysiology of cluster headache is complex and multifactorial, involving central and peripheral mechanisms that interact through dysregulated neuroanatomical pathways and altered neurochemical signalling. Functional neuroimaging studies have provided compelling evidence that the posterior hypothalamus plays a key role in both the initiation and maintenance of cluster headache attacks. This deep brain structure, located within the gray matter of the hypothalamus ipsilateral to the pain, was first identified as activated during CH attacks in PET studies, and has since been confirmed through more recent fMRI investigations. In a Study by Schulte, Sprenger, and May, functional MRI with trigeminal nociceptive stimulation revealed phase-dependent activation of the posterior hypothalamus in patients with cluster headache. The authors observed significantly stronger activation of this region in patients who were outside the active cluster period compared to those currently experiencing attacks. This finding supports the hypothesis that the posterior hypothalamus exhibits cyclical fluctuations in excitability. According to the authors, the posterior hypothalamus functions as an integrative hub fot both nociceptive input and circadian regulation. Its diminished responsiveness during active cluster phases may reflect an adaptive downregulation mechanism in response to chronic or repetitive stimulation, possibly as a protective response to excessive hypothalamic activation (Schulte et al., 2020)

Complementary structural data from Yang et al. provide additional support for a functional rather than anatomical alteration of the hypothalamus in CH. The authors found no significant volumetric differences in the hypothalamus between CH patients and healthy controls, suggesting that the structure is not anatomically damaged but undergoes functional reorganization in response to chronic pain input. Furthermore, they identified significant reduction in structural connectivity between the hypothalamus and prefrontal, temporal, and parietal cortices – regions involved in pain modulation, executive function, and emotional regulation. These disruptions imply impaired top-down control of nociceptive pathways, potentially contributing to attack persistence (Chong et al., 2020).

Further evidence of dysfunctional hypothalamic integration with other brain regions comes from a recent RS-fMRI study by Enchao et al., which employed independent component analysis. This study revealed significantly reduced coactivation between the hypothalamus and the salience network – including the anterior cingulate cortex and anterior insula – on both the ipsilateral and contralateral sides of the headache. Since the SN plays a central role in the cognitive-emotional modulation of pain and in autonomic regulation, reduced hypothalamus – SN connectivity may contribute to both impaired endogenous pain control and the autonomic symptoms characteristic of CH, such as lacrimation and nasal congestion (Qiu et al., 2015).

Alongside central dysfunction, the trigeminoparasympathetic reflex represents a fundamental peripheral mechanism in CH pathophysiology. This reflex arc involves bidirectional connections between the ophthalmic branch of the trigeminal nerve (V1) and the cranial parasympathetic system, especially the superior salivatory nucleus, the sphenopalatine ganglion (SPG) and the facial nerve (CN VII). During a CH attack, activation of the trigeminal nociceptive pathway leads to antidromic release of inflammatory neuropeptides, while simultaneously activating the superior salivatory nucleus, which sends parasympathetic output via the facial nerve to the SPG. Postganglionic fibbers from the SPG innervate the lacrimal gland and nasal mucosa, causing cranial autonomic symptoms such as conjunctival injection, lacrimation, nasal congestion, and rhinorrhoea (Goadsby, 2018).

The coordination between hypothalamic function, trigeminal pain pathways, and parasympathetic output is further influenced by several key neuropeptides.

Among the most important neuropeptides involved in the pathophysiology of CH is calcitonin gene-related peptide (CGRP). Studies have shown that intravenous infusion of CGRP provokes attacks in the patients with active episodic CH and chronic CH, while patients in remission remain unresponsive. CGRP acts primarily at the peripheral level, inducing vasodilation and activating CGRP receptors within the trigeminal ganglion and SPG, thereby triggering the trigeminal-autonomic reflex. Notably, autonomic symptoms have been observed to precede the onset of pain, suggesting that CGRP contributes to attack initiation through modulation of the trigeminal-autonomic reflex. The susceptibility to CGRP-induced attacks appears to depend on the disease state, supporting the hypothesis that the hypothalamus modulates neuronal excitability thresholds and predisposition to attacks (Snoer et al., 2019; Vollesen et al., 2018).

In addition to CGRP, neuropeptides such as pituitary adenylate cyclase-activating polypeptide (PACAP38) and vasoactive intestinal peptide (VIP) are also implicated in CH pathophysiology, although their exact roles are less well defined. PACAP38 and VIP infusions can trigger attacks in patients with episodic CH and chronic CH, though less consistently than CGRP. Patients in remission may display autonomic symptoms without full attacks following PACAP38 or VIP infusion, underscoring that peripheral parasympathetic activation alone in insufficient – central susceptibility, likely involving hypothalamic mechanisms, appears to be required. The actions of PACAP38 and VIP are thought to be primarily peripheral and mediated through VPAC1, VPAC2, and PAC1 receptors. However, the previous notion of PAC1 being the sole mediator of PACAP-induced attacks has been challenged by recent findings. PACAP also stimulates VIP release from neurons, suggesting the existence of complex neuropeptidergic network regulating both parasympathetic outflow and trigeminal activity. Moreover, VIP plasma levels in CH patients have been shown to fluctuate depending on disease activity, supporting the notion of dynamic neuropeptide regulation during active and remission phases (Deligianni et al., 2023; Pellesi et al., 2022).

Orexin A, produced in the lateral and posterior hypothalamus, modulates wakefulness, circadian rhythms, autonomic tone, and pain inhibition.

A 2015 study reported significantly decreased cerebrospinal fluid orexin A levels during active periods of cluster headache, suggesting that orexinergic hypofunction may contribute to loss of descending pain inhibition and sympathetic drive, favouring attack initiation and parasympathetic dominance (Barloese et al., 2015). However, more recent reviews have not confirmed these findings consistently, indicating that the role orexin A in CH remains uncertain and may vary between patient populations (Stanyer et al., 2024).

Alternative theories of CH pathogenesis propose the involvement of chronic low-grade inflammation within the cavernous sinus and adjacent regions, potentially linking vascular, trigeminal, and sympathetic structures within a confined anatomical compartment. This hypothesis integrates vascular and neural models of CH pathogenesis and may explain some of the variability in response to pharmacologic and neuromodulatory therapies (Buture et al., 2016).

Collectively, these findings point toward a multifactorial pathophysiological framework for CH, integrating hypothalamic dysfunction, neurovascular signalling, trigeminal-autonomic dysregulation, and possibly local inflammatory processes. Understanding the interplay among these components remains crucial for developing targeted and individualized treatment approaches.

Treatment

Management strategies of treatment CH are divided into acute, preventive and transitional therapies, with increasing emphasis on individualized and targeted interventions based on recent advances in pathophysiology.

1. Acute therapies

Triptans are considered a first-line pharmacological option for the acute treatment of CH, owing to their rapid onset of action and efficacy. According to a Cochrane systematic review, subcutaneous sumatriptan at a dose of 6mg is particularly effective. In two randomized, double-blind, placebo-controlled trials, approximately 48% of participants were pain-free and 75% experienced at least mild pain or no pain within 15 minutes of administration. In contrast, only 17% and 32%, respectively, achieved these outcomes with placebo. The number needed to treat (NNT) for pain-free status was 3.3, and for headache relief 2.4, underscoring the clinical effectiveness of subcutaneous sumatriptan.

In term of safety, adverse events were more frequently reported in the sumatriptan group (34%) compared to placebo (19%), yielding a number needed to harm (NNH) of 6.6. These events were typically mild to moderate and transient, with no serious adverse reactions directly attributable to the drug.

In comparison, intranasal zolmitriptan, though less effective than subcutaneous sumatriptan, has also demonstrated benefit. At a 10 mg dose, 12% of patients were pain-free and 28% had at least mild pain relief at 15 minutes post-dose, with corresponding NNTs of 11 for pain-free status and 4.9 for headache relief.

Adverse events were more common with the 10 mg intranasal dose (37%) compared to placebo (15%), with a NNH of 4.6 (Law et al., 2013).

Recent real-world evidence further supports the clinical use of sumatriptan. A retrospective analysis by Giani et al. (2021) examined 206 patients with CH and found that approximately 9% were non-responders to subcutaneous sumatriptan. These patients experienced longer and more frequent attacks, with a median attack duration of 100 minutes, compared to 60 minutes on responders (p=0.028) (Giani et al., 2021)

The 2023 European Academy of Neurology (EAN) guidelines reaffirm the place of subcutaneous sumatriptan 6mg as the first -line treatment for acute CH. Intranasal zolmitriptan (10mg) is recommended as a second-line option, particularly for patients who prefer of require needle-free administration (May et al., 2023b).

In parallel, inhalation of 100% oxygen via a non-rebreather mask remains another first-line for abortive CH treatment, especially in patients with episodic CH or those unable to use triptans. In recent real-world studies and international surveys, 100% oxygen administered at a flow rate of 12-15L/min for 15-20 minutes resulted in complete pain relief in approximately 54-56% of attacks, with up to 74% experiencing at least 50% relief, and minimal side effects reported by over 97% of users (Pearson et al., 2019; Petersen et al., 2021).

In direct comparisons, subcutaneous sumatriptan was slightly more effective than oxygen, particularly in chronic CH, with higher rates of complete pain relief (57% vs. 29%), but with a less favorable side effect profile (Petersen et al., 2021).

Patient preference often favors oxygen due to its excellent tolerability and safety, especially in populations with contraindications to triptans.

A randomized, crossover study by Dirkx et al. found no significant difference in effectiveness between oxygen at 7L/min and 12L/min, though more patients preferred 12l/min, suggesting that flow rate should be individualized (Dirkx et al., 2018).

Intranasal lidocaine, administered via soaked cotton pledges or spray targeting the sphenopalatine fossa, can provide rapid relief in some patients, although the evidence base is limited and response rates are generally modest. A 2019 international survey showed that only 2% of CH patients reported complete or very effective relief with lidocaine, and most described it as only minimally effective (Petersen et al., 2021). Nevertheless, due to its safety and non-systemic nature, lidocaine may be considered in selected cases, particularly where standard treatment is contraindicated.

2. Preventive therapy

Verapamil is the first line and most preferred preventive treatment for both episodic and chronic cluster headache, supported by consistent clinical and observational evidence. In a large real-world survey, 55% of patients used verapamil as monotherapy, with 56% achieving a ≥50% reduction in attack frequency, particularly at doses exceeding 480 mg/day (Petersen et al., 2021). Treatment typically begins at 240-360 mg/day and is titrated in 80-120mg increments every 10-14 days. Because of risk of dose-dependent cardiac conduction abnormalities such as bradycardia and AV block, regular ECG monitoring is required, especially at higher doses (Koppen et al., 2016). Despite potential side effects like constipation, hypotension, and fatigue, verapamil remains the most effective long-term preventive agent for cluster headache. Onset of effect is usually seen within 7-14 days of reaching a therapeutic dose, often warranting combination with transitional treatment e.g. corticosteroids (May et al., 2023b).

Short-term corticosteroid therapy, such as oral prednisone or intravenous methylprednisolone, is widely used for transitional management during cluster periods, allowing time for preventive medications to achieve efficacy. However, due to the risk of systemic side effects, corticosteroids are unsuitable for long-term use.

A multicentre, double-blind randomized controlled trial (2021) demonstrated that oral prednisone (100mg/day, with taper) significantly reduced the number of cluster attacks during the first 7 days of treatment compared to placebo (mean 7.1 vs 9.5 attacks; $p<0.05$), supporting its role as an effective short-term intervention in episodic CH (Obermann et al., 2021).

In a more recent observational study, patients with episodic CH who had not responded to oral steroids were treated with intravenous methylprednisolone (500mg/day for 5 days) combined with verapamil. By day 5,68% were headache-free, and 93% reported ≥50% reduction in daily attacks without serious adverse effects (Rubino et al., 2024)

Despite this efficacy, the use of corticosteroids is generally limited to 5-14 days due to potential side effects. As such, corticosteroid is best reserved as transitional therapy while preventive agents take effect (May et al., 2023b).

Lithium carbonate is a second line preventive treatment, particularly recommended in chronic cluster headache. However, high-quality recent randomized controlled trials evaluating its efficacy remain limited. Therapy is typically initiated at 600-1500 mg/day and titrated to maintain serum lithium levels between 0.6 and 0.8 mmol/L. Due to the narrow therapeutic window, regular monitoring of serum lithium levels, renal and thyroid function is essential (Diener & May, 2022; May et al., 2023c).

Topiramate is another second line preventive option. Robust and up-to-date data on its efficacy in cluster headache also remain limited. It is generally recommended in cases where verapamil or lithium are ineffective or contraindicated. Dosages between 50 and 200mg/day have been used, with a median time to clinical effect of approximately 2-4 weeks. Common side effects include cognitive difficulties, paresthesias, and weight loss, which may limit treatment adherence. Furthermore, topiramate has been associated with an increased risk of depression, a consideration of particular importance given the elevated risk of suicidal behaviour observed in patients with cluster headache (Ji Lee et al., 2019; N. L. T. Lund et al., 2023; May et al., 2023c).

3. Neuromodulation

Neuromodulation has become an area of growing interest in the management of cluster headache, particularly in patients with chronic or drug-refractory forms. These techniques aim to modulate pain processing pathways through targeted stimulation of peripheral or central nervous system structures, offering an alternative or adjunct to pharmacologic therapy.

Non-invasive vagus nerve stimulation (nVNS) has been the most extensively studies neuromodulatory treatment in CH. In the PREVA randomized controlled trial, nVNS used as an adjunct to standard of care resulted in a significantly greater reduction in weekly attack frequency compared to standard treatment alone, with a ≥50% response rate in 40% of patients versus 8% in controls. The device was well tolerated and free from serious adverse events, supporting its use in both prevention and, to some extent, acute treatment of chronic CH (Gaul et al., 2016).

Implanted sphenopalatine ganglion (SPG) stimulation has also demonstrated efficacy in patients with medically intractable chronic CH. In long-term follow-up studies, SPG stimulation was associated with sustained reductions in attack frequency and intensity, and some patients experienced acute relief within minutes of stimulation. While effective, the invasive nature of the procedure and surgical risks limit its use to carefully selected individuals (Jürgens et al., 2017).

Transcutaneous auricular vagus nerve stimulation (taVNS) has shown early promise in modulating central pain networks through stimulation of vagal afferents in the ear. Preliminary data suggest potential benefit in headache disorders, but its specific role in CH is yet to be clearly defined and further controlled trials are required (Jürgens et al., 2017)

Occipital nerve stimulation (ONS) has also emerged as a promising approach in patients with drug-resistant chronic CH. In a recent study, ONS achieved an overall response rate of 70%, and nearly half of patients reported ‘voltage tuning’ behavior, whereby they manually increased stimulation amplitude during attacks to achieve relief. This observation raises intrest in the potential use of ONS not only as a preventive measure but also as an acute treatment strategy for severe CH attacks (Kollenburg et al., 2024).

Overall, neuromodulation offers a valuable tool in the multidisciplinary management of CH. As the evidence base grows and device technology advances, these techniques may become increasingly integrated into clinical practice, particularly for patients unresponsive to pharmacologic strategies.

4. New treatment strategies

Novel treatment strategies and innovative approaches are a major source of hope for patients with cluster headache, especially that refractory to standard therapies. Among these, monoclonal antibodies targeting calcitonin gene-related peptide (CGRP) and other neuropeptides have shown promising results in clinical trials.

A randomized, double-blind, placebo-controlled Phase 3 trial investigated galcanezumab, a humanized monoclonal antibody against CGRP, in patients with episodic cluster headache. Monthly subcutaneous injections of 300 mg significantly reduced the weekly frequency of attacks during the first 3 weeks compared to placebo (mean reduction 8.7 vs. 5.2 attacks; $p=0.04$). At week 3, 71% of patients receiving galcanezumab achieved a ≥50% reduction in attack frequency versus 53% in the placebo group ($p<0.05$). The treatment was generally well tolerated, with injection site pain being the most common adverse effect (Goadsby et al., 2019). However, in a Phase 3 trial involving patients with chronic cluster headache, galcanezumab failed to demonstrate significant efficacy over placebo (mean change -5.4 vs. -4.6 attacks/week; $p=0.334$), suggesting possible differences in disease mechanisms between episodic and chronic forms (Dodick et al., 2020).

In the ALLEVIATE trial, eptinezumab (400mg intravenous infusion) was tested in patients with episodic cluster headache. Although the primary endpoint – reduction in weekly attack frequency at weeks 1-2- was not significantly different from placebo (mean change -4.0 vs. -4.5 attacks/week; $p=0.5$), a higher proportion of patients receiving eptinezumab achieved ≥50% reduction in attack frequency at week 2 (50.9% vs 37.3%; OR 1.77; $p=0.04$), week 3 (62.5% ws. 43.8%; OR 2.26; $p=0.004$), and week 4 (66.7% vs. 50.5% OR 2.14; $p=0.009$). The treatment was well tolerated, with adverse events reported in 25% of eptinezumab patients versus 26.5% in the placebo group (Jensen et al., 2025).

Pituitary adenylate cyclase-activating peptide 38 (PACAP-38), another neuropeptide implicated in the trigeminovascular system, has also emerged as a potential therapeutic target. Infusion of PACAP-38 has been shown to trigger attacks in patients with active cluster headache, suggesting its involvement in pathophysiology. Preclinical studies on PACAP-38 receptor antagonists indicate possible preventive effects, but robust clinical trials in humans are still lacking (Schindler & Burish, 2022).

These advances underscore the potential of targeted biological therapies to transform the management of cluster headache and improve outcomes in patients unresponsive to conventional treatments.

Conclusions

Cluster headache is a highly disabling neurobiological disorder with profound implications for patients physical, emotional and social health. Recent progress in elucidating its pathophysiology has paved the way for development of novel targeted therapies, such as CGRP monoclonal antibodies and neuromodulation techniques, which have shown promise in patients unresponsive to conventional treatments. Despite these advances, challenges remain in achieving early and accurate diagnosis, optimizing individualized treatment plans, and addressing the broader psychosocial impact of the disorder. Future research should aim to refine our understanding of CH mechanisms, identify predictive biomarkers for treatment response, and develop comprehensive management strategies that encompass both medical and supportive care to reduce the overall burden of the disease.

Disclosure:

Author's contribution:

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