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Hallmarks of primary headache: part 3 – cluster headache

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Abstract

Background Cluster headache (CH) is a rare primary headache disorder characterized by recurrent episodes of strictly unilateral excruciating pain accompanied by trigemino-autonomic signs, which significantly impacts the quality of life, social interactions, and occupational functioning of those who are affected. To promote a better understanding of this disabling condition and to foster research on the topic, this review provides a comprehensive description of the hallmarks of CH, including its clinical presentation, diagnostic challenges, pathophysiology, and current and novel therapeutic targets. It concludes by describing the disease burden and advocating for significant improvements in healthcare systems, and promoting health equity, as well as reducing stigma.

Principal findings Despite its distinctive clinical and chronobiological features, CH may be mistaken for other primary headache disorders or different types of orofacial pain. Key pathogenic characteristics include the activation of the trigeminal-autonomic system with the release of several neuropeptides, the involvement of the hypothalamus in regulating the circadian rhythm, genetic variants, and the mesolimbic system. Both invasive and non-invasive neuromodulation treatments have been used to target the trigemino-cervical, parasympathetic, and hypothalamic systems. Additionally, novel therapeutic targets are currently being study. Alongside canonical therapies, several complementary approaches have been explored over the years, with most evidence deriving from uncontrolled research involving individuals who do not respond to standard pharmacological treatments. Despite advancements in our understanding of this complex disease, CH continues to pose considerable social, economic, and psychological

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challenges. Advocacy is essential and should prioritize early diagnosis, alleviate stigma, provide specialized training for healthcare professionals, and offer support to and through patient associations.

Conclusions CH is characterised by a complex, multifactorial, pathophysiology that is still not fully understood. Precise diagnosis, additional research studies, and robust psychosocial and institutional support are necessary to improve the quality of life for individuals affected by this debilitating condition.

Keywords Primary headache, Hypothalamus, Circadian rhythm, Trigeminal-autonomic system, Neuropeptides, Treatments, Neuromodulation, Psychological factors, Advocacy

Introduction

Cluster headache (CH) is a primary headache disorder classified under the trigeminal autonomic cephalalgias (TACs) and it is considered one of the most intense and debilitating pain condition in humans. Clinically, CH is characterised by severe and strictly unilateral pain, predominantly involving the territory of the first division of the trigeminal nerve, accompanied by autonomic symptoms. Attacks of CH generally last between 15 and 180 min, exhibit circadian and circannual recurrence, and may be associated with agitation or restlessness [1]. Although generally the disease is characterized by episodes of bout – the period in which the patient experiences the recurrence of attacks daily or every other day – and periods without attacks, approximately 15–20% of patients experience a chronic variant of CH with any periods without attacks or remissions that last less than three months. Among them, an indeterminate percentage of patients may develop a drug-resistant type of chronic CH (rCCH), suggesting that other strategies than conventional therapy, such as non-invasive or invasive neuromodulation, are required for some individuals. The historical prominence of CH in males has diminished over the decades, however a distinct male predominance of the illness persists [2–5]. Certain experts ascribe this declining tendency to changes in women's lifestyles, which more resemble those of men, and to advancements in the diagnostic accuracy for female patients [6].

Notwithstanding its distinctive clinical presentation, CH frequently remains underdiagnosed and unacknowledged in clinical practice, resulting in a long lag between the onset of the disease and obtaining an accurate diagnosis and appropriate treatment [7]. Indeed, a recent meta-analysis reported a diagnostic delay of approximately 10 years for CH diagnosis, with markedly prolonged delays in patients with rCCH relative to those with non-rCCH. However, they noted a decrease in this delay over time since the 1960s, with a continuous reduction observed every decade after 2000, suggesting that awareness of this condition has improved among clinicians over the years [8].

Clinical, biochemical, and electrophysiological studies have recognised the crucial role of the trigeminal-parasympathetic system and the hypothalamus in the aetiology and recurrence of CH pain; nevertheless, the sequence of activation of these separate systems remains unclear. Additionally, while the hypothalamus is primarily recognised for regulating the seasonal and circadian patterns of attacks, additional structures seem to play a role, including the brainstem monoaminergic systems in the midbrain – particularly the dopaminergic system in chronic cases – and the descending pain control systems. However, the exact pathophysiological cascade and structures involved are still not completely understood.

This lack of understanding is also witnessed by the restricted therapeutic alternatives, comprising solely sumatriptan and oxygen for acute management, steroids for bridging therapy, and a scarcity of genuinely effective prophylactic agents aside from verapamil. Additionally, despite multiple attempts to use alternative pharmacological and non-pharmacological methods, their use is limited by the lack of controlled clinical trials and their efficacy being restricted to a specific subset of patients.

To delineate the hallmarks of CH across several domains, we provide a comprehensive description of several aspects of CH. Through different subsections, each designed to present the aspects that characterize CH-specific traits, this review aims to summarize the most thorough and accurate research available on this topic. These included CH clinical presentation, diagnostic challenges, pathophysiology, and current and novel therapeutic targets. Finally, it concludes by describing the disease burden and advocating for significant improvements in healthcare systems, reducing stigma, and promoting health equity.

Clinical features of episodic and chronic CH

CH is a debilitating disorder characterized by severe, unilateral pain typically located around the eye. As one of the most common TACs, autonomic symptoms are typical during CH attacks. CH can be divided into episodic and chronic subtypes. Those with episodic CH have bouts that last from 7 days to one year, separated by pain-free periods for at least 3 months, when untreated. Most cluster periods usually last between two weeks and three months [1]. On the other hand, those with chronic CH present with persistent attacks for more than one year

without any remission periods or with less than three months of remission [9].

The clinical features of these subtypes reveal significant differences in attack frequency, bout duration, and associated symptoms. Individuals suffering from episodic CH experience well-defined cycles of recurrent attacks, often referred to as "bouts", which can last for weeks to months. These bouts are commonly followed by extended periods of remission, sometimes lasting months or even years [10]. In contrast, patients with chronic CH experience attacks without substantial remission periods, leading to frequent bouts that can persist indefinitely [11].

CH episodes typically manifest as short but intense attacks, with each attack lasting between 15 min and three hours [9] on average of 55 to 130 min without any significant difference between episodic and chronic CH [12, 13]. During an active bout, patients may experience varying frequencies of attacks, ranging from one attack every other day to as many as eight attacks within a single day. The average frequency reported within a bout can vary, with many patients reporting two to three daily attacks [10]. The episodic nature might also be influenced by factors such as smoking, with approximately 70–90% of patients with CH having a history of smoking, which correlates with an increase in attack frequency and duration of the bouts [14]. In fact, a causality between smoking and CH was recently demonstrated by a Mendelian randomization study [15].

In contrast, chronic CH is characterized by a more relentless pattern of attacks. Patients with chronic CH experience a higher frequency of attacks, with some individuals enduring as many as 10 or more headache episodes each day during active bouts, which can last for years without significant relief [11]. Patients with chronic CH often report similar attack durations to those with the episodic form. However, the frequency and lack of remission can exacerbate the individuals' experience of pain and incapacitation.

In very rare cases, bilateral CH has been reported [16]. However, most patients with CH presented strictly side-locked headache, meaning that a patient's headache episodes were mostly confined to one side within a bout. The intensity of the headache is usually excruciating. In fact, some considered CH one of the most intensely painful human conditions reported [17]. However, a proportion of patients with CH demonstrates "side shifting" either within or between bouts. Side shifting between bouts has been reported at around 13–18% [18]. Within individual bouts, a study [18] indicated that approximately 33% of patients with chronic CH patients experienced side shifts, compared to 14% of their episodic CH counterparts while another study on Nordic cohort observed similar prevalence of 13–15% between episodic and chronic CH [19]. A recent study reported that the presence of side-shifting was associated with a significantly increased odds (OR = 2.24) of chronic CH compared to episodic CH [20].

Patients with CH frequently exhibit restless and agitated behaviours, presenting with continuously moving in an unsuccessful effort to alleviate their pain. Approximately 80–90% of individuals become restless in the Western cohorts [21] but lower at around 50% in the Eastern cohorts [22, 23]. The associated symptoms of CH are notable for their specificity to the attack's side. The most common cranial autonomic symptoms (CAS) are lacrimation/conjunctival injection (reported by > 90% of patients). However, rhinorrhea, miosis, ptosis, and eyelid oedema are also common [9], and rhinorrhea has been reported less in chronic CH [24]. These features distinguish CH from other headache disorders, such as migraine, where similar CAS may not present unilaterally [25]. A careful distinction from trigeminal neuralgia involving the first division of the trigeminal nerve may be required in selected cases. However, the neuralgiform pain character, the sporadic and mild degree of intensity of CAS and the absence of restlessness during the painful attacks of trigeminal neuralgia, make the clinical distinction with CH reasonably straightforward [26]. Notably, visual disturbances such as unilateral visual sensitivity can also occur, primarily affecting the same side as the headache [27]. Specific data differentiating the prevalence of individual CAS between episodic CH and chronic CH are limited. Both subtypes exhibit similar autonomic features, but comprehensive studies directly comparing the frequency of each CAS are lacking. However, results from an extensive survey suggest that the highest pain intensity (numeric rating scale = 10/10) is linked to an increased number of CAS, indicating a proportional relationship between pain severity and autonomic symptom expression [17].

In regard to the sex-related differences in clinical features, studies from large cohorts have reported older onset age [4, 28, 29] and a higher proportion of smokers and alcohol consumers [4, 28] in male patients. Male patients also demonstrate a higher proportion of conjunctival injection [4, 30] and a lower proportion of eyelid oedema [4, 30], ptosis [30, 31], restlessness [30, 31], pacing [4, 28], and nausea [4, 28, 29] during attacks compared to female patients. Two studies [30, 31] showed that among patients with CH, female patients were diagnosed with chronic CH more. In contrast, others [4, 28, 29] found no significant sex difference. Female patients with CH also reported higher comorbidity with migraine [4, 28, 31], which is reasonable considering the female predominance of migraine per se.

For episodic CH, there is a characteristic circannual pattern, often peaking in the spring and fall, possibly aligning with temperature changes [32] and daylight

changes [33], environmental stressors or lifestyle changes during these times [12, 13]. Conversely, due to the incessant nature of chronic CH, the triggers for the bout period may be less distinct [11]. However, such circannual fluctuations of attack frequency have still been reported in patients with chronic CH who demonstrate higher attack frequency during certain times of the year than the rest [34]. The circadian pattern is also a signature of CH, with a clear peak between 21:00 and 03:00 [35]. The individual pattern is exact and varies only by minute in many patients on a day-to-day basis. Triggers for attacks have also been reported. Alcohol consumption has been identified as a significant trigger reported by up to 50–80% of patients with CH, with a slightly higher rate (65%) in episodic CH compared to chronic CH (54%) [18]. Sleep has also been reported as a trigger in 80% of a 275-subject cohort [36]. Other common triggers include smells, bright/flashlights, hot showers/heat, nitroglycerin intake, etc [37, 38]. The sustained hypoxemic event cause by either sleep apnea, poor ventilation/stagnant air, or change of altitude, could provoke the attacks as well [39]. Interestingly, these triggers only trigger attacks during the bout period for episodic CH and usually have no effect during the out-of-bout period. There is a lack of research comparing the differences between episodic and chronic CH regarding their triggers.

Additionally, the pre-cluster symptoms, frequently presenting as localized pain and sensations, may alert patients to the impending onset of a bout and tend to be more recognized in individuals with a history of multiple bouts [40]. Patients who experience frequent cluster bouts may become more familiar with recognizing these signs. However, the related symptoms can vary significantly between individual experiences [41, 42].

Research shows that patients with episodic CH report more symptoms before a headache attack compared to those with chronic CH [5]. Patients with chronic CH tend to report less predictability in their symptomatology, as the continuous nature of their condition makes patterns harder to discern.

Neurobiological mechanisms underpinning these clinical features highlight the role of the hypothalamus in CH pathophysiology [43]. Activation of the hypothalamus during an attack may explain the circadian patterns and the subsequent discharge of pain and CAS [44]. A recent study also found that the sphenopalatine ganglion (SPG) volume is larger on the painful side, and the volume of ipsilateral SPG is associated with the number of CAS in episodic CH [45]. In chronic cases, repeated activations of the hypothalamus due to constant attacks [46] may lead to neurotransmitter exhaustion [47], disturbing the circadian rhythmicity of hormones, such as testosterone and cortisol, and further complicating the management options. Such insights remind healthcare providers of the importance of considering long-term disease management strategies for those who suffer from chronic CH.

In summary, both chronic and episodic CH presents with a set of distinctive clinical features characterized by severe unilateral pain and ipsilateral autonomic symptoms. The differing attack frequencies, bout durations, and symptomatology distinguish the episodic and chronic CH, highlight the complexity of CH. The necessity for individualized treatment approaches to manage the debilitating nature of CH effectively should be underlined.

Genetic basis

CH is recognized as a complex disease, due to interactions between genetic and environmental factors and to date, various molecular genetic clues have been identified. First degree relatives of patients with CH have a 5–18 increased risk of developing the disease compared to the general population while second-degree relatives of patients have an 1–3 increased CH risk [48, 49]. Inheritance is likely to be autosomal dominant with low penetrance in some families, although there may also be autosomal recessive or multifactorial inheritance in others [50]. CH has also been reported to be significantly increased in monozygotic twins than in dizygotic twins [49, 51].

Results from Linkage studies in CH have so far been negative. Calcium channel alpha 1 subunit (CACNA1A) micro satellites have been screened in CH families from the Netherlands and in a Swedish cohort, both studies were reported negative [52, 53]. A genome wide scan of 400 micro satellites markers in CH families from Denmark, Italy, Sweden and UK was additionally also reported negative [54]. Several genetic association studies have been performed in CH patients using the candidate gene strategy. The putative pathogenetic role of posterior hypothalamus in CH pathophysiology as well as the chronobiological features of the disease suggested a role for genes related to hypothalamic and chronobiological functions in the disease. Multiple studies investigated the association between CH and the Hypocretin Receptor 2 gene (*HCRTR2*), that is expressed in the posterior hypothalamus. In an Italian cohort, a significant association between allele G of the G1246A polymorphism (rs2653349) was found [55]. Haplotype analyses have further supported a role for *HCRTR2* in CH and proposed that rs2653349 can lead to minor changes in the mRNA structure, affecting both mRNA stability and the dimerization process of the *HCRTR2* gene [56, 57]. Nonetheless, the suggested association with rs2653349 could not confirmed by a recent meta-analysis although showed a weak association with rs9357855 [58]. Variance in genotype and allele frequencies among the different populations examined may explain these discrepancies. At

present, therefore, the *HCRTR2* gene remains an interesting candidate gene for involvement in the pathophysiology of CH.

Considering the periodical occurrence of CH bouts, genes that regulate chronobiological function have been investigated. Several studies genotyped CH patients and controls for the rs1801260 polymorphism of the *CLOCK* gene. So far, however, no association has been identified between CH and this SNP [59–62]. A more recent study also explored the association with two other SNPs (rs11932595 and rs12649507) of the *CLOCK* gene and reported a significant association of the disease with rs12649507 [63]. *CRY1* and *CRY2* are genes deeply involved in the regulation of the circadian clock. In a Swedish CH cohort, a strong association was found between rs8192449 and CH [64]. The *PER1*, *PER2*, and *PER3* genes are light sensitive clock genes and have been investigated in relation to CH in Swedish and Norwegian cohorts [65, 66]. The results indicated no involvement of these genetic variants in the disease.

According to clinical studies, more than 50% of CH patients have attacks triggered by alcohol consumption, suggesting a causative role for genes related to alcohol metabolism and alcohol dependence in the genetic predisposition to the disease. The alcohol dehydrogenase 4 (*ADH4)* gene encode the pi subunit of the alcohol dehydrogenase (ADH) enzyme and significantly modulates alcohol metabolism. An Italian study found a significant genetic association between *ADH4* SNP rs1126671 and the disease [67]. Another Italian study explored the association between the rs1126671 and rs1800759 polymorphisms of the *ADH4* gene in CH patients versus controls finding significantly different allele and genotype frequency between sporadic CH and controls [61]. The attempt to further replicate the association between polymorphisms of the *ADH4* gene and CH failed in case-control cohort studies performed in Swedish, Chinese, and Greek cohorts [62, 68, 69].

So far there has been limited focus on the genetic aspects of calcitonin gene-related peptide (CGRP) and its receptors in CH, but one genetic variant in the receptor activity-modifying protein 1 gene (*RAMP1*), part of the CGRP receptor complex, has been linked to CH in a Swedish cohort [70].

In a recent meta genome wide association study (GWAS) including 10 European cohorts and one East Asian eight loci were identified [15]. Three of these loci interestingly overlap with identified migraine loci; *FHL5*, *PLCE1* and *LRP1* [71]. Mendelian randomization analysis further implicated smoking as causal risk factor. The GWAS top hit on chromosome 2 include *MERTK* (Mer tyrosine kinase protooncogene), a gene crucial for regulating microglia mediated inflammation. *MERKT* is primarily active in the brain's supporting cells, microglia, and has an important role in inflammation and phagocytosis of harmful molecules and cell debris in the brain. MERTK gene expression has been studied in patient-specific tissue, which shows increased levels of MERTK mRNA and its ligand Gal-3 in serum from study participants with CH [72]. Both MERTK and Gal-3 are further expressed in the trigeminal ganglion, involved in pain signaling in the facial region, in tissue from rodents. These findings, strengthens the hypothesis that the MERTK gene may play an important role in the pathophysiology of CH.

A recent study from France, using the whole genome sequencing (WGS) strategy, searched for candidate genes and new genetic variants of the disease investigating a multigenerational CH pedigree. The WGS on four members of the pedigree found that two family members showing the same phenotypic circadian pattern (familial periodicity) of symptoms had two genetic risk loci in the *HCRTR2* and in the *CLOCK* genes [73]. Thus, the risk of CH appears to be significantly increased by the concomitant presence of these polymorphisms.

Pharmacogenetic studies investigating the role of gene polymorphisms in drug responses in CH have been performed. In an analysis of 184 CH patients, no association between the *HCRTR2* G1246A polymorphism and treatment response to triptans, oxygen, verapamil, or corticosteroids was found [74]. Contrariwise, a polymorphism of the *GNB3* significantly influenced the chance of responding to treatment with triptans in CH patients [75]. A similar trend was observed in a Greek CH cohort; however, the association did not reach significance [69]. A Swedish study shows that genetic variants such as rs1024905 located on chromosome 12 and previously linked to triptan usage in migraine, can influence triptan usage in CH in Sweden. The cumulative effector score of five variants also indicates a complex genetic contribution to triptan usage [76]. Genotypes of the 5-HT transporter gene-linked polymorphic region (*5-HTTLPR*), and *CYP3A4* genes do not influence treatment response to triptans or verapamil in CH patients [77, 78].

Increased knowledge in the genetics field of CH can improve diagnosis and treatment by identifying biomarkers and novel drug targets, as well as developing future treatment strategies. In the past years there have been a significant process in the genetics of CH. Several candidate genes have been screened in CH cohorts worldwide, but with conflicting results. This is mainly due to few replication studies, small cohorts and geographical differences. Genome wide association studies have on the other hand identified eight significant loci, where three of them are shared with migraine, and the prioritized genes show enrichment in arterial and brain tissues.

Molecular pathways

The trigeminovascular and cranial parasympathetic systems are activated during CH attacks, leading to the expression and release of vasoactive neuropeptides, including CGRP, PACAP, VIP and NO. This section will review the role of these molecules in CH and will highlight the presence of other potential modulators of CH pathophysiology.

Calcitonin gene-related peptide (CGRP)

CGRP is a neuropeptide that is expressed in the areas involved in the pathophysiology of CH, including the trigeminal ganglia (TG), the trigeminal nucleus caudalis (TNC) and the hypothalamus [79]. CGRP activates the canonical CGRP receptor that is formed by the calcitonin-like receptor (CLR) coupled to the RAMP1 and receptor component protein (RCP). CGRP also has lower affinity for other receptors, such as the amylin subtype 1 receptor (AMY1), albeit less so in primates compared to rodents [80]. CGRP binding to its receptor results in the activation of complex intracellular pathways mostly mediated via cAMP signalling [80].

CGRP has been linked to CH pathophysiology in a variety of studies. CGRP is elevated in plasma in acute cluster headache in both spontaneous [81] and triggered attacks [82], and its levels are normalised by oxygen and sumatriptan. CGRP levels are elevated in saliva [83] and tears [84] during CH attacks when compared to healthy controls. CGRP provokes CH attacks in patients who are in the active, but not in the remission phase of the disease [85]. Importantly, treatment with galcanezumab 300 mg s/c effectively reduced the frequency of attacks in episodic CH [86], although it was not effective in the chronic variant [87]. Fremanezumab was ineffective in a placebo-controlled trial in episodic cluster headache with a four-week endpoint [88]. Fremanezumab for chronic CH was also discontinued after an interim analysis showed no efficacy [89]. Most recently, it has been shown that eptinezumab 400 mg intravenously while not reducing attack frequency against placebo did have a greater 50% responder rate in episodic CH [90]. In an open-label study in chronic CH, eptinezumab 400 mg was well tolerated and apparently clinically useful over twelve months [91].

Pituitary adenylate cyclase-activating polypeptide (PACAP)

The neuropeptide PACAP is expressed in CH relevant areas, including the trigeminal ganglia, the sphenopalatine ganglia, the otic ganglia, the trigeminal nucleus caudalis and the hypothalamus, among other regions [92, 93]. PACAP is found in two different isoforms, PACAP27 and PACAP38, the latter being the predominant mammalian form, that bind to three G-protein-coupled receptors: PAC1, VPAC1 and VPAC2. Binding of PACAP to its receptors activates the adenylate cyclase, inducing the increase of intracellular cAMP [94]. Binding to the PAC1 receptor increases the levels of intracellular calcium and activates protein kinase C signalling [93]. PACAP38 has also been found to promote pain behaviour in mice by activating the Mas-related G-protein coupled receptor member B2 (MrgprB2) in meningeal mast cells, suggesting the potential relevance of this receptor for PACAP's actions [95].

Like CGRP, PACAP is released during CH attacks. An exploratory study ($n = 5$) found that levels of PACAP38 in plasma are higher during CH attacks when compared to the remission phase, but that PACAP38 levels are more elevated in healthy controls when compared to CH participants in the remission phase [96]. However, further studies with larger sample sizes are needed to understand the expression patterns of PACAP in the different phases of CH.

Other key studies highlight the relevance of PACAP for CH biology. The infusion of PACAP38 provokes CH-like attacks in episodic CH participants in the active, but not in the remission phase, and in chronic CH participants [97]. Interestingly, PACAP38-induced CH attacks are not linked to changes of plasma CGRP, VIP, tryptase or histamine [98, 99].

Currently, there are no treatments targeting PACAP for CH. However, a proof-of-concept trial has shown the efficacy of an anti-PACAP antibody for migraine [100]. These encouraging results highlight the need to perform further trials focusing on CH patients to increase the therapeutic options for them.

Vasoactive intestinal polypeptide (VIP)

VIP is from the same peptide family, secretin-glucagon, as PACAP, with which it shares nearly 70% sequence identity [101]. Due to this similarity, VIP and PACAP bind to the same receptors: VPAC1 and VPAC2 receptors with a similar affinity, whereas PAC1 with 1000-fold lower affinity for VIP. VIP is expressed in areas that are relevant for CH biology, including the parasympathetic ganglia, specifically the sphenopalatine ganglion [92], and hypothalamus [102].

The studies that assess the role of VIP in CH are few, although they indicate a potential implication for its pathophysiology. Like CGRP and PACAP, VIP levels are elevated during CH attacks [81] and infusion of VIP induces CH-like attacks in episodic CH active phase and in chronic CH participants [97]. However, VIP-induced CH attacks did not alter the levels of plasma CGRP, tryptase or histamine [98] and PACAP- or VIP-induced CH attacks are not associated with changes in plasma levels of VIP [99].

Nitric oxide (NO)

Nitric oxide (NO) is a signalling molecule widely expressed throughout the body that plays a role in several functions that are linked to CH pathophysiology, such as processing sensory information, pain sensitization and circadian regulation [103]. It is synthesized by three isoforms of nitric oxide synthases (NOS) – endothelial, neuronal and inducible NOS. The neuronal NOS (nNOS) is expressed in areas relevant to CH biology, including the hypothalamus and trigeminal and parasympathetic ganglia [104–106].

Although it is not possible to measure the levels of NO due to its short half-life, its levels have been assessed indirectly by measuring the products of its oxidation, nitrite and nitrate. Two studies have shown higher levels of nitrite and nitrate in CSF and plasma of CH patients in their active period when compared to remission and healthy controls [107, 108], indicating the relevance of NO for CH biology. Another argument in this favour is that nitroglycerin, an NO donor, induces CH attacks [109, 110].

Other modulators of CH

Adenosine triphosphate (ATP)-sensitive potassium (K_{ATP}) channels have been linked to the pathophysiology of primary headaches, including CH. K_{ATP} channels are expressed in several tissues, including the CNS, and are key regulators of the vascular tone, among other functions. Studies suggest that K_{ATP} opening increases vasodilation which may activate and sensitize perivascular nociceptors [111]. This was tested in a study were the infusion of levcromakalim, a K_{ATP} channel opener, induced CH attacks in episodic CH patients in their active phase and in chronic CH patients. However, further studies with larger sample sizes are needed to validate these results and to better understand the role of K_{ATP} channels in CH biology.

Melatonin is a hypothalamic hormone that is only secreted in darkness. Its role in CH biology has been suggested due to its anti-nociceptive and anti-inflammatory properties and its implication in circadian and circannual regulation [112]. Different studies support this potential role, as melatonin levels are lower in CH patients when compared to healthy controls and treatment with melatonin reduced attack frequency in a small randomized placebo-controlled study [113]. However, larger studies would clarify its involvement in the disease.

Orexin A and B are hypothalamic neuropeptides involved in the promotion of arousal and in the regulation of nociception, body temperature, feeding behaviour and neuroendocrine system, among other functions [112]. Lower levels of orexin A were found in episodic and chronic CH patients, suggesting the potential role of orexins in CH [114].

Concluding remarks

In summary, studies support the role of CGRP, PACAP, VIP and NO in the pathophysiology of CH. Further research should focus on understanding the pathways regulated by these and emerging molecules to discover new therapeutic targets and to optimise current therapeutic strategies for CH.

The trigeminal autonomic reflex

The trigeminal autonomic reflex (TAR) is a complex, bidirectional neural circuit in which trigeminal nociceptive afferents activate parasympathetic efferents, contributing to the hallmark cranial autonomic features of CH [115]. While the role of this reflex in generating autonomic symptoms has been well documented, its direct involvement in modulating headache intensity and duration remains under ongoing investigation.

Anatomy and reflex pathway

The trigeminal nerve is divided into three branches: ophthalmic (V1), maxillary (V2), and mandibular (V3) [115]. Pain-sensing fibers that transmit nociceptive signals from the dura mater and meninges predominantly travel through V1 [116], which is central to CH-associated nociception. Activation of these C- and Aδ-fibers leads to the release of key neuropeptides, including CGRP, substance P, and neurokinin A, into the trigeminovascular system, resulting in vasodilation and neurogenic inflammation [117]. The afferent signals from these fibers converge in the trigeminocervical complex (TCC), where second-order neurons project to thalamic nuclei and cortical regions, including the insular cortex, anterior cingulate cortex, and primary somatosensory cortex, facilitating the perception of pain [117].

Collateral projections from the TCC reach the superior salivatory nucleus (SSN) in the pontine tegmentum [116]. Parasympathetic preganglionic fibers exit the SSN via the greater petrosal branch of the facial nerve and synapse in several extracranial ganglia, including the SPG, otic ganglion, and carotid ganglion [116]. Postganglionic fibers from the SPG innervate the lacrimal and nasal glands as well as meningeal blood vessels, producing typical autonomic features such as tearing, nasal discharge, and conjunctival injection. The presence of direct connections between trigeminal neurons and the SPG highlights the intimate integration of sensory and autonomic pathways in CH pathophysiology.

Neuropeptides modulation

The activation of the trigeminovascular system leads to the release of several neuropeptides and neurotransmitters from trigeminal sensory nerve endings, including CGRP, neurokinin A, substance P, NO, and PACAP [117, 118]. Simultaneously, postganglionic parasympathetic

neurons release VIP, PACAP, acetylcholine, and NO, contributing to both vascular dilation and glandular secretion [115]. Among these, CGRP has garnered significant attention for its role in CH pathophysiology [81, 82]. One study reported elevated plasma levels of both CGRP and VIP in the ipsilateral external jugular vein during spontaneous CH attacks, with levels returning to baseline following treatment with oxygen or subcutaneous sumatriptan [81]. In a cohort of 30 episodic CH patients, those in the active phase exhibited higher basal CGRP levels than those in remission, with nitroglycerine-provoked attacks causing further CGRP elevation that normalized upon remission [82]. Additionally, tear-fluid CGRP concentrations are elevated in both episodic and chronic CH during active attacks compared to controls [84].

In a randomized, double-blind, placebo-controlled crossover trial, 31 patients received 20-minute infusions of CGRP or saline on separate days [119]. Blood samples taken at multiple time points, including the onset of provoked CH-like attacks, revealed that 16 of 31 participants developed attacks (all of whom were in the active phase). Chronic CH patients had lower baseline CGRP levels than episodic CH patients in remission, and CGRP infusion increased plasma CGRP levels without affecting PACAP38 but elevated VIP levels [119]. A prospective case-control study involving 100 episodic CH patients in bout, 101 chronic CH patients, and 100 controls demonstrated that although CGRP levels are higher during bouts than remissions, both patient groups have lower CGRP levels than controls, suggesting a complex interplay among multiple signalling molecules rather than a sole dependence on CGRP [120].

Infusions of PACAP38 or VIP can trigger CH-like attacks without altering plasma CGRP or tryptase, and histamine (surrogate markers of mast cell activation), indicating that additional neuropeptides contribute to attack initiation [98]. Both substance P and neurokinin A, known vasodilator peptides, contribute to neurogenic inflammation by inducing cytokine release. Their immunoreactivity fluctuates during spontaneous and histamine-triggered attacks, and they are co-released with CGRP upon trigeminal ganglion stimulation [121–124]. Elevated levels of NO, a critical signalling molecule, have been observed in plasma and cerebrospinal fluid during both active and remission phases, underscoring its dual role in neurotransmission and vascular regulation [108, 125]. Neuropeptide Y, although synthesized primarily in sympathetic neurons, is also present in parasympathetic ganglia and inhibits trigeminocervical complex neuronal firing via the Y_1 receptor, promoting vasoconstriction [126]. Acetylcholine, the principal parasympathetic neurotransmitter, is co-released with VIP and PACAP from SPG fibers innervating the meninges, which can induce mast cell degranulation and the release of pro-inflammatory mediators, further stimulating trigeminal nociceptive pathways [127]. Together, these observations highlight the complex, finely balanced neuropeptide network that contributes to CH pathophysiology, with no single agent acting in isolation.

The role of the hypothalamus in trigeminal autonomic reflex

Peripheral activation of the afferent and efferent arcs of the trigeminal autonomic reflex alone is insufficient to induce CH attacks [128, 129]. For example, levcromakalim, an ATP-sensitive potassium channel opener, can provoke CH attacks in episodic CH patients during the active phase and chronic CH patients, but not in episodic CH patients during remission [111]. Furthermore, CAS do not precede headache onset, suggesting that levcromakalim simultaneously triggers both autonomic symptoms and headache [111]. Similarly, in a double-blind crossover study, infusions of PACAP38 and VIP triggered cluster-like attacks in episodic CH patients in the active phase and chronic CH patients but not in episodic patients in remission [97]. These findings suggest that peripheral substances can only provoke CH-like attacks when the underlying "permissive" state is present, and the hypothalamus has been proposed as a critical modulator of this state [85].

Functional MRI studies have shown increased activation of the anterior hypothalamus during painful mechanical trigeminal stimulation, which triggers the trigeminal autonomic reflex [130]. Preclinical studies further reveal bidirectional connections between hypothalamic and trigeminal nuclei, with several hypothalamic nuclei regions responding to nociceptive dural stimulation [131, 132]. These data support the modulatory role of the hypothalamus in trigeminal nociceptive processing and implicate it as a critical hub in the trigeminal autonomic reflex pathway.

Clinical implications

SPG stimulation has been linked to CH attack remission in clinical studies [133]. In a double-blind randomized controlled trial, CH patients underwent high-frequency (HF) or low-frequency (LF) SPG stimulation for 3 min on two separate days, with 6 patients completing the study [134]. Three patients experienced CH-like attacks during or within 30 min of stimulation, all of which were subsequently treated with HF SPG stimulation. One patient reported a CH-like attack following LF stimulation, which was also resolved with HF SPG stimulation [134]. A separate double-blind, sham-controlled crossover trial randomized 20 CH patients to either 30 min of LF SPG stimulation or sham stimulation on two separate days [129]. Although LF SPG stimulation induced autonomic symptoms, it did not provoke CH attacks, suggesting that

parasympathetic outflow alone is insufficient to trigger an attack [129]. These results underline that activation of the trigeminal autonomic reflex alone does not directly initiate CH attacks, but modulation of its function may offer therapeutic potential. However, modulating the trigeminal autonomic reflex and altering its function to some extent could be a practical approach in treating CH. Hypothalamic, SPG, and vagal nerve stimulation modulate the trigeminal autonomic reflex [135–137]. High-frequency SPG stimulation, in particular, depolarizes ganglionic neurons and inhibits parasympathetic outflow to the eye and nasal mucosa, with approximately two-thirds of CH patients experiencing significant pain relief in clinical trials [138]. Proposed mechanisms by which SPG stimulation exerts its effects include: (1) interrupting the parasympathetic postganglionic outflow and thereby inhibiting the trigeminal nociceptor activation, (2) modulating sensory processing within TNC, and (3) modulating hypothalamic activity, since the SPG receives parasympathetic fibers from the SSN, and SSN receives input from the hypothalamus [139].

Conclusion and future directions

The trigeminal autonomic reflex is a crucial neural mechanism underlying the pathophysiology of CH, involving intricate interactions between nociceptive and parasympathetic systems. Peripheral activation of the trigeminovascular system initiates parasympathetic outflow, which manifests as the characteristic autonomic features of CH, while central hypothalamic mechanisms regulate the reflex's susceptibility to attack. This understanding has revealed multiple therapeutic targets, ranging from peripheral neuropeptides to central modulators. Future research should focus on elucidating how hypothalamic control intersects with peripheral signalling and explores combined therapeutic strategies that simultaneously disrupt both arms of the reflex arc.

Hypothalamic mechanisms in CH

The hypothalamus belongs to the limbic system and is a small yet highly complex and functionally diverse brain region that is highly interconnected with other parts of the central nervous system and maintains direct connections with the vasculature. Serving as a critical brain-hormonal interface, it regulates and modulates a wide array of physiological systems, many of which may be dysregulated in the pathophysiology of primary headache disorders. These include amongst others body temperature regulation, sleep, food and water intake, autonomic nervous system control, circadian and circannual rhythms, and pain-modulating systems [140, 141]. It is noteworthy that the 24-hour biological clock is primarily regulated by the suprachiasmatic nucleus (SCN) in the anterior hypothalamus. CH is known to follow strict circadian rhythm in over 70% of patients, suggesting a possible involvement of this area in the generation of cluster attacks [142].

Several clinical features of CH, including cranial autonomic dysfunction and the characteristic temporal pattern of the disease, strongly implicate the hypothalamus as a key structure involved in both prodromal manifestations and the initiation of headache attacks [141]. This hypothesis is further supported by anatomical connections between the hypothalamus and both the trigeminovascular and parasympathetic nervous systems, both of which have been implicated in CH pathophysiology [9]. Moreover, numerous neuroimaging studies have identified the hypothalamus as a key player in CH pathogenesis, particularly with regard to attack generation and disease chronification, which will be discussed in the subsequent paragraphs.

May and colleagues demonstrated increased regional cerebral blood flow in the posterior hypothalamic grey matter ipsilateral to the attack side during nitroglycerin-induced CH-like attacks, as observed using positron emission tomography (PET) [143]. A similar finding has been reported in spontaneous CH attacks [144]. It needs to be pointed out that this finding, along with the below mentioned findings linking the cluster headaches with hypothalamic activation, are not in the hypothalamus proper but in the posterior inferior border between the hypothalamus and the tegmentum (Fig. 1). This finding has been replicated using arterial spin labeling functional magnetic resonance imaging (fMRI), which demonstrated that CH patients exhibit increased blood flow of the posterior hypothalamus during attacks when compared to either the (in-bout) interictal period or to healthy controls [145]. Furthermore, in a state dependent (in-bout ictal vs. interictal) resting-state fMRI study, Morelli and colleagues found posterior hypothalamic activation ipsilateral to the headache [146]. Another study utilizing PET and an opioidergic radioligand demonstrates an inverse relationship between the duration of CH and opioid receptor binding in the ipsilateral hypothalamus, suggesting that descending opioidergic mechanisms within the hypothalamus may contribute to the maintenance of cluster attacks [147].

In addition to the role of the hypothalamus in attack generation, other studies sought to examine the long-term structural changes of the hypothalamus in CH. A pivotal study combining functional and structural data found a co-localization of functional activity in the individual attack and an increase in grey matter of the same area [148]. Voxel-based morphometric studies comparing the in-bout and out-of-bout phases in patients with episodic CH [149, 150], as well as the comparison between CH patients and healthy controls [151], found no significant changes in hypothalamic volume. However, in a larger study utilizing the same algorithm for

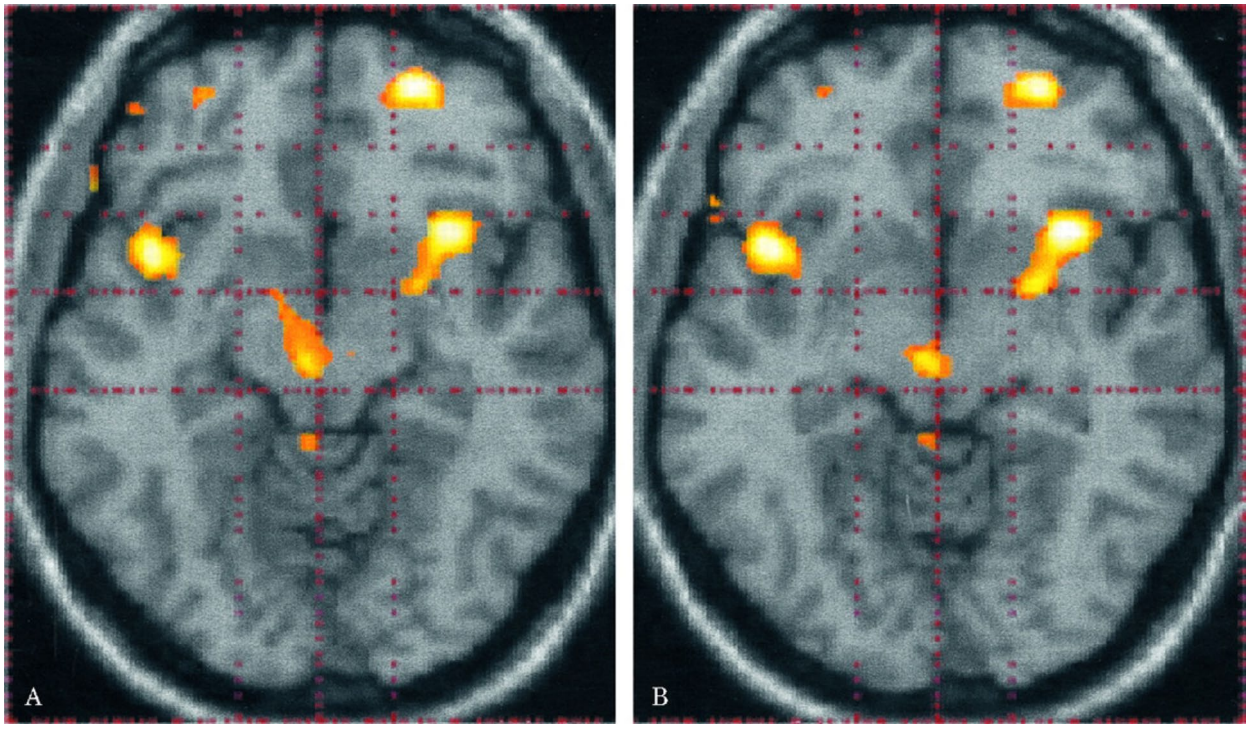

Fig. 1 Posterior hypothalamic activation ipsilateral to the side of headache during an attack in comparison to the headache-free state as demonstrated through the use of a positron emission tomography scan. It is noteworthy that functional imaging studies have repeatedly demonstrated activation in the posterior hypothalamic gray matter at the level of the junction with the midbrain. This activation (of this part of the hypothalamus) is not observed in cases of migraine or other forms of experimental headache. The Journal of Headache and Pain needs to secure permission to reproduce the figure originally published in Neurology (https://doi.org/10.1212/WNL.52.7.1522)

automatic segmentation of hypothalamic subunits, Ferraro and colleagues identified an increased volume in the ipsilateral paraventricular nucleus and preoptic area of the hypothalamus in patients with chronic CH compared to those with episodic CH [152]. Their findings are consistent with those reported in the study by May and colleagues [148] and those of Arkink and colleagues, who also reported an increased anterior hypothalamic volume ipsilateral to the headache side in chronic CH patients compared to healthy controls [153]. Additionally, bilateral hypothalamic volumes were found to be larger in CH patients compared to both healthy controls and migraine patients, suggesting distinct structural alterations specific to CH disorder [153]. Furthermore, a diffusion tensor imaging study revealed that CH patients exhibited lower fractional anisotropy and higher mean diffusivity metrics in the hypothalamus relative to healthy subjects [154]. Magnetic resonance spectroscopy studies in both episodic (in- and out-of-bout) and chronic CH patients demonstrated a reduction in N-acetyl aspartate levels and a decreased choline/creatine metabolite ratio in the hypothalamus compared to healthy controls [155, 156].

Several studies have identified aberrant resting-state functional connectivity in patients with episodic CH, both during and between attacks, particularly between the hypothalamus and key regions of the pain-processing network, such as the prefrontal cortex, anterior cingulate cortex, contralateral thalamus, ipsilateral basal ganglia, insular cortex, inferior parietal lobule, parahippocampal gyrus, and bilateral cerebellar hemispheres [43, 146, 157–161]. Moreover, a study examining in-bout interictal episodic CH patients demonstrated reduced functional connectivity between the hypothalamus and the salience network compared to healthy controls [160]. In contrast to the functional and structural studies, findings in hypothesis-free resting-state imaging have, however, not yet been reproduced.

In chronic CH patients, functional connectivity alterations have been observed in the posterior hypothalamus, as well as in diencephalic-mesencephalic regions ipsilateral to the headache side [162]. In addition to the resting-state fMRI, a task-specific fMRI study investigated how the hypothalamus responds to trigeminonociceptive stimuli and found that the posterior hypothalamus in episodic CH has higher activation out of bout, but decreased activation in bout [46]. This finding contrasts the previous prevailing hypothesis based on PET studies that during a CH bout, the posterior hypothalamus becomes hyperactive. Instead, it shows that the CH patients have a hyperactive hypothalamus at baseline, and that activation is counterintuitively reduced in the in-bout state, possibly due to neurotransmitters depletion caused by

frequency attacks [46]. The results of task-specific fMRI and PET [46, 143] should not be considered as contradictory, as both methods have different temporal resolution and may suggest a disproportionate blood flow vs. oxygen metabolism change [163]. Nevertheless, both approaches documented functional changes in the hypothalamus during the cluster bouts.

Evidence of the hypothalamic involvement in the generation of attacks led to the introduction of deep brain stimulation of the posterior hypothalamic grey matter as a treatment option for patients with intractable CH, particularly those with chronic forms of the disorder without remission periods, where disability is extremely high and alternative treatment options have been exhausted [164]. This invasive treatment showed a significant long-term effect in about 50–82% of CH patients [165–167]. The mechanism by which hypothalamic stimulation aborts or even prevents CH attacks remains incompletely understood. Psychophysical measurements in patients with hypothalamic stimulation showed a trigeminal dermatome-specific pain modulatory effect [168], reflecting the close anatomical connection between the hypothalamus and the spinal trigeminal nucleus [169]. Nevertheless, May and colleagues used PET to study the acute effects of hypothalamic stimulation and found that stimulation of the posterior hypothalamic area induced bidirectional (both excitatory and inhibitory) modulatory effects in brain regions known to be involved in pain processing [170]. These findings argue against a nonspecific antinociceptive effect or simple inhibition of hypothalamic activity. Instead, they suggest that hypothalamic deep brain stimulation exerts its effects through complex functional modulation of the pain-processing network, underscoring its role as a therapeutic target in cluster headache [170]. Finally, although the cluster attacks are most likely generated in the hypothalamus, the participation of the peripheral nociceptor is indispensable for the headache. This is evidenced by the neurostimulatory treatment options, such as sphenopalatine ganglion stimulation, which have been shown to prevent clinical cluster headache without a known mechanism of modulating the hypothalamus [171].

Central mechanisms other than hypothalamus

Despite the established role of the hypothalamus in the circadian rhythmicity and circannual rhythmicity of CH attacks [172, 173], growing evidence indicates that other brain structures and network-level alterations may also contribute to the underlying pathophysiological mechanisms [174].

The brainstem structures are considered to play a pivotal role in CH pathophysiology [175, 176], particularly through descending pain modulation and autonomic regulation pathways [177]. The periaqueductal gray, the locus coeruleus, and the dorsal raphe nuclei are key components of these circuits and are known to modulate the nociceptive trigeminal inputs, possibly contributing to CH attacks [174, 178]. Interestingly, a recent study demonstrated that the most discriminative MRI patterns for distinguishing migraine and CH patients from healthy controls comprised the functional connectivity of the periaqueductal gray and the hypothalamus [179]. Notably, a study conducted on a small sample of healthy individuals showed a limited circadian modulation of the functional connectivity of brainstem nuclei involved in pain processing, and no fluctuations in pain threshold [180]. While preliminary and limited by the small sample size, this evidence opens interesting questions regarding the extent to which brainstem nuclei contribute to the circadian modulation of pain processing in CH.

Recently, the ventral tegmental area (VTA)—a midbrain structure and central hub of the dopaminergic mesocorticolimbic system—has emerged, along with the broader mesocorticolimbic network traditionally associated with reward and motivation processes (including also the prefrontal cortex, nucleus accumbens, hippocampus, and amygdala), as a crucial component in the pathophysiology of CH. Multiple lines of evidence—including findings from several neuropsychiatric and chronic pain conditions, the effectiveness of VTA deep brain stimulation (DBS) in chronic CH, and CH-specific neuroimaging results—converge to support the involvement of this dopaminergic circuit in the disorder.

Abnormalities within the mesocorticolimbic system are thought to contribute to pain chronification [181] and have been identified as a transdiagnostic marker across various neuropsychiatric disorders [182], which are frequently comorbid with CH [183]. Although not constituting direct evidence, these associations point toward a possible involvement of this network in the disorder. More direct and robust evidence comes from studies on VTA-DBS, which has demonstrated greater efficacy than posterior hypothalamic stimulation—the first region historically targeted in DBS interventions for CH [184]—in reducing both the frequency and the intensity of attacks in severe chronic cases [185].

Moreover, providing more direct evidence of the involvement of the mesocorticolimbic circuit, a series of functional neuroimaging studies in patients with chronic and episodic CH have progressively highlighted altered functional connectivity within this network.

In particular, resting-state functional connectivity abnormalities have been observed in chronic CH between the posterior hypothalamus and diencephalic regions, including VTA [186], supporting the hypothesis of an integrated dysregulation between homeostatic and motivational networks in the pathophysiology of the disorder. Along the same line, reduced resting-state

functional connectivity between the prefrontal cortex and amygdala and structural alterations in diencephalic areas (encompassing the VTA, nucleus accumbens, hippocampus, and prefrontal cortex) have been observed [187]. Notably, these mesocorticolimbic regions exhibited an unexpected volume increase, unlike the volume reductions typically reported in chronic pain conditions [188, 189], suggesting CH-specific features in the chronic form. A recent study used the Monetary Incentive Delay (MID) fMRI task [190] to robustly trigger the activity of the mesocorticolimbic system across CH patients showing middle prefrontal cortex dysfunction in both chronic and episodic CH, but VTA alterations only in the chronic group, supporting a possible role of this region in pain chronification. Notably these alterations were unrelated to mood disturbances, nicotine use and CH phase (in-bout and out-of-bout). Another recent study [191] conducted on a large sample of episodic CH patients provided further evidence showing anatomical and functional alterations within the mesocorticolimbic system, in patients studied during the bout period but outside of attacks. Specifically, structural changes were observed in subregions of the amygdala and hippocampus, accompanied by widespread functional alterations involving the hypothalamus and thalamus as well. Although the precise functional significance of these results remains to be fully understood, overall, all these findings point to a general mesocorticolimbic imbalance as a core feature of CH pathophysiology.

Another network thought to contribute to CH is the salience network. This important functional circuit mainly comprises the dorsal anterior cingulate cortex, anterior insula, and frontal operculum and is involved in attentional, affective, and autonomic modulation and coordination. Functional connectivity changes in salience network, even during headache remission [192] suggested that this network may be persistently affected in CH patients, possibly contributing to their susceptibility to pain and autonomic dysregulation.

Importantly, several studies have highlighted a disrupted interplay between the salience network and other brain networks and regions in patients with episodic CH. Specifically, reduced functional connectivity between the salience network and the left executive control network has been observed, suggesting potential difficulties in switching between internally and externally oriented cognitive states during in-bout period [193]. Moreover, altered interactions between the salience network and the hypothalamus [159], as well as between the salience network and the thalamus in the in-bout phase [194], were observed further supporting the role of salience circuit dysregulation in the pathophysiology of CH.

The thalamus is another key brain structure significantly involved in CH pathophysiology due to its role—among many others—in the processing and integration of nociceptive stimuli. Evidence suggests that the thalamus contributes to headache sensitization, through mechanisms similar to those observed in migraine patients, where thalamic activity correlates with hyperalgesia and allodynia [195]. Direct evidence for the involvement of the thalamus in CH was provided by the observation of altered fractional anisotropy of this structure [193], as well as by findings showing that CH patients can be distinguished from migraine patients based on decreased functional connectivity between the left thalamus and parietal regions—including the precuneus and angular gyrus—which are part of the default mode network (DMN).

Although further studies are needed to clarify the involvement of DMN in CH pathophysiology, increased functional connectivity between this network and the executive control network was recently observed in patients with CH [193]. The DMN, known for its role in self-referential thought processes and typically antagonistic to networks such as the salience network during pain processing [196], may underlie some of the cognitive-affective alterations associated with CH.

Importantly, recent functional imaging studies have revealed the existence of a complex network of interconnected regions within the cerebellum, including the prefrontal and insula cortices, as well as the amygdala. These regions have been shown to be involved in the processing of pain and emotional responses, suggesting a potential influence on the clinical symptoms of CH. The precise mechanisms by which these regions may modulate pain perception, emotional responses, and behavioural performance remain to be fully elucidated. Furthermore, structural imaging studies have demonstrated that patients suffering from chronic CH exhibit a reduced thickness in the anterior lobe of the cerebellum when compared to healthy individuals [197], thereby further substantiating the notion that the cerebellum plays a pivotal role in CH pathophysiology.

The pituitary gland may also be implicated in a subset of patients. The presence of functional abnormalities or microadenomas has been demonstrated to exacerbate symptoms, particularly in the presence of hormonal imbalances such as hyperprolactinemia [198].

Altogether, the evidence reviewed highlights that CH is not the result of a localized brain dysfunction but rather reflects widespread disturbances involving both subcortical structures—such as the brainstem, thalamus, and hypothalamus—and large-scale network dysfunctions, particularly within the mesocorticolimbic, salience, and the default mode networks. Although this supports the conceptualisation of CH as a multisystem disorder, a comprehensive understanding of the functional meaning

and temporal dynamics of these alterations remains elusive.

The lack of a robust unifying interpretative framework underscores the need for longitudinal studies across the different phases of the disorder in large sample of CH patients, aimed at disentangling the role of brain networks reorganization in the pathophysiology of CH and their relationship with the clinical and neuropsychiatric data.

Electrophysiological aspects of CH

Three core features of cluster headache—excruciating pain, autonomic disturbances, and a tendency to occur during sleep—have been investigated through various electrophysiological approaches. These studies have provided objective insights into the pathophysiological processes underlying the clinical presentation of the disorder.

Among these features, pain processing has been the most extensively studied, using a range of electrophysiological techniques including the nociceptive blink reflex (nBR), laser-evoked potentials (LEPs), trigeminal evoked responses, and pain-related evoked potentials (PREPs) (Table 1). These methods have revealed alterations in sensory and pain processing involving both trigeminal and extra-trigeminal regions in CH [199]. Although these alterations can be bilateral, most are more pronounced on the symptomatic side and during the active phase [200, 201]. Indeed, two studies documented lateralized habituation deficit of the nBR in the active phase of episodic CH [202, 203], reflecting an impairment of sensory filtering that could share some similarity with migraine [204]. Contrasting results were reported by Holle et al., who found no differences in nBR habituation between healthy controls and patients with CH, irrespective of disease subtype or activity stage. However, it is important to note that recordings were performed while patients were receiving acute and prophylactic medications, which may partly explain the discrepancies with earlier studies [205]. By recording the nBR and the PREP and comparing the headache and non-headache sides, the same authors showed asymmetry of trigeminal nociceptive processing and central facilitation primarily at the brainstem level [200]. Interestingly, some of these alterations can persist during remission and vary in magnitude depending on the disease phase and chronicity. This evidence suggested a role for the supraspinal central mechanisms in facilitating the alterations of trigeminal nociceptive processing and favouring the transition to the chronic state [200]. Complementing this, Ellrich et al. [206] reported bilateral alterations in LEPs, suggesting broader central involvement beyond the side of attack. Indeed, though CH is strictly unilateral in presentation, there is some evidence of broader functional involvement in pain processing. Lozza et al. [207] used both cranial and extracephalic stimulation (index finger) to assess inhibition of the blink reflex and found that inhibitory deficits were present across both regions, suggesting that brainstem disinhibition is not confined to trigeminal circuits. Although Perrotta et al. [208] did not stimulate extracephalic sites directly, they identified trait- and frequency-dependent habituation deficits to trigeminal stimulation, implying dysfunction in more widespread central regulatory systems. Consistent with these findings, evidence from interventional studies further substantiates the interpretation of supraspinal dysfunction in pain modulation. Busch et al. [209] examined the effect of greater occipital nerve blockade on the nBR in chronic CH patients. They observed a reduction in R2 reflex area and increased latency on the injection side only, indicating localized modulation of trigeminal processing. However, this was not accompanied by significant clinical improvement, suggesting that while the reflex arc was physiologically affected, it May not play a direct role in mediating pain relief. These results were not replicated in a more recent study in a group of 33 patients with episodic and chronic CH, where the nBR was recorded before and 30 min, 1 week, and 4 weeks after GON block [210]. Similarly, Haane et al. [211] found that although effective in aborting attacks, high-flow oxygen therapy did not alter nBR parameters, highlighting some degree of independence between clinical efficacy and immediate brainstem reflex modulation. In contrast, Jürgens et al. [168] reported that DBS of the posterior hypothalamus led to bilateral increases in thermal detection thresholds, pointing to a more diffuse supraspinal modulation of pain-related sensory systems. While not a direct nociceptive reflex study, this intervention illustrates how central pain control structures interact with sensory perception in a state-dependent and bilateral manner. Collectively, this evidence supports asymmetric brainstem dysfunction along with a generalized disruption of central pain modulation at the supraspinal level in CH.

CAS are hallmark features of cluster headache, and objective electrophysiological studies have investigated both central and peripheral autonomic function. Using dynamic pupillometry, Micieli et al. [212] found altered pupillary dynamics during active periods, including abnormal constriction and dilation velocities, consistent with autonomic imbalance. In a subsequent study, the same authors [213] showed reduced amplitude and delayed latency of the trigemino-pupillary reflex, indicating compromised sympathetic responses. Another study that compared face and extremity sympathetic skin responses revealed face sympathetic hypoactivity on the symptomatic side, failing to show any differences in the extremity skin responses [214]. Further evidence in favour of autonomic system dysfunction comes

Table 1 List of neurophysiological studies that investigated the pain processing in subjects with cluster headache. Abbreviations: auc = area under the curve; br = Blink reflex; ch = cluster headache; cCH = chronic cluster headache; dbsh = unilateral deep brain stimulation of the posterior hypothalamus; eCH = episodic cluster headache; ePH = episodic paroxysmal hemicrania; gon = greater occipital nerve; hc = healthy controls; i.v.= intravenously; moa = migraine without aura; n = number; nBR = nociceptive Blink reflex; LEP = laser-evoked potential; PREP = pain-related evoked potentials; tsep = trigeminal somatosensory evoked potentials

Publication year and Authors	Sample size (*n*)	Phase (in-bout/out-of-the-bout)	Methods	Main findings
1997, Lozza et al. [212]	-eCH, *n* = 10 -HC, *n* = 10	In-bout	BR after conditioning by supraorbital or index finger stimuli	-CH: • No changes of R2 threshold, latency or area -After paired supraorbital stimuli: • More rapid R2 recovering in eCH patients on the symptomatic side -After index stimulations: • More rapid R2 recovery on both symptomatic and non-symptomatic sides in eCH compared to HC. Partial reversion of the R2 suppression induced by index finger stimuli in 2 eCH subjects after Naloxone i.v. administration
2003, Van Vliet et al. [206]	-eCH, *n* = 28 -HC, *n* = 22	-In-bout, *n* = 28 -Out-of-bout, *n* = 22	TSEP and BR repeated measurement in two time point (in-and out-of-bout)	-eCH in-bout: • Increased N2 TSEP latencies on the symptomatic side in comparison to the non-symptomatic side and with the same side out-of-bout • Increased N1, P1 and N2 latencies on the symptomatic side in comparison to HC -eCH out-of-bout: • Increased N1 latencies of both sides in comparison to HC • No differences of TSEP amplitudes and BR latencies in comparison to HC
2007, Ellrich et al. [211]	-CH, *n* = 25 (16 eCH, 9 cCH) -HC, *n* = 10	-In-bout, *n* = 7 -Out-of-bout, *n* = 10	LEP	-cCH: • Reduced P2 amplitude and delayed N1c in comparison to HC -eCH in-bout: • Reduced P2 latency on the headache side -eCH out-of-bout: • reduced N2P2 ratio on the headache side -CH: • in 19/26 examinations LEP deviated from normative data in HC without any specific pattern of altered parameters
2007, Busch et al. [214]	-cCH, *n* = 15	cCH	nBR before and after unilateral GON block	-cCH: • Decrease of the R2 response areas and increase of R2 latencies after the GON block only on the injection side
2008, Perrotta et al. [208]	-eCH, *n* = 27 -MoA, *n* = 22 -HC, *n* = 20	In-bout	nBR elicited on the symptomatic side	-eCH: • Deficit of habituation in the R2 and R3 components compared with HC and MoA -eCH: • More pronounced lack of habituation in comparison to MoA
2009, Jürgens et al. [217]	-CH, *n* = 26 (11 cCH with DBSh; 15 cCH without DBSh) -HC, *n* = 29	cCH	Perception and pain thresholds for hot and cold stimuli	-cCH with DBSh: • Increased cold pain thresholds at the first trigeminal branch on the stimulated side in comparison to HC, and higher cold detection thresholds in comparison to cCH without DBSh -cCH with DBSh: • No changes after short-term interruption of stimulation

Table 1 (continued)

Publication year and Authors	Sample size (*n*)	Phase (in-bout/out-of-the-bout)	Methods	Main findings
2012, Holle et al. [210]	-CH, *n* = 66 (46 eCH, 20 cCH) -HC, *n* = 30	-In-bout, *n* = 18 -Out-of-the-bout, *n* = 28	nBR	-CH (independently from the subtypes and the phase): • No differences in habituation in comparison to HC • No side-to-side differences of habituation between headache side and non-headache side
2012, Holle et al. [205]	-CH, *n* = 66 (46 eCH, 20 cCH) -HC, *n* = 20	-In-bout, *n* = 18 -Out-of-the-bout, *n* = 28	nBR and PREP	-CH (independently from the subtype): • Decrease in nBR latency ratio (headache side/non-headache side) in comparison to HC -eCH: • Increase in AUC ratio in patients with episodic CH in-bout only -cCH: • Decrease N2 latency ratio of PREP
2015, Coppola et al. [207]	-eCH, *n* = 18 -HC, *n* = 18	In-bout	nBR	-eCH: • Decrease in reflex area on both sides in comparison with HC • Deficit of habituation only on the affected side • Positive correlation between the habituation slope and the number of days since the onset of the bout and the daily attack frequency
2016, Haane et al. [216]	-CH, *n* = 10 (3 eCH, 5 cCH)	In-bout	nBR after high-flow-oxygen	-CH: • No effects of oxygen, immediately and over time, on the nBR • No differences between the symptomatic and asymptomatic side
2018, Perrotta et al. [213]	-eCH, *n* = 28 -ePH in-bout, *n* = 18 -HC, *n* = 21	-In- bout, *n* = 16 -Out-of-bout, *n* = 12	nBR	-eCH (both in-and out-of-the-bout) and ePH: • Lower mean percentage decrease of the R2 area across all blocks at 0.2 to 1 Hz stimulation frequency in comparison to HC • Frequency-dependent habituation deficit of trigeminal nociceptive responses at higher SFs
2025, Naber et al. [215]	-CH, *n* = 33 (eCH, *n* = 17; cCH *n* = 16)	In-bout	nBR 30 min before and 30 min, 1 week, and 4 weeks after GON block	-CH: • No increased R2 latencies after GON infiltration were observed • No correlation between R2 latencies and clinical response were observed

from Tassorelli et al. [215], who used the cold pressor test to elicit simultaneous pupillary and cardiovascular responses. They showed that CH patients exhibited blunted autonomic reactivity, again pointing to dysfunction in central autonomic control mechanisms. Evers et al. [216] evaluated peripheral autonomic potentials and found reduced and delayed responses, reflecting altered function in peripheral autonomic reflex arcs. These instrumental findings reveal measurable dysregulation of the autonomic system in CH, affecting both central integration and peripheral execution of autonomic responses. These abnormalities correspond with the hallmark attack-related symptoms such as lacrimation, rhinorrhoea, and ptosis.

Finally, the strong circadian and sleep-related patterns of cluster headache have prompted electrophysiological studies into sleep physiology. According to Gorgoni et al. [217], who reviewed available polysomnographic data, CH patients—particularly during active phases—exhibit altered sleep architecture. This includes fragmentation, reduced sleep efficiency, and abnormal Rapid-Eye-Movement (REM) regulation. These findings suggest that instability in sleep-wake transitions, especially those involving REM sleep, may play a role in attack initiation. Although early studies lacked detailed sleep staging, findings such as those by Polich et al. [218] and Silvestri et al. [219] noted atypical cortical activity and EEG abnormalities during nocturnal attacks, hinting at state-dependent

vulnerabilities in sleep. Complementary findings from Jürgens et al. [168], where posterior hypothalamic stimulation altered both pain perception and thermal thresholds, reinforce the view that the hypothalamus is a critical node linking sleep regulation, circadian rhythms, and pain modulation.

Taken together, electrophysiological studies in CH consistently reveal central and lateralized dysfunctions in pain processing, widespread abnormalities in autonomic control, and disrupted sleep physiology, all of which have been captured using reliable neurophysiological techniques. Collectively, these findings not only reflect the complexity of CH but also underscore its distinct neurophysiological fingerprint—one that bridges pain, autonomic function, and chronobiology.

The chronobiology of CH

In its essential form the strictly unilateral CH attacks strike at night, typically after 1–2 h of sleep, every night for 1 to 2 months only to wane off after weeks or months. Unsurprisingly, the severity of the attacks and this curious timewise manifestation has prompted considerable scientific interest into the sleep and chronobiology of CH (Fig. 2).

Sleep

CH attacks tend to occur at fixed, predictable times often during sleep. This awakens patients with CH and thereby severely disturbs their night-rest. In clinical anecdotes, patients with CH may often deprive themselves of sleep to prevent attacks and may be afraid to take naps during the day because attacks may strike [220]. A frequently conveyed clinical request is to please help someone with CH to sleep again [221].

Approximately 80% of patients with CH report attacks during sleep and 30% report attacks during daytime naps [222]. Clinically, attacks that start while awake and during sleep are similar. Attacks typically occur 90 min after sleep onset, suggesting a relationship with REM-sleep [223]. However, combining the fragmented descriptions of several studies, 30% of attacks occurred during REM-sleep, and 70% during non-REM-sleep [223–229]. Sleep quality is very low, severely impacting quality of life, both inside and outside clusters [221]. Longer sleep latency has been found during attack episodes and the frequency and duration of REM-sleep was also reduced in CH patients. Obstructive sleep apnea has been found in 20–90% of patients with CH but whether this is a coincidence or causal remains uncertain [230]. Sleep

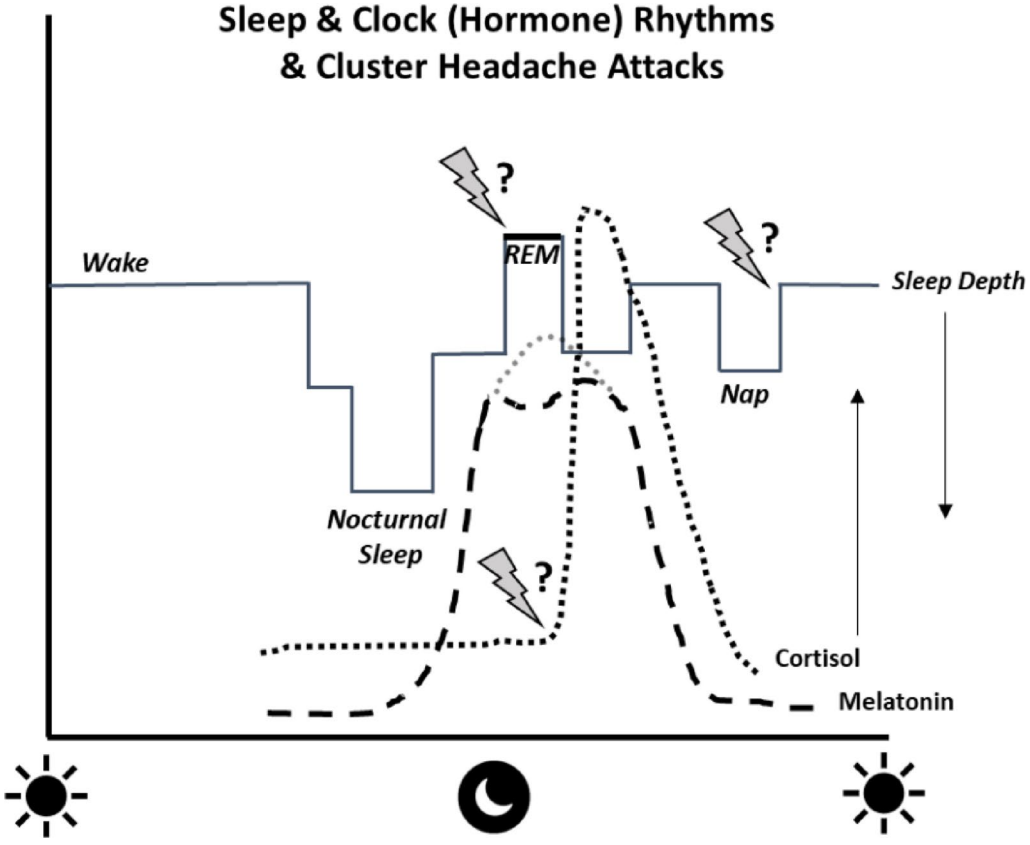

Fig. 2 Hypnogram overlaid with attack pattern and hypothetical implicated hormone fluctuations. Attacks might be related to sleep stage transitions during the night or daytime naps, or to relatively low melatonin and/or cortisol levels

apnea events have been hypothesized to be related to CH attacks and in uncontrolled studies their treatment was reported to have a beneficial effect on CH attacks [231]. If true, this would warrant screening and aggressive treatment of sleep apnea in CH. Controlled trials looking into this showed increased prevalence of sleep apnea in CH, especially in the active cluster periods [223, 232, 233].

Despite the high prevalence of poor sleep quality in CH patients, improvement of sleep quality is generally neglected in CH treatment or has only attracted minimal attention. Poor sleep quality may aggravate pain attacks by chronic sleep deprivation induced by nocturnal pain attacks leading to a vicious cycle. Only a few, mostly unsuccessful, attempts have been tried to influence nocturnal pain attacks in patients via changes of sleep structure or sleep quality. Sodium oxybate is a naturally occurring neurotransmitter and a GABA-B receptor agonist used in the treatment of narcolepsy. In contrast to benzodiazepines, sodium oxybate will deepen sleep (increased slow-wave sleep) [234]. In an open label case series 4 patients with refractory chronic CH and disturbed sleep were treated with sodium oxybate. This was effective in all 4 patients as shown by an immediate reduction in pain frequency (up to 90%) and pain intensity (> 50%) of nocturnal pain attacks and improved sleep quality [235, 236]. These findings emphasize the need for randomized, controlled trials aimed at improving sleep in CH.

Chronobiology

Among diseases and disorders, CH is amongst those with the strongest chronobiological features. This applies to both daily attacks and clusters of attacks.

Concerning circadian rhythmicity, with some variation across the studied populations, 60–80% of sufferers report predictability in the occurrence of their attacks [35]. Attack risk is highest early in the night, peaking around 2 a.m. (perhaps coinciding with REM-sleep or end of the first sleep cycle), which has been a very robust finding over many years of CH research. Apart from circadian rhythmicity, half of patients report circannual rhythmicity [222]. Over the course of the seasons, the month of October carries with it increased risk of clusters or worsening of the chronic condition [35, 222]. Some studies have found that the disorder may be influenced by daylight, latitude or cultural factors such as daytime napping or others [222, 237].

Despite this short- and long-term predictability, it is evident that CH is also a dynamic condition. For example, there are indications that over time the chronobiological distinctiveness may fade [238]. Additionally, from a diagnostic point of view, the chronic condition may become episodic and vice versa and independently of this the rhythmicity may change [239]. Complexity is high as there may be patterns which manifest outside of a yearly pattern [240, 241]. This may also be the case for daily (infradian, > 24 h) patterns.

Along these lines, in episodic patients, rhythmicity seems strongly circadian (24 h) and in chronic more ultradian (< 24 h) [242]. Remarkable differences in subgroups of patients outside the episodic-chronic spectrum have also been found. For example, circadian rhythmicity may be more frequent in women compared to men [31] and also phase shifted [30]. Further, patients with familial CH (i.e. those who have family members with CH) have a highly pronounced increased nocturnal risk of suffering attacks (2 a.m.) [239], a finding which implicates intrinsic 24-hours oscillators, for example the suprachiasmatic nucleus.

Looking towards medications known to influence biological chronorhythms, older reports of differential responses to melatonin, verapamil and lithium between subgroups of CH may support involvement of mechanisms controlling homeostasis and sleep [243, 244]. Melatonin levels have been found to be reduced in CH which has led to several efforts to study the prophylactic effects of administration of the sleep hormone [243]. However, the only relevant trial dates from 1996 and was performed in 20 cases, of whom half had a significant reduction in headache frequency. Two subsequent case-series yielded contrasting results. A median dose of 10 mg melatonin May be effective in around 30% of cases [245]. So, melatonin is often mentioned as a therapeutic option for CH, but the evidence is limited. No randomised, adequately powered trial has been performed.

Conclusion

The association between CH and sleep and chronobiology is quite distinct but essentially remains a pathophysiological curiosity as the gap towards clinical applications of this knowledge have not been bridged yet. Still, anything that can be done to improve the dreadful disorder, including diagnosis and treatment of possible co-occurring sleep disorders, such as sleep apnea, should be undertaken [246]. Studies investigating timing of treatment are very few and do not yet provide solid direction yet. Patients should be encouraged to keep a headache and sleep diary to identify possible aggravating factors. From a scientific perspective, the predictable timing of attacks and the relation with sleep point to a pivotal role of the hypothalamus, especially the lateral hypothalamus (sleep-wake balance) and the suprachiasmatic nucleus (biological clock).

Personality traits of patients with CH

Increasing attention is being paid to the potential role of psychopathological factors, including personality traits, in determining both the expression and progression of

CH. This shift reflects the principles of the biopsychosocial model of health, which posits that disease arises from the complex, multidirectional interactions among biological, psychological, and social factors [247]. In this context, examining personality traits [248] in CH may offer valuable insights into behavioural tendencies and lifestyle patterns commonly observed in this population. Certain traits could influence pain perception, treatment adherence, and overall outcomes. Moreover, identifying personality profiles might support the development of more tailored interventions, particularly in chronic sufferers. In this section, we review the current literature on personality features and related psychopathological aspects in CH.

Emotional and personality dimensions in CH

Although depression is one of the most common psychiatric comorbidities in CH [249], recent studies have shifted attention toward more stable personality features that may underlie or interact with emotional vulnerability in this population. CH patients have been found to score significantly higher on alexithymia [250], a personality construct defined by difficulties in identifying and expressing emotions [251]. This impaired emotional insight may contribute both to emotional vulnerability and to maladaptive coping strategies in the context of chronic pain. Further supporting this view, a Rorschach-based study [252] confirmed the presence of alexithymic tendencies in CH, highlighting features such as concrete and stereotyped thought, reduced emotional responsiveness, and limited relational adaptability, patterns commonly observed in psychosomatic profiles [251, 253].

These emotional and relational patterns have led researchers to explore whether CH might also be linked to more enduring personality configurations that go beyond episodic distress. In line with this perspective, Mongini et al. [254] investigated the impact of personality traits on pain perception in primary headache patients using the Minnesota Multiphasic Personality Inventory – Second Edition. Those patients identified as having an "emotionally overwhelmed" profile reported higher affective pain scores, regardless of headache severity. This suggests that certain personality characteristics may intensify the emotional experience of pain, possibly through mechanisms like poor affect regulation or heightened attention to bodily sensations. These traits may not simply coexist with CH but actively shape its subjective burden.

While no single personality profile appears to define CH, certain traits recur across studies. An historical work by Cuypers [255], using the Freiburg Personality Inventory, suggested elevated nervousness and diminished masculinity in CH patients compared to migraineurs. Using the Karolinska Scales of Personality, Levi et al. [256], highlighted that patients with episodic CH showed elevated levels of anxiety, reduced socialization, and greater hostility, in line with subsequent research. More recently, Piacentini [257], using the Millon Clinical Multiaxial Inventory-III, reported that over 90% of CH patients showed clinically significant personality traits, with a predominance of obsessive-compulsive, histrionic, narcissistic, and avoidant features. These same findings were recently confirmed by Telesca [258] highlighting that such personality features represented the most pervasive traits in CH. Interestingly, the authors also identified three distinct psychological profiles based on disease characteristics and personality measures. These profiles reflected marked heterogeneity within the CH population, and included, among others, a subgroup characterized by emotional dysregulation and low social engagement. This variability suggests that CH patients cannot be considered as a psychologically homogeneous group, but rather require individualized clinical attention based on their specific psychological features.

This heterogeneity was also evident in the comparative study by Munoz [259] who analysed the personality traits of 80 CH patients and 164 migraine patients using the Salamanca screening test. CH patients most frequently exhibited traits from Cluster A (odd or eccentric), while Cluster C traits (anxious or fearful) were more common among migraineurs. For instance, 53% of CH patients had anankastic (obsessive-compulsive) traits and 43% had schizoid tendencies. This pattern suggests a paranoid-schizoid position in many CH patients, which may influence their response to pain and determine inadequate copying strategies. Importantly, these findings support the idea that emotional reactivity, difficulty in emotional disclosure, and rigidity in interpersonal dynamics may be central features in the personality profile of CH sufferers.

Psychosocial functioning and behavioural patterns

One particularly interesting aspect of personality functioning in CH concerns the direction in which emotional suffering is expressed. While it has often been assumed that patients with CH might be more prone to externalized anger or irritability, the empirical evidence offers a different pattern. A multicentre controlled study [260] found no increase in overt or outward-directed aggression among CH patients. Instead, what emerged was a significant rise in self-directed aggression, especially in individuals with chronic CH. This internal hostility was closely linked to greater headache-related disability. These data suggest a reciprocal relationship between emotional suffering and disease burden, where psychological distress both reflects and potentially exacerbates the severity of the condition. These emotional dynamics may also contribute to changes in social behaviour and interpersonal functioning.

From a social point of view, many CH patients appear to experience a reduction in social support and relational integration. As noted by Blomkvist [261] they tend to have fewer close connections and lower expectations for future social involvement, suggesting a more withdrawn and self-reliant coping style. Interestingly, this is sometimes accompanied by an optimistic outlook, which may serve as a compensatory mechanism to preserve a sense of control.

This psychological profile often coexists with behavioural patterns that may further impact disease management, including unhealthy lifestyle habits and risk-prone behaviours [262]. Manzoni [263], in a sample of 374 CH patients, found high rates of these behaviours, especially among those in self-employed or high-responsibility occupations. Similarly, the Danish Cluster Headache Survey [264] confirmed elevated substance use among CH patients compared to controls, suggesting a possible propensity toward impulsivity or compulsivity.

Lambru and Matharu [265] explored the link between head trauma and CH, proposing that distinctive personality traits, such as sensation-seeking or emotional dysregulation, might increase the risk of injuries or substance abuse. Though speculative, these interpretations could be linked to earlier findings by Saper [266] and Graham [267], who described CH patients as emotionally intense, anxiety-prone, and prone to "type-A" behavioural patterns. An extensive genome wide association study in 4,777 cluster headache patients identified genetic risk variants, showing that cigarette smoking, risk-taking behaviour, attention deficit hyperactivity disorder (ADHD), depression, and musculoskeletal pain were significantly associated to CH [15]. Impulse behaviours may be associated with the underlying biological basis found in ADHD, further studies are needed to clarify this issue.

Taken together, the evidence reviewed highlights a complex and nuanced psychological profile in CH patients, where specific personality traits may interact with emotional regulation, behavioural tendencies, and social functioning. These patterns, while heterogeneous, could share common features that deserve meaningful clinical implications—particularly in terms of diagnosis, disease burden, and treatment.

Clinical implications and final considerations

Although there is no single personality profile specific to CH, several traits—such as obsessive-compulsive, histrionic, paranoid, and schizoid features—appear more frequently in this population than in other headache disorders. Patterns of emotional detachment, impulsivity, and low social engagement are also common and may contribute to increased disability and treatment complexity.

While current evidence provides valuable insights, methodological limitations—such as small samples and reliance on self-report tools—warrant caution. Future research should incorporate longitudinal designs and clinician-administered assessments to better capture the role of personality in CH. In very conclusion, what is evident is that a clearer understanding of the most recurrent psychological features in CH —particularly emotional instability, internalized hostility, and social withdrawal —could offer a useful framework for interpreting patient behaviour and guiding more personalized therapeutic approaches.

Old and new Pharmacological targets: historical aspects and mechanisms of action

Old targets

Histamine

One of the first potential drugs for CH treatment was histamine. Since the very first description by Bayard T. Horton in 1939 [268, 269], he proposed that histamine could be a diagnostic and therapeutic aid in the syndrome, to the point that it still inadequately named "histaminic cephalalgia" by some authors [268, 270, 271].

Ergotamine

Even before the recognition of "Horton syndrome" or "Histaminic cephalalgia", in 1937 Wilfred Harris reported that subcutaneous injections of ergotamine tartrate alleviated "migrainous neuralgia" headache, nowadays considered to probably be CH patients [269]. Indeed, in 1941, Bayard T. Horton also communicated that ergotamine could alleviate "histaminic cephalalgia" [271, 272].

Methysergide

Methysergide was explored as a possible migraine treatment in 1959 for the first time [273], and in 1961 Harris published the first study that evaluated the efficacy of the drug in migraine and CH prevention, showing a reduction in the frequency of CH attacks with respect with the baseline [274]. Since that first study, adverse effects have commonly been observed. Together with the occurrence of fibrotic complications, this ultimately led to the abandonment of methysergide [273, 274].

Caffeine

Caffeine is a non-selective antagonist of A_1 and A_2A adenosine receptors [275]. Within the effects of caffeine, vasoconstriction of cerebral blood vessels was thought to be an effective way to alleviate various headache disorders, including migraine, tension-type headache, and CH [275]. Evidence in CH treatment is weaker than with other drugs, and in many cases, it is used in various preparations, such as coffee, energy drinks or in combination with other drugs, such as aspirin, ergot derivates

or butalbital. In a large survey published in 2019 that evaluated the employed drugs for CH treatment, 41/1604 (2.5%) participants reported to use caffeine as an acute treatment, and 17% of them reported high effectiveness of it [276]. In addition, 112/589 (19%) of patients had used combinations of ergots and caffeine too [276].

Lithium

The use of the lithium salt as a remedy in CH is another example of a serendipitous finding which was first suggested by Karl Ekbom in 1974 [277]. The pharmacological effect of lithium for CH has been evaluated since the 1980´s and has indicated a good effect, especially in chronic CH, though the treatment comes with a myriad of adverse effects, and the dosage is notoriously difficult to titrate [278]. While lithium's mechanism of action in CH is undetermined, several clues from its effect in bipolar disorder can be found. Lithium has been shown to promote inhibitory neurotransmission via facilitating the pre-synaptic release of GABA and upregulation of post-synaptic $GABA_A$-receptors [279]. Interestingly, GABA has been noted as a dominant neurotransmitter in the hypothalamus [280]. Moreover, lithium can inhibit post-synaptic G-proteins and has downstream inhibitory effects on the adenylyl cyclase system [281].

Further, long-term lithium treatment has been shown to increase neuronal monoamine synthesis, particularly that of the indolamine 5-hydroxytryptamine (5-HT) [281]. This ties well together with the inhibitory effect 5-HT (and triptans) has on trigeminal neurons [282].

Steroids

In 1975 Jammes communicated the results of the first double-blind, placebo-controlled, single crossover study that showed that prednisone decreased the CH attack frequency in 17/19 treated patients with prior failure to other therapies, such as ergotamine, methysergide, caffeine, phenobarbital and other analgesics [283]. Three years later Couch and Ziegler communicated the results of a retrospective study that showed that 14/19 CH patients treated with 10–80 mg of prednisone per day had at least a 50% relief in the headache, However, 79% of patients experienced a CH recurrence when the drug was tapered down [284].

Oxygen

In 1981, Lee Kudrow communicated for the first time that 100% oxygen at 7–10 L was able to abort CH attacks within minutes [285]. Subsequent studies showed that oxygen effectively aborted attacks when the inhalation is started at the onset of the attack (in 50–85% of patients [278]. While oxygen treatment has the advantage of no adverse effects, it requires patients to keep oxygen tanks at home which may be impractical.

Oxygens mechanism of action has long been considered to be vasoconstriction [286], which is somewhat at odds with the current understanding of headache pathophysiology. While the mechanism requires further clarification, studies have shown that oxygen can inhibit neuropeptide release and neuronal activation in the trigeminocervical complex [81, 287].

Verapamil

The first scientific evidence supporting the use of verapamil in CH was published in 1983 by Meyer and Hardenberg, in a series of five patients that received it [288]. Verapamil binds to a relatively large range of voltage-gated calcium channels (CaV). Among them Cav1.2, a subunit of the 'long-lasting' L-type calcium channels, has been noted as important as it is expressed by trigeminal neurons [289, 290]. Further, verapamil is reported to inhibit potassium channels. Verapamil can easily cross the blood-brain barrier (BBB) and elicit a central effect. Conversely, the recommended doses for verapamil (160–720 mg/daily) are quite high, likely due to the fact that verapamil is a substrate for p-glycoprotein (an efflux protein situated at the BBB) [291].

Verapamil's mechanism of action in CH is not yet determined. However, it has been suggested to modify CGRP-release via blocking of presynaptic calcium channels [290], and to modify circadian rhythm via interactions with calcium channels in the hypothalamus [288]. Another possible mode of action could be the prolongation of the action potential, elicited by calcium channel blockers (CCBs), reduces the frequency of neuron 'firing' across the trigeminal system. Interestingly, verapamil has been shown to dose-dependently inhibit amplitude and frequency of epileptic after-discharge, an estimate of local excitability, in male rats [292]. Thus, speculatively, verapamil could reduce the amount of pain signals sent from the trigeminal system to higher order pain centres. In addition, the initial hypotheses supported that CCBs could be effective in migraine and CH due to the vascular changes observed during headache episodes.

It should be noted that though most available data on CCBs effect on CH comes from verapamil, other voltage-gated CCBs such as nifedipine (30–180 mg/daily) and nimodipine (60–120 mg/daily) have also demonstrated a high efficacy in the prophylactic treatment of CH [288]. Which can both cross the BBB to some extent.

Triptans

The first preliminary evidence of sumatriptan in CH acute treatment was published in 1989 [293], subsequently confirmed in a randomized, double-blind, placebo-controlled crossover study that included 49 CH patients, published in 1991 [294]. The rationale for their use in CH was also linked to their vasoconstrictive properties (via

agonism of 5-HT_{1B} receptors) when migraine was considered to be of vascular origin. Contemporarily, triptans have been shown to inhibit the release of neuropeptides (e.g. CGRP) from trigeminal neurons (which express 5-$HT_{1B/D}$ receptors) [295, 296] and can inhibit neuronal firing in the trigeminal ganglion (TG) of rats [297]. Therefore, triptans likely have a triple effect on pain modulation relevant to both CH and migraine; (1) inhibition of neuropeptide release, (2) inhibition of neuronal firing, and (3) vasoconstriction. The balance between the 3 different mechanisms remains an enigma.

Figure 3 summarizes the timeline of the first evidence of efficacy for older drugs in the treatment of cluster headaches.

Future/evolving targets

CGRP-targeting drugs

CGRP is increased in plasma of CH patients during attacks when compared to out-of-bout periods [298]. This plausibly has a sensitizing effect on the facial sensory nerves relevant to CH and migraine. In support, sensory C-fibre projections from the maxillary nerve pass through the SPG [299]. The SPG is important to CH pathophysiology as a major efferent parasympathetic relay [300], and its neurons express CGRP receptors [301]. Thus, the release of CGRP from C-fibre boutons projected via the maxillary nerve may activate CGRP receptors expressed on SPG neurons. The CGRP release could sensitize the SPG neurons in a similar way as likely occurs in migraine pathophysiology [302].

Psilocybin and lysergic acid diethylamide (LSD)

Psilocybin and LSD have been suggested to abort CH attacks and increase remission periods between bouts [303]. While the exact mechanism of action is not elucidated for psilocybin or LSD in CH, the plausible target for them is a broad variety of 5-HT receptors in both the CNS and PNS. LSD is readily able to cross the BBB, while psilocybin first requires enzymatic dephosphorylation into its active, and more lipophilic, form psilocin to cross [304].

Ketamine is a NMDA receptor antagonist that inhibits glutamate-mediated excitatory neurotransmission. This may decrease periaqueductal gray substance, dorsal raphe nucleus and locus coeruleus activation, also decreasing nociceptive signals to the trigeminal nucleus caudalis and ultimately reducing the CGRP release [305].

Proto-oncogene tyrosine-protein kinase MER (MERTK)

Recent GWAS studies have revealed an upregulation of the MERTK receptor in CH patients [306, 307]. Activation of the MERTK receptor induces the MAPK/ERK1/2 pathway and is further involved in phagocytotic and neuroinflammatory processes [72]. Speculatively, MERTK

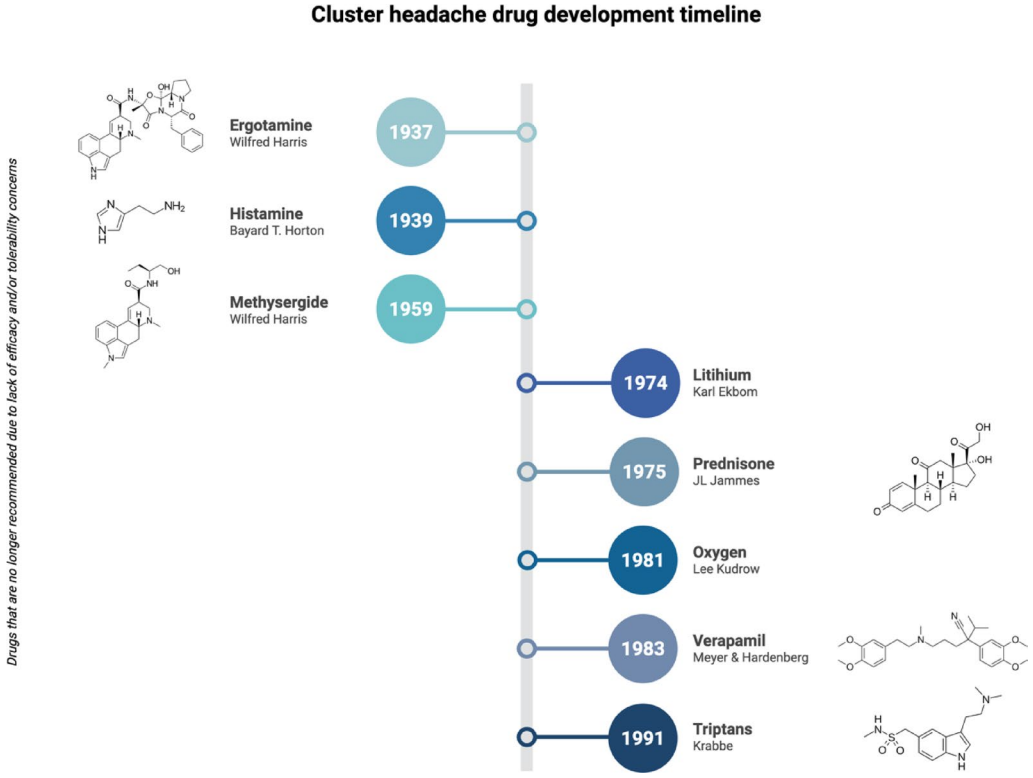

Fig. 3 Timeline of the first evidence of efficacy for older drugs in the treatment of cluster headaches

has been suggested to be involved in neuron-glia interactions relevant for the hypersensitization to pain in CH [72]. Though this work is in its infancy it is an interesting and novel target for CH.

Current acute and Bridge Pharmacological treatments of CH

Treatment of CH requires acute, transitional and preventive drug treatment. Acute therapy (i.e., oxygen, triptans) is used for acute attack abortion or suppression, but does not influence the duration of the cluster episode. Preventive treatment aims to terminate the cluster episode, while transitional therapy aims to induce a rapid cessation or reduction in attack frequency to bridge the period needed for the preventive therapy to become effective.

Acute treatment

Several substances have proven efficacy to abort the acute CH attack in randomized, controlled clinical trials (RCTs).

Oxygen

Inhalation of 100% oxygen with a non-rebreathing face mask is one of the most frequently used acute therapies, as it has no adverse events. Two RCTs with have assessed the efficacy of oxygen vs. regular air inhalation in the acute treatment of CH attacks and 12 L/min for 15 min vs. regular air inhalation. The dose used in the first trial was 6 L/min for up to 15 min and the majority (56%) of participants reported substantial headache relief [308]. In the second trial, oxygen was breathed at 12 L/min for 15 min and 78% of participants were pain-free compared to 20% that breathed regular air [309]. 100% oxygen should be offered to treat acute CH attacks.

Triptans

A comprehensive Cochrane review found six randomized, RCT for the acute treatment of CH attacks [310]. For many patients subcutaneous sumatriptan 6 mg is the preferred choice as it is generally considered to work faster [310]. In one of the RCTs 36% of patients were pain free within 10 min and 48% (63/131; range 46–49%) within 15 min post injection [311]. Numbers needed to treat (NNT) for subcutaneous sumatriptan 6 mg were 3.3 (95% CI 2.4 to 5.0) [15] in one study and 2.4 (95% CI 1.9 to 3.2) in the other [312]. Alternatively, intranasal zolmitriptan 5 mg or 10 mg has proven efficacy in two RCTs [313, 314]. Pain-free response was reached within 30 min in 63% of the participants treated with the 10 mg dose, in 48% of those treated with the 5 mg dose. NNTs for intranasal zolmitriptan 10 mg were 11 (6.4 to 49) and 4.9 (3.3 to 9.2) respectively [314]. Unfortunately, Zolmitriptan is only available in the 5-mg formulation, but it May represent an option in patients that do not like to inject themselves. Sumatriptan 20 mg nasal spray was also effective in one RCT [315] with 47% of participants becoming pain free at 30 min. Oral Zolmitriptan 10 mg was also effective but required a longer time to work [316]. Triptans are contraindicated in subjects with cardiovascular disease. Adverse events associated with triptans are nausea, vomiting, dizziness, fatigue, paraesthesias, feeling of heaviness, non-chest tightness and unpleasant or bitter taste. Triptans are recommended not to be used more than twice a day, so that patients with CH tend to overuse triptans if an effective preventive treatment is not timely started. While a 15-year follow-up of one patient that took sumatriptan in excessive doses between 12 and 222 mg (average of 150 mg during one year) without complications [317], some cases of myocardial infarction have been reported in CH patients with and without cardiovascular risks, which suggests caution and adequate education of the patients.

Intranasal Lidocaine

One crossover RCT, one non-randomized trial and two case series have described the efficacy of lidocaine for the acute treatment of CH attacks [318–321]. Either 4% or 10% lidocaine (1 ml) were used. The crossover RCT included only nine patients with nitroglycerin induced CH attacks [321] who were treated with lidocaine 10%, cocaine 10% or a placebo solution applied to the nostril ipsilateral to pain. The pain stopped on average 37 (± 7.8) min after lidocaine application and 31 (± 13.1) min after cocaine application, with both drugs being superior to placebo. While the evidence is weak, lidocaine use can be considered if standard treatment fails [322].

Ergotamine

Dihydroergotamine (DHE) is an injectable alternative to triptans, but not generally available and with more side effects. The evidence of efficacy is based on small retrospective studies suggesting that intravenous DHE may be effective in both inpatient and outpatient settings [323]. It has a long half-life and may therefore also be used as transitional therapy (see paragraph below).

Octreotide

Subcutaneous octreotide 100 µg was assessed in 57 participants with CH in a RCT versus placebo. Headache relief (mild to no pain) was achieved in 57% of subjects at 30 min with octreotide vs. 36% with placebo ($p < 0.01$) [324]. Adverse events were diarrhoea, abdominal bloating, nausea, dull background headache, and injection-site reactions. Octreotide may be useful as second-line agent for the acute treatment of CH attacks, but evidence is thin.

Transitional treatment

Transitional treatment is required in almost all CH patients in addition to the acute treatment of attacks in order to shorten or interrupt the active cluster episodes as soon as possible and to ameliorate the pain until preventive treatments start to work [325].

Corticosteroids

Approximately one third of patients receive corticosteroids for the abortion of the cluster episode. Some small open studies reported a negative outcome [270, 326, 327], others suggested effectiveness of corticosteroids [283, 328–331]. A vanguard placebo-controlled trial with 19 CH participants reported that 14 were free of pain after one single dose of corticosteroid. However, the study had some methodological limitations that make interpretation of results difficult [283]. A large RCT (n. 118) showed that 100 mg prednisone reduced the mean number of CH attacks by 25.3% (−2.43 attacks [95% CI −4.83 −0.03]) within the first week and performed significantly better than placebo (prednisone: 7.1 attacks (SD: 6.5, 95%CI 5.3 8.9); placebo: 9.5 attacks (SD: 6.0, 95%CI 7.9 11.2], $p = 0.02$)). Seventeen patients (34.7%) even reported complete cessation of attacks within the first week and 25 patients (49%) reported an attack reduction ≥ 50% within the first week. No relevant adverse events were observed during prednisone treatment [331]. A typical regimen May include a short course of oral prednisone 100 mg for 5 days, followed by a tapering down period. Two non-randomized studies assessed the efficacy of high-dose intravenous methylprednisone (250-500 mg). After treatment the CH attacks were significantly less frequent compared with previous episodes and different treatments [329, 330].

Occipital nerve block

Efficacy and safety of greater occipital nerve blocks (GONB) was documented by several randomized controlled trials [332–334]. Cortivazol (3.75 mg in 1.5 ml saline), or a mixture containing a long-acting salt of betamethasone (dipropionate 12.46 mg), a rapid-acting salt of betamethasone (disodium phosphate 5.26 mg) mixed with 0.5 ml xylocaine 2% respectively, was used in these studies [332, 333]. A recent large placebo-controlled trial in episodic CH patients randomized active GONB (2 ml methylprednisolone (80 mg) and 2 ml lignocaine (2%)) and placebo (4 ml saline injections). The weekly attack frequency reduced by −11.1 (95% CI: −8.5 to −4.4) for the active group compared to −7.7 (95% CI: −11.8 to −9.8) for placebo (mean difference − 3.4 (95% CI: −5.2 to −1.7, $p < 0.001$). Treatment-emergent adverse effects (TEAE) were reported in 18 (90%) of 20 patients who received the active drug and in 18 (90%) of 20 patients who received placebo ($p = 0.38$). The most common TEAE were local site bleeding and mild and transient pain. No serious adverse events were reported [334].

Ergotamine

Subcutaneous or intramuscular DHE is used 2 or 3 times a day for a week and may be continued once or twice a day for another week if tolerated. Contraindications are vasoconstriction-related side-effects, and its availability is limited in some countries. Methysergide is probably effective, even though there are no controlled trials available. Concerns with concomitant triptan use as well as potential fibrotic complications over longer treatment periods limits its use [335]. In a retrospective study most patients were headache free within two days with 1 mg DHE 2–3 times daily [336]. 16% became headache free after the first dose and it May protect patients with frequent attacks from further attacks for up to 12 h (i.e., overnight). Intranasal DHE showed insufficient efficacy in one RCT [337].

Triptans

Sometimes long-acting triptans are used as short-term prophylactic therapy before verapamil or lithium start to work even though RCTs are still missing. Frovatriptan 2.5 mg was tested in nine subjects with episodic CH with 8 of them reporting complete pain relief at 48 h. Patients received frovatriptan for up to three weeks once or twice daily until their verapamil dosage was considered sufficient [338]. However, a multi-center, placebo-controlled, randomized, double-blind, prospective trial with frovatriptan 5 mg vs. placebo in episodic CH, prematurely discontinued due to infeasibility, showed no significant differences in the primary and secondary endpoints [339]. Naratriptan 2.5 mg once or twice daily improved headaches in seven out of nine CH patients and eletriptan 40 mg was also tested successfully in one patient [340]. Oral sumatriptan was not effective in this indication [341]. The use of triptans as a transitional treatment may pose the risk of medication overuse headache and prevents the use of sumatriptan for the acute treatment of attacks.

Current preventive treatments of CH

Traditional preventive treatment of CH mostly includes several non-specific pharmacological agents with limited evidence (Table 2). Verapamil is considered a first line preventive option (medication of choice) for episodic and chronic CH based on consensus opinion, open label studies, and a couple of small randomized controlled trials [342, 343]. The mechanism of action of verapamil has not been fully elucidated; however, it is thought to modulate circadian rhythms and calcitonin gene-related peptide [289].

Table 2 Non-specific therapies for cluster headache

Medication	Mechanism of Action	Dose	Evidence	Adverse Events/ Monitoring	Comments
Verapamil	Calcium channel blocker; inhibits cortical spreading depression and vascular reactivity	240–960 mg/day (divided doses)	**Gold standard** for prophylaxis	Bradycardia, hypotension, constipation, ECG monitoring (AV block, QT prolongation)	High doses often required; regular ECGs essential
Lithium	Modulates neurotransmitters (serotonin,dopamine); affects second messenger systems	600–1500 mg/day (target serum: 0.4–0.8 mmol/L)	Good evidence, especially for chronic cluster	Renal and thyroid function, lithium levels, tremor, nausea, polyuria	Narrow therapeutic range; frequent monitoring needed
Topiramate	Blocks voltage-gated sodium channels; enhances GABA activity	50–200 mg/day	Limited evidence, off-label use	Cognitive dysfunction, nephrolithiasis, paresthesia, weight loss	Off-label; reserved for refractory cases
Melatonin	Regulates circadian rhythms; antioxidant properties	9–12 mg at bedtime	Moderate evidence, particularly for episodic cluster	Drowsiness, vivid dreams, hormonal effects	Useful for nocturnal attacks; well-tolerated

The recommendation is supported by small RCTs and open label studies including a multi-center, randomized placebo-controlled, crossover study [344]. After a 5-day run-in, 30 participants were randomized to verapamil (120 mg tid) or placebo (tid) for 2 weeks. The primary endpoint was reduced attack frequency; intensity and duration of attacks and use of abortive agents, mostly subcutaneous sumatriptan, was captured with a headache diary. In the verapamil arm, 80% were responders versus in the placebo arm there were non-responders. In a multicenter, double blind, cross-over trial, verapamil was also compared to lithium carbonate for chronic CH prevention; lithium carbonate and verapamil were both effective, however, participants on verapamil had fewer adverse effects and the latency period was shorter than for lithium carbonate [345]. Higher doses of verapamil may be more effective; however, adverse events may be limiting including constipation, gingival hyperplasia, and serial electrocardiograms are needed to evaluate for electrocardiac abnormalities [346].

The mechanism of action of lithium for the preventive treatment of CH is not fully elucidated; however, lithium is thought to act on several neurotransmitter systems and signal transduction pathways [347]. According to the European Academy of Neurology guidelines [342], lithium carbonate 600–1500 mg should be considered for both episodic and chronic CH when there is a lack of response to verapamil. The recommendation is supported by some randomized controlled trials [348, 349] with mixed results, and by positive open label studies [350–352]. Due to narrow therapeutic windows there is a risk of toxicity, drug levels should be checked routinely for safety but not efficacy. In addition, chemistry, liver, renal and thyroid function need to be monitored. Lithium should be avoided with concurrent indomethacin use; concurrent use of verapamil may also enhance excretion of lithium [342].

Among newer treatments, monoclonal antibodies targeting the CGRP pathway have shown promise, though with subtype-specific limitations (Table 3). Galcanezumab, an anti-CGRP ligand monoclonal antibody, at the 300 mg dose, significantly reduced attack frequency in episodic cluster headache in a randomized controlled trial during weeks 1 to 3 [86]. However, this benefit could not be replicated in chronic CH [87]. Similarly, erenumab, a CGRP receptor antibody, failed to show efficacy in a randomized, double-blind, placebo-controlled phase 2 trial in chronic CH (CHERUB01) [353]. In interim analyses for primary endpoint of mean change from baseline in the weekly average number of CH attacks at week 4, fremanezumab showed futility in Phase 3 trials for both episodic and chronic CH (ENFORCE) [354, 355]. Eptinezumab, a monoclonal antibody to CGRP administered intravenously, failed to show efficacy on the primary outcome measure in a phase 3, parallel-group, double-blind, placebo-controlled trial (ALLEVIATE) for prevention of episodic CH [90]. However, eptinezumab treatment was associated with numerically higher responder rates and improvements in average daily pain and patient-reported outcomes In an open label study longer term safety and efficacy for prevention of chronic CH (CHRONICLE trial), the participants reported improvements in attack frequency, pain severity and patient-reported outcomes [91].

Topiramate has shown some benefit in open-label studies and small trials, although its efficacy is inconsistent and limited by tolerability concerns [356, 357]. Sodium valproate has also been evaluated in small series with

Table 3 CGRP targeted therapies for cluster headache

Medication	Mechanism of Action	Dose	Evidence	Adverse Events/ Monitoring	Comments
Galcanezumab	Monoclonal antibody against CGRP ligand	300 mg monthly (higher than for migraine)	**Positive evidence only for episodic cluster**	Injection site reactions, constipation	**Only approved therapy for episodic cluster headache**; not for chronic cluster
Fremanezumab	Monoclonal antibody against CGRP ligand	No established dose for cluster	Insufficient evidence	Injection site reactions	Not approved for cluster headache
Erenumab	Monoclonal antibody against CGRP receptor	Not approved for cluster	Negative trials	Constipation, hypertension, injection site reactions	No approval; trials failed to show efficacy
Eptinezumab	Monoclonal antibody against CGRP ligand	400 mg every 12 month	Controversy results	Nasopharyngitis, hypersensitivity reactions	IV administration only; not approved for cluster e
Rimegepant	Oral CGRP receptor antagonist (Gepant)	No approval for cluster	No evidence	Nausea, urinary tract infections	Approved only for migraine (acute and prevention)
Atogepant	Oral CGRP receptor antagonist (Gepant)	No approval for cluster	No evidence	Nausea, constipation, fatigue	Approved only for migraine prevention

modest effect, but the evidence base remains insufficient to support routine use [358].

Melatonin is a hormone produced by the pineal gland, regulated by the suprachiasmatic nucleus, and is associated with shifts in circadian rhythms, and the sleep-wake cycle. The circannual urinary melatonin concentrations is lowered in individuals with episodic CH [359]. The European Academy of Neurology recommends melatonin when standard therapies fail [342], although evidence remains limited and heterogenous. In a double-blind placebo-controlled pilot study with parallel group consisting of 20 participants with CH, (2 chronic, 18 episodic), melatonin 10 mg taken in the evening was found to be more effective at reducing headache frequency than placebo [360]. Specifically, 5 out of 10 participants had a reduction in attack frequency 3–5 days after treatments; participants with chronic CH and those that received placebo did not response. Adverse events were not reported for either group, suggesting a potential utility for adjunctive therapy despite the low response rate.

Naratriptan, a long-acting oral triptan, has been used in selected cases with predictably nocturnal CH, administered in the evening to pre-empt nighttime attacks. While evidence is limited to case series and clinical experience, some reports suggest that naratriptan 2.5 mg given prophylactically may reduce the frequency or intensity of nocturnal attacks [361]. This approach may be considered in patients for whom standard prophylaxis is insufficient or contraindicated. Ergotamine, though now rarely used, has demonstrated efficacy in nocturnal CH when administered in sustained-release formulations or intravenously during inpatient settings [362, 363].

OnabotulinumtoxinA has been evaluated in small case series using an adapted PREEMPT injection protocol, originally developed for chronic migraine or sphenopalatine injections. Although some patients with chronic CH have reported benefit, controlled trials are lacking, and its application remains experimental [364–366].

In practice, combination therapy is frequently employed, particularly in chronic or refractory cases. Clinicians may combine verapamil with lithium, corticosteroids, or nerve blocks, often tailoring regimens to the patient's comorbidities and response. While such multimodal strategies are considered clinically reasonable, controlled data on specific combinations are lacking.

Finally, several experimental and lesser-studied therapies have been reported. Intranasal capsaicin and its synthetic analog civamide may reduce attack frequency via desensitization of trigeminal afferents [367]. Clomiphene citrate, a selective estrogenic receptor modulator, has been proposed in individual cases, presumably via hypothalamic modulation [368]. Additionally, ketogenic diets have been associated with reduction in attack frequency

in select patients, possibly through metabolic and anti-inflammatory mechanisms [369].

Alternative medical approaches on CH treatment

Despite pharmacological advancements, many CH patients remain refractory to conventional treatments. As a result, there has been growing patient-driven interest in alternative medical approaches, including herbal therapies, dietary supplements, psychedelics and compounds such as sodium oxybate. We evaluate the current evidence and therapeutic potential of these alternative approaches in the management of CH (Table 4).

Herbal therapies

Evidence for plant-based compounds in CH is observational, with cannabis and kudzu (*Pueraria lobata*) being the most studied.

Kudzu root is traditionally used in Chinese medicine. In a survey of 235 CH patients, 16 self-administered kudzu. Among these, 69% reported reduced attack intensity and 56% a decrease in attack frequency [370]. Notably, a dose-response relationship was observed. Side effects were minimal, mostly mild gastrointestinal discomfort.

Cannabis use is more prevalent among CH patients compared to the general population [371, 372]. Research on its therapeutic potential is scarce and mainly focused

Table 4 Alternative treatment options in cluster headache: an overview abbreviations: CH: cluster headache; IV: intravenous; IN: intranasal; GI: gastrointestinal; RCT: randomized controlled trial; mg: milligram; kg: kilogram; IU: international units; LSD: lysergic acid diethylamide

Substance	Administration and dosing	Preventive or abortive	CH subtype	Level of evidence	Summary of outcomes
Herbal therapies					
Kudzu	Oral, tablets or decoction of dried root. Typically 1–3 times daily, dose range: 613–1500 mg	Preventive	Chronic, episodic	Case series	May reduce attack frequency, intensity and duration in some. Well tolerated, mild GI side effects
Cannabis	Inhaled or oral (e.g. tablets dronabinol 5 mg)	Primarily abortive	Chronic, episodic	Case report, survey studies	Highly variable. Some report quick pain relief (~ 26–29%), others worsening of attacks (~ 22–25%) or no benefit
Dietary supplementals					
Vitamin D	Oral, tablets 10,000 IU/day	Preventive	Chronic, episodic	Survey study	May reduce attack frequency, severity, and duration. Toxicity risks with high-dose regimens
Magnesium	IV, 1000 mg (repeated in responders)	Preventive	Mainly episodic	Case series	Possible benefit primarily in cases with low ionized magnesium. Small sample size, unclear outcome measures and study design limit generalizability
Melatonin	Oral, tablets 9–10 mg nightly (case reports use 3–15 mg)	Preventive	Mainly episodic	RCT, single-blind crossover, case series and reports	Reduces attack frequency in some, particularly in episodic CH. Well tolerated
Sodium Oxybate	Oral, tablets 3–9 g/night in 2 doses. Titration required.	Preventive	Chronic, episodic	Exploratory RCT, open label trial, case series and report	Possible reduction of (nocturnal) attacks and improved sleep; acceptable tolerability. Small RCT showed benefit at 1 week but not at 2, likely due to dropout
Psychedelic compounds					
Psilocybin	Oral, typically as capsules or dried mushrooms, 'pulse dosing' 3 doses (e.g. 0.143 mg/kg psilocybin) every 5 days	Preventive	Chronic, episodic	Exploratory RCT, surveys, case series and report	Possible attack frequency reduction. Larger effect in chronic CH. In some, effects are prolonged. Well-tolerated in trial settings
LSD	Oral, typically as liquid or blotter. Both psychedelic and non-psychedelic doses. Dosing intervals range from once every 5–7 days to monthly.	Preventive	Chronic, episodic	Case series, survey studies	Indications of attack cessation, prolonged remissions, also at sub-hallucinogenic doses
Ketamine	IV: 0.25-0.5 mg/kg; single or up to 4 biweekly infusions IN (spray): 15 mg every 6 min up to 5 times (max. 75 mg)	IV: preventive IN: abortive	Mainly chronic	Open label trials, case-series	Preventive: ≥50% reduction in 54–76% of chronic patients, effects lasting weeks to months reported Abortive: no effect at 15 min, but 59% mean pain reduction at 30 min. No serious adverse events reported
BOL-148	Oral, tablet, 3 mg every 5 days	Preventive	Mainly chronic	Open label trial	Non-hallucinogenic LSD analogue; reduces attack frequency and/or intensity in preliminary data. Well tolerated

on cannabis as an abortive treatment [373–375]. One case experienced symptom alleviation within 5 min after inhaling marijuana and 15 min after an oral dose of dronabinol 5 mg [373]. In survey studies, 25.9 and 29.4% of users experienced attack relief, while most reported either no benefit or worsening of attacks [374, 375]. These findings underscore the variability in reported efficacy and cannabis' potential to worsen symptoms [371].

Dietary supplementals

Evidence for dietary supplements in CH management remains limited compared to more established data in migraine prophylaxis. Some studies have explored potential roles for vitamin D and magnesium.

Vitamin D deficiency is notably prevalent in CH patients [376]. High-dose supplementation (10,000 IU/day) with Omega-3 fish oil was associated with reductions in attack frequency, severity and duration in a presented abstract [377]. However, clinical trials are lacking and high-dose vitamin D treatment should include medical monitoring and personalized dosage adjustments due to toxicity risks [378].

Intravenous magnesium sulphate provided relief in 41% of 22 patients, primarily those with low baseline ionized magnesium levels [379]. Yet methodological limitations, including the open-label design, unclear outcomes and small sample size, limit interpretability. Oral magnesium supplementation, although researched in migraine, lacks evidence for CH. Intravenous magnesium combined with ketamine is addressed under '*Ketamine*'.

Sodium oxybate

The sodium salt of gamma-hydroxybutyrate (GHB) exhibits GABAergic activity and is primarily used in narcolepsy. Its sleep-modulating effects have prompted exploration in CH [236, 380, 381]. A case report in episodic CH and an open-label study in four chronic patients reported reduction in attack frequency, mainly nocturnal, alongside improved sleep parameters [236, 380]. Side effects such as dizziness, vomiting, and weight loss were reported. A small randomized, double-blind trial including eight episodic and chronic patients also found a significant reduction in nocturnal attack frequency after one week of treatment [381]. However, effects lost statistical significance after two weeks, possibly due to patient dropout (predominantly among placebo-treated individuals with increased headache attacks). Larger controlled studies are necessary and planned to validate these preliminary findings (NCT06950281).

Psychedelic compounds

Psychedelic compounds are potent neuroactive substances that influence perception, mood, and cognition [382]. Classic psychedelics, such as lLSD and psilocybin, mainly act through serotonin receptor agonism. They are distinguished from non-classical compounds like ketamine, which share clinical similarities, but have different mechanisms of action.

Classic psychedelics

Anecdotal reports and patient advocacy groups have long suggested that psychedelics may abort CH attacks, prolong remission periods, and reduce attack frequency [383]. Most data originate from uncontrolled case studies or surveys, which notably describe beneficial effects from certain psychedelics, particularly psilocybin and LSD [303, 371, 375, 383–385]. Sub-hallucinogenic doses appear to retain therapeutic benefits while minimizing psychoactive effects [303]. Moreover, the beneficial effect of these psychedelics may be prolonged, lasting longer than would be expected based on their pharmacokinetics.

Clinical trials are sparse, but the concept of 'pulse dosing' involving repeated low doses spaced over days, has been investigated for psilocybin. In one study of 14 CH patients, a low-dose psilocybin regimen of three doses five days apart led to non-significant attack frequency reduction compared to placebo (−3.2 vs. −0.03 attacks per week) [386]. A larger effect was observed in participants with chronic CH. A blinded extension demonstrated approximately 50% reduction in attack frequency following repeat dosing, even in initial non-responders [387]. An open label trial including 10 patients with chronic CH and employing a similar dose of psilocybin, dosed every week for 3 weeks, showed a significant but variable reduction in attack frequency (~ 31%) compared to baseline [388]. Across these studies psilocybin was well-tolerated, without serious adverse effects.

While no controlled LSD trials have been published, two randomized studies are currently ongoing, employing hallucinogenic and sub-hallucinogenic doses (NCT03781128 and NCT05477459. respectively).

Other serotonergic psychedelics, such as Lysergic acid amide (LSA) and N, N-Dimethyltryptamine (DMT) are used by CH patients [375, 389]. LSA as a prophylactic, DMT is also employed as abortive treatment. Both have been reported as beneficial, although controlled studies are lacking.

Ketamine

This NMDA receptor antagonist' therapeutic potential has primarily been evaluated in case series among refractory chronic CH patients, with varying dosing regimens [390–393].

Two series combining intravenous ketamine (0.5 mg/kg over 2 h) with magnesium sulphate showed ≥ 50% attack frequency reduction in over 75% of patients, with remissions lasting up to several weeks [392]. Another series using intravenous ketamine alone (0.5 mg/kg every 2

weeks, up to four sessions) reported termination of episodes in all episodic patients and temporary remission of attacks in 54% of chronic patients, with effects lasting 3–18 months [391]. A recent case series utilizing intravenous S-ketamine (0.25 mg/kg over 1 h) showed complete remission in 80% of participants, although remission duration varied significantly (1–26 months) [393].

Intranasal ketamine (15 mg every 6 min, max. 75 mg) as acute treatment in chronic CH did not meet its primary endpoint of ≥ 50% pain reduction after 15 min. However, among 16 patients who refrained from using conventional rescue medication after 15 min, the mean pain reduction reached 59% at 30 min [390].

Across these studies, ketamine was generally well-tolerated, with mild and transient side effects.

To our knowledge, no controlled studies have been published. However, a placebo-controlled trial investigating ketamine and magnesium infusion in chronic CH is now recruiting (NCT04814381).

BOL-148

This non-hallucinogenic structural analogue of LSD, demonstrated efficacy in a small case series in five CH patients, four of whom chronic [394]. BOL-148 substantially reduced attack frequency in four out of five patients. The patient who did not experience a significant reduction in attack frequency reported a decrease in attack intensity. BOL-148 was well-tolerated and not associated with psychoactive side effects.

Conclusion

The accumulating evidence suggests that certain psychedelics, BOL-148, selected herbal and dietary supplements, melatonin and sodium oxybate, may offer a promising alternative or adjunctive treatment for CH. However, robust clinical validation is lacking and significant barriers, including regulatory challenges, persist. Future research should focus on clarifying the precise mechanisms of these compounds and developing safe, legally accessible treatment options for CH patients.

Non-invasive neuromodulation in CH

Neuromodulation has emerged as a promising alternative to pharmacological treatments in primary headache disorders with some applications also in CH. Invasive modalities are usually offered for medically refractory patients [395]. Non-invasive modalities may be used earlier in the patients' treatment pathway as an alternative or addonto pharmacological therapies [396]. Barriers to the wider use of these therapies have historically been the lack of robust evidence, largely dictated by the difficulty in producing a reliable sham in clinical trials and the high costs of the devices, which have discouraged some health authorities to cover the cost of these therapies, thereby limiting their wider use [397].

Vagus nerve stimulation

Stimulation of the cervical branches of the vagus nerve to modulate pain and other symptoms in CH has been attempted by using the gammaCore device. This is small, portable device containing two electrodes that transcutaneously stimulate the vagus nerve with a 1 ms burst of five kHz sine wave (24 V peak, 60 mA) stimulation repeated at 25 Hz for 90 s [398]. The vagus nerve provides parasympathetic innervation to the autonomic nervous system, involved in a variety of autonomic functions including the respiratory, cardiovascular, and nociceptive systems. This stimulation is thought to activate lowthreshold myelinated Afibers, producing an antinociceptive effect on the secondorder neurons of the spinothalamic and spinoreticular tracts within the TCC [399]. Transcutaneous vagus nerve stimulation (t-VNS) in animals has been shown to be able to modulate trigeminal activity and to inhibit the response of TCC neurons to trigeminal stimulation [400].

An fMRI study that investigated the neuromodulatory role of vagus nerve stimulation to the trigeminal autonomic reflex, showed that t-VNS may modulate functional connections between important areas for head pain and CH namely the pons, the spinal trigeminal nuclei and the hypothalamus [135].

The therapeutic effect of t-VNS in CH has been evaluated in two randomised-controlled trials, an open-label prospective study and real-world studies. Two randomized doubleblind shamcontrolled trials (ACT1 and ACT2 studies) were conducted to evaluate the efficacy of t-VNS using gammaCore device in CH [401, 402]. The primary endpoint of ACT1 was the response rate, defined as the proportion of subjects who achieved pain relief (pain intensity of 0 or 1) at 15 min after treatment initiation for the first CH attack without rescue medication use through 60 min. The study did not meet the primary endpoint. Indeed, a response was achieved in 26.7% of t-VNS treated subjects vs. 15.1% of sham treated subjects ($P = 0.1$). ACT2 was a smaller study compared to the ACT1 but with a similar methodological design. The primary efficacy endpoint was the proportion of all treated attacks that achieved pain-free status within 15 min after treatment initiation, without rescue treatment. Even in this trial, t-VNS (14%) was not superior compared to sham (12%) treatment in the total cohort. In both trials, t-VNS was superior to sham in the episodic CH group compared to chronic CH group. Given that the current pathophysiological hypotheses for CH suggest that the two subtypes of CH follow the same biology, these results are difficult to explain. When evaluated as a prophylactic treatment in an open label small study in chronic CH,

t-VNS plus standard of care (SoC) was superior to SoC alone at least for short term prevention (40% vs. 8.3% responders) [403].

A company funded small retrospective audit conducted in three headache services in the United Kingdom (UK), found positive results in chronic CH patients treated with gammaCore. However, these patients were known responders to t-VNS. Furthermore, the GONB, which is the preventive treatment that has amongst the best evidence of efficacy and tolerability in episodic and chronic CH, was not tried before using t-VNS in this study [404], suggesting that the patients evaluated in this study were non-difficult-to-treat. When used the refractory chronic CH patients, an independent realworld prospective analysis coming from a single headache centre in the UK suggested the poor effectiveness of t-VNS in their patients, with only one patient out of 12, responding for up to a year to gammaCore therapy [405]. A subsequent open-label study in a similar population showed a 50% response rate in 43% of patients. However, the follow-up duration of this study was only 3 months, which does not allow to draw any conclusion on the sustained effect of this therapy overtime [406].

Other non-invasive stimulation techniques

In small open label studies, also other non-invasive stimulation techniques have been applied.

Transcranial magnetic stimulation (TMS) has been tested in an open-label observational study including 19 patients suffering from chronic CH. A beneficial outcome of repetitive (10 Hz) TMS over the M1 area was reported. Paroxysmal pain and number of attacks were reduced when comparing baseline with 15 days poststimulation measures [407]. Although in this report permanent pain was reported in eight of the CH patients, it remains unclear if those fulfilled the definition of chronic CH; therefore, no clear data are available on the use of TMS in chronic CH.

Transcranial direct current stimulation (tDCS) (anode at Fz, cathode over C7) for refractory chronic CH patients has only been studied in a proof-of-concept study [408] with a mean attack frequency reduction by 35%. The method was well tolerated. There are no more data available on this method in chronic CH at the moment.

Thirty-six patients with chronic CH were treated by transcutaneous electrical nerve stimulation (TENS) of the GON for 8–12 consecutive weeks [409]. Weekly attack frequency decreased from 15.7 at baseline to 11.0 with TENS. 13 of the 36 (36%) patients had a minimum 30% reduction in attack frequency. Not all patients benefitted from TENS, but the treatment responders had a substantial improvement in their CH.

In conclusion, t-VNS is currently the only non-invasive neuromodulation therapy with some controlled evidence in CH. The available body of evidence suggests that t-VNS may be effective as an acute attack therapy in patients with episodic CH. However, it is unclear whether t-VNS would be effective in patients who fail to respond to both subcutaneous sumatriptan and oxygen inhalation, which are very effective and more cost-effective than gammaCore. Open-label evidence on prevention of chronic CH suggest that t-VNS might be beneficial in some patients, but not in those with refractory chronic CH, at least long-term. Further methodologically robust randomised controlled trials are warranted to clarify its role in the arsenal of treatments for CH.

Invasive neuromodulation

There are currently three invasive neurostimulation methods that have been tested in CH. T: posterior hypothalamic deep brain stimulation, occipital nerve stimulation and spheno-palatine ganglion stimulation. The evidence of efficacy is limited for the first two, moderate for spheno-palatine ganglion stimulation [342]. Altogether, their high cost, access limitations and potential side effects make them indicated only for rCCH.

Deep brain stimulation (DBS)

Given its implication in autonomic function and chronobiology, as well as attack-related hypermetabolism demonstrated in the posterior hypothalamus ipsilaterally to the site of CH attacks, the hypothalamus emerged as a central target for potential neuromodulation in CH. Nearly 25 years ago, Leone et al. reported for the first time the effectiveness of posterior hypothalamic DBS used compassionately in a patient suffering from a very severe form of rCCH [410]. Then, the same team published the first case series with 5 rCCH patients treated with DBS who were pain-free after 2 to 22 months of follow-up monitoring [411]. In the aftermath, others, in different experienced centers, replicated the same procedure of DBS in rCCH. A recent systematic review on preventive treatment of rCCH reported more than a hundred published cases of patients treated by DBS and a meta-analysis of the reported data resulted in a pooled response rate of 77% (OR 0.770 [95% CI 0.594–0.957]) [412]. This response rate must be interpreted with caution as it results from data obtained under uncontrolled conditions, especially as a French randomized control crossover study including 11 patients did not show significant differences among the sham and active periods (both lasting one month) regarding weekly attack frequency [413]. Nevertheless, the effectiveness observed in the case reports and case series does not seem to be related to a placebo effect since a blind-to-the-patient interruption of DBS has been achieved in many cases, with a relapse on each interruption and an improvement when the stimulator has been turned back on [414].

DBS appears to induce a long-term therapeutic effect as reported by Leone et al. in 70% of patients with a median follow-up of more than 8 years [415]. To date, the cost-effectiveness of DBS in rCCH has not been evaluated. Given the changes in the stimulation target over time and between the different teams, a meta-analysis aimed to construct a probabilistic stimulation map of effective DBS and identified 2 hotspots of stimulation covering the midbrain ventral and retrorubral tegmentum [415]. Identifying the optimal stimulation target is essential to ensure the best therapeutic effect, but also to understand the DBS mechanism of action in CH. Studies using brain PET [170] and quantitative sensory testing [168] argue against an unspecific antinociceptive effect or a pure inhibition of an overactive central generator but suggest functional modulation of a pain-processing network. In addition, the efficacy of DBS in CH is supposed to depend on stimulated volumes that results in slow modulation of this network, in line with the long latency to obtain a preventive effect (minimum of 1-3months and even longer) and evidence that acute DBS is not useful to stop CH attack [416].

Major complications have been reported in 17% of subjects, including one death of day 3 of surgery due to intracerebral hemorrhage [417]. Software-related adverse events most commonly are gaze disturbances, dizziness, in general reversible with adjusting stimulation parameters. Hardware-related adverse events are electrode migration or breakage, wound dehiscence, skin erosion, and battery failure, that may need reoperation. Surgical-related adverse-event are lead misplacement, infection and intracerebral haemorrhage [418].

Occipital nerve stimulation (ONS)

The principle of ONS is to deliver continuous stimulation to the greater occipital nerve and/or to the lesser occipital nerve, via a subcutaneous implanted electrode adjacent to the nerve, producing paraesthesia that should cover the occipital region. Originally described by Weiner [419] to control occipital nerve neuralgia, this technique has been proposed to treat primary headaches, including chronic CH, ONS was initially considered to be acting through a 'gate control theory-like' mechanism involving a modulation of convergent nociceptive inputs in the TCC [420]. Twelve studies involving a total of more than four hundred patients were published and the meta-analysis of the reported data estimated the pooled response rate of 57.8% (OR 0.573 [95% CI 0.481–0.665]) [412]. The data included in this meta-analysis are mainly derived from open studies due to the paraesthesia induced by the stimulation, which makes it difficult to conduct controlled studies. Notwithstanding, these challenging hindrances have been overcome by the ICON Study, based on the hypothesis of a dose-response efficacy, in which a very low-intensity but still sufficient to induce paraesthesia have been used as sham versus a full intensity stimulation [421]. Surprisingly both 100% ONS intensity and 30% ONS intensity resulted substantially with the same rate of success in reducing attack frequency [422]. ONS appears to induce a long-term therapeutic effect as reported by Brandt et al. with a follow-up of 2–8 year [423] and by Leplus et al. with a mean follow-up of 43.8 months [424]. Regarding its cost-effectiveness, ONS is also dominant in a long-term perspective [425]. A recent study performed in rCCH patients treated by ONS showed that voltage tuning may cease and/or terminate CH attacks [426]. Despite its uncontrolled conditions, this study raises interests in the eventual use of ONS for the acute treatment of attacks and supports the 'gate control theory-like' mechanism of action of ONS. Software-related adverse events are local pain and neck stiffness. Surgical-related adverse-events are infection that is local but requires removal of the device. Hardware-related adverse events are mainly electrode migration (due to neck movements) and battery exhaustion (due to high level of power consumption) that need reoperation. The risk of both hardware-related adverse events could be limited by use of a dedicated lead (Ankerstim® developed by Medtronic with a specific CE mark for CH treatment) and rechargeable implantable pulse generator respectively.

Spheno-palatine ganglion stimulation

Hypothalamic dysfunction is assumed in CH pathophysiology to cause secondary parasympathetic activation involving paraventricular nucleus, superior salivatory nucleus and sphenopalatine ganglion. Given its easy access in the pterygopalatine fossa, the SPG was considered a potential target for stimulation to induce an inhibition of postganglionic parasympathetic outflow and stop CH attacks. With this aim, a chronically implantable neuromodulation device (Pulsante®), specifically designed for acute SPG stimulation, has been developed by the company Autonomic Technologies (ATI) and had been the subject of clinical development in the treatment of rCCH. A multiple CH attack was conducted in 28 rCCH patients who randomly treated 566 attacks with full, sub-perception or sham stimulation and the proportion of treated attacks with pain relief at 15 min following SPG stimulation was significantly greater with full than with sub-perception and sham stimulation (67.1%, 7.3% and 7.4% respectively, $p < 0.0001$) [138]. In a long-term study lasting 24 months and involving 33 rCCH patients, SPG stimulation was an effective acute therapy for 45% of participants, and 33% had decreased frequency of attacks [300]. In a real-world study involving 88 CH patients considered as difficult to treat, 68% of patients had improvement, with 55% having a 50% reduction in

attack frequency at 1 year and 32% of patients experiencing acute pain relief in at least 50% of the treated attacks [427]. SPG stimulation is often presented as the invasive neuromodulatory technique with the highest level of evidence for efficacy in the treatment of CH, but it is important to emphasize that this high level only applies to its use as an attack treatment. Similarly, SPG stimulation is often presented as a minimally invasive neuromodulation technique, but it is important to remember the high rate of reported adverse effects observed during the clinical development of the Pulsante® device given 81% with almost facial sensory disturbance, although reversible, and near 20% of reoperation related to lead misplacement or lead migration [138]. Finally, SPG stimulation has limitations in its high cost (without cost-effectiveness data available) and the specialized surgical facilities required.

Nerve blocks

Greater occipital nerve block (GONB)

GONB is recommended for the preventive/transitional treatment of CH by the American Headache Society evidence-based guidelines (Level A: established as effective) as well as by the recently published European Academy of Neurology guidelines [342, 428]. A consensus on the best procedure to perform GONB is lacking. However, the injections are frequently given ipsilateral to attacks at the medial third between the inion and mastoid process [429]. For the treatment of CH, GONB is usually performed, with a combination of corticosteroid and local anaesthetics. Most commonly the use of methylprednisolone (80 mg) and lidocaine (2 ml, 2%) have been reported in the literature [430]. The mechanism of actions of these agents and the block are not fully understood. Preclinical and clinical evidence suggests that stimulation or inhibition of the greater occipital nerve modulates the neuronal activity of the TCC, a pivotal area of the trigemino-vascular system [431, 432]. Similarly, the specific mechanism of action of steroids in CH remains unclear besides its general anti-inflammatory effect. It has been suggested that nociceptive C-fibers in substantia gelatinosa are reversibly blocked by corticosteroids [433]. Steroids may also prolong the effects of local anaesthetic [434].

GONB proved effective as a transitional treatment for CH in three RCTs [332–334] and several open-label observational studies [430].

Ambrosini et al. [333] assessed the efficacy of unilateral GONB performed with a mixture of rapid-acting and long-acting betamethasone plus xylocaine in 16 patients with episodic CH and 7 patients with chronic CH [433]. Four subjects were on a stable oral preventive medication at the time of enrolment; in addition, verapamil was started after 1 week from GONB in participants with persistent CH attacks. Eighty-five and 61% of CH subjects who received GONB were pain-free after 1 and 4 weeks, respectively, compared to 0% in the placebo group [333].

In the trial by Leroux et al. [332], 28 patients with episodic CH and 15 with chronic CH were randomized to receive three unilateral suboccipital injections of cortivazol (2–3 days apart) or placebo. GONB was performed as add-on treatment to verapamil [434]. The percentage of patients reporting less than two CH attacks per day within four days after the third GONB was 95% for CH subjects who received cortivazol compared to 55% of participants in the placebo group [434]. After 15 days from GONB, the number of CH attacks per day was lower in individuals who received cortivazol, although the percentage of subjects with a 50% reduction in CH attack frequency was comparable between active con placebo groups [332].

More recently, the ANODYNE study was designed in accordance with the guidelines of the International Headache Society for controlled trials in CH [334, 435]. Thirty-nine episodic CH subjects were randomized to receive GONB (methylprednisolone plus lidocaine) or placebo. A stable oral preventive medication was allowed at baseline; in addition, verapamil was started or titrated in subjects still reporting CH attacks one week after GONB. At the end of the 4-week follow-up period, a more pronounced reduction in weekly attack frequency was reported after GONB (−7.7 attacks) compared to placebo (−3.4 attacks). In addition, a higher proportion of participants achieved pain remission after the first and second weeks after GONB. By contrast, the rate of complete remission after 3 and 4 weeks was comparable between GONB and placebo groups, with this finding possibly explained by the planned titration of verapamil, or by the occurrence of spontaneous CH remissions. At the end of the 4-week follow-up, 29 participants (12 in the active GONB group, and 17 in the placebo group) were on verapamil treatment, without difference in daily dose. The ANODYNE trial included an additional 8-week open label phase at the end of the double-blind treatment period. Noteworthy, 5 participants from the placebo group required an additional GONB during the open-label phase, while no subjects from the active GONB performed a second treatment.

Few data are available regarding the duration of pain-freedom and the consistency of response across subsequent GONB [430]. In the open-label study performed by Lambru et al. [436], 83 chronic CH subjects underwent unilateral GONB with methylprednisolone and lidocaine [436]. Noteworthy, a sub-group of participants received up to four quarterly GONB procedures. After the first GONB, a positive response (complete remission, or 50% reduction in attack frequency) was described in 57% of participants, with a median duration of the therapeutic response of 21 days [436]. In addition, around 70% of

patients were pain-free after the third and fourth GONB. These findings support a consistent and reproducible effect of GONB as a preventive treatment for chronic CH.

Regarding safety and tolerability, several evidence suggests that GONB is a safe, well-tolerated, and minimally invasive procedure. The reported adverse events were described as mild and transient, with injection site pain being the most prevalent one. Less frequent adverse events were local numbness, local bleeding, neck stiffness, dizziness, syncope, local alopecia [332–334, 430, 436].

Besides GONB, oral prednisolone as a transitional treatment in episodic CH has been shown to be effective in an RCT [331]. In the absence of any head-to-head RCT comparing oral prednisolone with GONB, it is uncertain which one is superior, or whether both are equally effective. GONB offers the advantage of smaller dose of steroids, minimal systemic side effects and drug interactions. Contrarily, its invasiveness (though minimal) and lack of a standardized protocol, especially defining the timing and frequency of repeat injections in episodic CH and chronic CH patients are considered as disadvantages.

Sphenopalatine ganglion block (SPGb)

Sphenopalatine ganglion block (SPGb) has been tested as acute and preventive treatment for cluster headache. Several technical procedures have been described, ranging from an easy-to-perform local intranasal application of anaesthetic to endoscopically guided drug injection in the pterygopalatine fossa [437]. At state of the art, SPGb is considered by available guidelines as a second-line acute treatment for CH attacks. Specifically, the American Headache Society rated SPGb with a Level C (possible effective) recommendation, while in the European Academy of Neurology guidelines it is considered only for patients with contraindications for triptans [342, 428]. It is worth noting that these recommendations are mainly based on open label studies, case reports, or treatment of experimentally nitroglycerin triggered CH attacks [320, 321, 438].

SPGb has been tested as a preventive treatment for CH as well. In the study by Felisati et al. [439], 20 subjects with drug-resistant chronic CH underwent SPGb with local anaesthetic and steroid under endoscopic control. Eight subjects became pain-free, with the duration of the clinical improvement lasting from 1 to 24 months. Nasal epistaxis and transient diplopia were reported as SPGb-related adverse events. In 2010, the same group performed an uncontrolled trial in 15 drug-resistant CH individuals [440]. SPGb was performed with triamcinolone, bupivacaine, and mepivacaine with adrenaline under endoscopic control. A complete remission was achieved in 8 out 15 participants (54%), with a duration of pain-freedom ranging from 1 to 28 months. SPGb-related adverse events were two cases of severe nasal epistaxis and one case of transient reduced buccal opening [440].

A novel approach is represented by injection of onabotulinumtoxinA toward the sphenopalatine ganglion [441–443]. In the pilot study by Bratbak et al. [441], a single injection of 25 or 50 IU of onabotulinumtoxinA towards the SPG was tested in 10 participants with drug-resistant chronic CH. The procedure was performed via a transnasal approach aided by surgical navigation under general anaesthesia. One serious adverse event was reported, namely a severe epistaxis; in addition, three subjects suffered a transient accommodation disturbance in the ipsilateral eye, while another subject reported reduced buccal opening and masticatory strength. Regarding efficacy, a reduction in CH attack frequency per week was reported up to 6 months after treatment, with the most prominent benefit achieved by 3 months post-treatment. Seven participants were later enrolled in long-term (18 to 24 months) extension study [442]. Five patients repeated the treatment (up to 6 times during the 24-month follow-up) using a novel percutaneous infrazygomatic approach under local anaesthesia. Weekly CH attacks reduced from 14.3 ± 8.9 to 3.1 ± 3.8 and to 6.1 ± 4.8 after 18 and 24 months, respectively. Transient accommodation difficulties, jaw pain, reduced buccal opening and moderate epistaxis were reported by two participants [442].

In the open-label series by Simmonds et al. 31 drug-resistant chronic CH subjects were treated with 25 IU of onabotulinumtoxinA towards the SPG according to the previously described procedure [443]. A total of 206 procedures were considered for a safety analysis. Overall, 63 adverse events were described, with one serious adverse event reported (Hospitalization for facial asymmetry who resolved within 12 weeks). The most prevalent adverse event was intermittent visual disturbance, accounting for 23 out of 63 adverse events, followed by pain at incision site ($n = 11$) and jaw problems ($n = 11$). Two-month effectiveness data were available for 14 chronic CH subjects, for a total of 92 SPGb procedures. Bearing in mind the limitation related to the high lost to follow-up rate, SPGb with onabotulinumtoxinA induced a reduction of 11.1 in weekly CH attacks after the first treatment, with a rate of 50% responder ranging between 53 and 69% during the 4-month follow period.

Cluster headache prognosis

Research on the prognosis of CH is limited compared to that on migraine and tension-type headache. Data on the natural history of CH, including information on morbidity and potential factors influencing the course and response to treatment, come primarily from retrospective

or longitudinal studies. When addressing CH prognosis, different situations must be envisaged, including transition from episodic to chronic pattern, remission, variation in bouts frequency, change in bouts features and, as the worst scenario, patients' suicide. Although evidence is scarce, it seems that the possibility of modification over time is related to the form of CH at onset. According to a pioneering Italian study of Manzoni, the vast majority of those who onset with an episodic form (i.e. 81%) will maintain an episodic pattern; the same figures for those with a chronic pattern is lower (i.e. 52%) but, notably, approximately 33% will revert to an episodic pattern [444]. This information seems to be consistent with a more recent one by Søborg and colleagues who followed up 430 patients with CH over a five-year period: the cumulative risk of pattern change was 19.8% over five years, and it was 25% in terms of becoming episodic from a chronic pattern, and 12.3% in terms of becoming chronic from an episodic pattern [20].

CH prognosis is uncertain, especially when considering chronic CH, for which therapeutic strategies are limited. Factors associated with chronicity in CH are like those observed in other primary headaches, including more frequent attacks and longer periods of remission, longer disease duration, overuse of analgesics, especially opioids, and mental illness [11]. The chronic form of CH is associated with greater disability than other chronic primary headaches [445]. Although men are more frequently affected, women are more resistant to treatment [446]. Conversely, patients with episodic CH have been shown to have a better chance of effective treatment of acute attacks, both with oxygen and sumatriptan, than patients with chronic CH [447]. An important worsening factor for CH prognosis which is significantly associated with treatment resistance is delayed diagnosis and limited access to healthcare resources [264].

Remission rates have been occasionally investigated. As reported in some studies, the rates of remission seem to peak after 3–5 years (e.g. 18.5% after three years [444] and 12% after 4 years [448]. Besides remission, some kind of change in the presentation of attacks or bouts has been observed in terms of frequency reduction over time [10]. There is a lack of studies reflecting long-term prognosis because they do not follow patients over a longer period. Single studies have suggested that some patients experience long-term remission [448, 449]. However, the main methodological limitation of clinical observational studies is that patients usually only seek specialist care when they have active disease. In fact, among patients with active CH, a reduction in bouts duration was observed in 6% of patients [444], whereas this figure increased to 23% is both patients with active disease and remitted patient are included [450]. It has likewise to be noted that it was once observed that between-bouts intervals seem to increase by approximately six months (from 1.4 to 1.9 years) over a 6-year period [450].

Lee et al. analyzed the natural course of untreated CH in a group of 42 patients who were not observed for an average of 7.5 years [238]. It was shown that the clinical features of CH—side-locked unilaterality, autonomic symptoms, and seasonal and circadian rhythmicity—become less prominent over time. Remission, defined as symptom-free (1) for longer than twice the longest between-bout period and (2) for ≥ 5 years, occurred independently of age. Advanced age was not a predictor of remission, while patients in remission have a trend toward less prominent circadian and circannual rhythmicity at baseline, fewer lifetime bouts and shorter disease durations [238].

Last, suicide has historically been considered as common in patients with CH, to the point that CH has also been defined as "suicide headache". This might be due to first descriptions of this condition but also to the relevant comorbidity with depression: in fact, patients with CH show an almost 3 times increased odds of lifetime depression compared to those without CH [249]. However, suicide events are not commonly reported, at least in contemporary periods, whereas suicidal ideation is common. A large US study reported suicidal ideation in 55% of the sample and suicide attempts in 2% [37]. This study, however, did not distinguish between passive suicidal ideation (i.e. have you thought that it was better to die?) and active suicidal ideation (i.e. have you thought of killing yourself?), which was instead addressed by Ji Lee and colleagues [451]. Passive and active suicidal ideation was reported by 64.2% and 35.8% of patients during attacks and by 4.0% and 3.5% of patients in interictal phases; suicide attempts were instead reported by 2.3% and 1.2% of patients during the attacks and in interictal phases, respectively. Last, a study by Koo and colleagues compared a group of patients with CH against a group of age and gender-matched controls for suicidal ideation and lifetime suicidal planning and attempts [452]. They found that passive and active suicidal ideation was more common among patients (59% and 47%) than among controls (34.8% and 26.7%), whereas both lifetime suicidal planning and lifetime suicide attempts were not significantly more common in patients (25% and 8%) than in controls (15.6% and 6.7%).

In conclusion, knowledge of CH prognosis is scarce, probably because most of the research carried out so far has focused on understanding the mechanisms of CH and attempting to find new therapeutic strategies. CH, especially the chronic and treatment-resistant form, generally has an uncertain prognosis, but some kind of partial improvements have been observed: reversing to an episodic pattern in up to 33% of patients; remission in

bouts duration in up to 23% of patients and increase in between-bouts interval time.

Negative prognosis also exists. In fact, most patients will show a stable pattern, and the risk of suicide is to be seriously taken into consideration: in fact, suicidal ideation might involve up to 60% of patients, and suicidal attempts 2–7% of patients.

Therefore, a lot of questions remain unanswered on CH disease course and prognosis, in particular the implications of changes in CH attacks' frequency and severity as factors that might predict CH remission. Long-term cohort studies are needed which follow populations of different ages and with different disease courses, to better address prognosis of CH. Also, an effort to maintain patients in cohort studies for a long period of time is of importance, to avoid losing information on those patients who dropped out likely because they improved.

Definition and management of refractory cluster headache (rCCH)

rCCH refers to chronic CH that remains disabling and frequent despite adequate trials of evidence-based, standard recommendation at recommended dose and duration. The burden of refractory cases is markedly high, rCCH patients frequently experience significant impairments, including restrictions in daily functioning, sleep disruption, and comorbid depression [453]. The exact prevalence of rCCH remains unclear. A recent multicenter study found that over two-thirds (68.2%) of chronic CH patients met criteria for refractoriness, with 60.2% experiencing high disease activity despite treatment [8].

Similar to refractory migraine, refractory cluster headache is not formally defined in the International Classification of Headache Disorders, 3rd edition (ICHD-3) [1], emphasizing a gap in standardized diagnostic framework for treatment-resistant cases. The definition of rCCHis pivotal for both clinical management and research, ensuring that patients receiving advanced or invasive therapies are genuinely resistant to standard treatments.

Table 5 European headache federation (EHF) diagnostic criteria for rCCH

A	**Headache attacks fulfilling the ICHD-3 beta criteria for chronic CH, or probable CH and B-E criteria.**
B	At least three severe CH attacks per week that impact patients' quality of life despite preventive or symptomatic treatment
C	Failed consecutive prophylactic treatment trials with at least three agents that showed efficacy over placebo in randomized controlled studies, used at the maximum tolerated dose over a sufficient period of time
D	Symptomatic chronic CH is ruled out by negative investigation with brain MRI and MRA, eventually supplemented with carotid CT angiograms or triplex carotid ultrasound
E	Not better accounted for by another ICHD-3 beta diagnosis

Standard preventives like verapamil, lithium, and topiramate often failed, leading many patients to rely on off-label therapies [412]. Among advanced treatments, onabotulinumtoxinA and ONS showed the most consistent benefit, offering hope for this highly disabled population. Early recognition and specialized care may help improve outcome.

Consensus diagnostic criteria for rCCH

Although the ICHD-3, does not formally recognize rCCH as a distinct diagnostic entity, it provides diagnostic criteria for chronic CH, which is defined by attacks fulfilling the criteria for cluster headache that occur for at least one year without remission, or with remissions lasting less than three months [1, 454]. Thus, in the case of CCH the characteristic bouts of episodic cluster headache are missing.

In 2014, the consensus statement by the European Headache Federation provides the first formal clinical definition of rCCH, bring attention to a critical gap in the classification of patients with chronic CH who fail to respond to standard preventive therapies [455]. These criteria require at least three severe CH attacks per week despite at least three consecutive trials of adequate preventive treatments have been tested (Table 5). To note, treatments that showed efficacy over placebo in RCTs for chronic CH include verapamil, lithium, oral or iv steroids, GONB, topiramate, methysergide, ergots, civamide and long acting triptans. Among them verapamil has better documentation. Interestingly, some medicines may be not available across all European countries. However, the criteria, particularly regarding treatment resistance, must remain adaptable to emerging therapeutic advances, especially when the CGRP monoclonal antibodies gain validation for cluster headache prevention in the market.

Management for rCCH

Once a patient is diagnosed with rCCH—clinicians must consider alternative therapeutic options beyond standard pharmacological therapy [342]. These include warfarin, psilocybin, intravenous dihydroergotamine, galcanezumab and onabotulinumtoxin A, along other options. However, most patients with rCCH will need to try neuromodulation approaches.

Warfarin showed good efficacy (number needed to treat of 2.6) in a randomized, crossover, placebo-controlled trial [456]. Warfarin also significantly reduced attack frequency, duration, and intensity. Although the exact mechanism remains unclear, proposed actions include modulation of neurogenic inflammation and hypothalamic pathways. While the only RCT to date showed a non-significant reduction in attack frequency [386], small open-label and extension studies reported significant improvements with psilocybin, with 30–50%

reductions in attacks and prolonged remission [387]. Though early evidence is promising, larger trials are needed to confirm efficacy and guide safe, targeted use in this difficult-to-treat population. Retrospective data indicate that intravenous DHE may be effective for rCCH, particularly the episodic form [362]. DHE acted rapidly and was generally well tolerated, with few adverse events. Galcanezumab, a CGRP-targeting monoclonal antibody, has shown efficacy in one RCT for episodic CH but not conclusively in chronic CH [457]. However, real-world data suggest potential benefit of high doses of galcanezumab (240-360 mg monthly) in refractory CH cases and should be included in the armamentarium for rCCH [458–460]. Observational, real-world studies have provided evidence for the efficacy of onabotulinumtoxinA in rCCH, which was administered according to the PREEMPT [461]. Whether cannabinoids are helpful or not in rCCH remains debatable [462]. Because PACAP is expressed with the parasympathetic system, treatments targeting the PACAP signaling may be effective in cases of rCCH, but this remain to be proven in clinical tests [463]. Ketogenic diet has been reported to help patients with rCCH as well [412].

The field of neuromodulation is emerging as a promising and alternative therapeutical option for rCCH, offering relief when other treatments have failed. Neuromodulation includes invasive and non-invasive techniques targeting either central or peripheral parts of the cephalic nervous system including autonomic circuits that are involved in CH, particularly abnormal activity in the posterior hypothalamus and trigeminal-autonomic pathways [412]. A recent meta-analysis found that among invasive neuromodulation techniques for rCCH, ONS was the most studied with a pooled response rate of approximately ~57%. The highest pooled response (77%) was obtained by hypothalamic DBS which was the second most frequent technique tested for rCCH. DBS data were more heterogeneous than ONS, since the stimulation targets differ in the studies included in the analysis. Furthermore, DBS studies reported more serious adverse events than in ONS studies [412]. In a 9-year follow-up study invasive occipital nerve stimulation (iONS) provided sustained relief in rCCH with a 70% average reduction in attack frequency and 40% of patients shifting to an episodic form. However, 33% required device removal due to complications, and all patients needed additional surgeries [464]. Other neuromodulation techniques include serial GONB, sphenopalatine ganglion radiofrequency or stimulation, vagus nerve stimulation, percutaneous bioelectric current stimulation and upper cervical cord stimulation [412]. Overall, noninvasive and peripheral neuromodulation (e.g. vagus nerve or sphenopalatine ganglion stimulation) have lower-level evidence for rCCH.

Cluster headache in children and adolescents

Epidemiology and clinical features

The epidemiology of CH in children and adolescents is limited by the lack of large population studies. Changeableness of headache phenotypes across the developmental age and verbal limitations of children to describe subtle clinical features required for diagnosis represent other obstacles [465]. Furthermore, a variable number of cases exhibit migraine-like features, which can pose a diagnostic challenge for those lacking experience [466, 467].

In a nationwide sample of 5,671 children aged from 5 to 12 years old, the prevalence of children with headache attacks characterized by severe unilateral fronto-orbital pain, lasting from 15 to 180 min and not fulfilling criteria for migraine and/or tension-type headache, was 2.1%. Among them, there were no cases with parents reporting prominent cranial parasympathetic autonomic features accompanying the attacks [468]. The prevalence CH in paediatric age is only available from clinical samples of tertiary care centers specialized in headache in youth and retrospective clinical studies of adults with CH, both potentially influenced by selection and recall bias. In a multicenter study with 6,629 children and adolescents attending 27 headache centers in Italy, only two cases of CH were diagnosed in one year (0.03% of the total cases) [469]. In retrospective clinical studies of adults with CH, the prevalence rate of childhood-onset disease ranges from 5 to 27.5% [465, 470, 471]. The peak age of onset of the episodic CH is from 15 to 18 years of age [465, 472], while, curiously, the chronic subtype can start as early as 1 year of age [472]. According to a recent systematic review and meta-analysis, the 1.8 sex ratio of childhood-onset CH [467] is lower than that (4.3) of adult-onset CH [5], although a decreasing trend of the male predominance has been reported over the last ten years [37, 276].

The study of headaches peculiarities at developmental age is a unique opportunity to deeper understand neurobiological, clinical, and evolutionary aspects of headache disorders with potentially impacts on therapeutic interventions. Due to its rarity in childhood, identifying peculiarities of CH is challenging. However, a number of peculiarities of CH in children has been reported in case series, systematic reviews and meta-analysis, including: (a) less numerous attacks during a given bout [467, 473, 474]; (b) less frequent and shorter cluster periods [467, 473, 474]; (c) the presence of pain-free intervals lasting several days within the cluster period [474, 475]; (d) less pronounced ipsilateral autonomic manifestations and associated restlessness behaviour during the attacks [467]; (e) more prototypical migrainous features (photophobia, phonophobia, pain aggravated by physical activity, nausea, and vomiting) [1], and co-occurrent diagnosis of migraine [470]; and (f) a favourable response

to indomethacin treatment [466, 474, 476–478]. Conflicting findings predominantly come from retrospective studies of CH in adults reporting more similarities than possible peculiarities of CH in childhood. Among these, the circannual periodicity of attacks, the circadian rhythm of attacks, the equal proportion of migraine-like features, and the complete ipsilateral cranial autonomic signs deserve to be mentioned [467, 472].

Despite the overlapping characteristics of CH and migraine in children, as well as some similar features of CH and other trigeminal autonomic cephalalgias, the idiosyncratic headache pattern of CH tends to emerge and helps the clinician in the correct diagnosis. However, secondary causes must be carefully ruled out by appropriate investigation, especially intracranial neoplasms (e.g., prolactinoma, hypothalamic pilocytic astrocytoma) and rhinosinusitis, in addition to other less reported causes as cerebrovascular diseases, head and neck trauma, optic neuritis, and Graves' disease [470].

Therapy

As for other primary headaches, the therapy of CH in youth derives from what is currently used in adult CH patients. Usually, CH treatments are divided in three types (acute, preventive, and transitional) based on the intervention timing.

Acute treatments

Inhalation of 100% oxygen at a dose of 7–12 L/min for 15 to 30 min through a non-breathing mask, commonly considered as the most effective acute treatment, is particularly suitable for children and adolescents due to the lack of adverse effects [342, 479, 480]. Subcutaneous sumatriptan proved scarcely useful when used in paediatric patients [470, 474]. On the contrary, triptans administered as nasal spray (sumatriptan and zolmitriptan) have some evidence of efficacy [477]. Some retrospective studies reported the use of non-recommended drugs, such as NSAIDs, acetaminophen, rizatriptan, and oral sumatriptan [470, 477]. Notably, the results with these therapies are generally poor.

Preventive treatments

Verapamil, topiramate, and melatonin may be useful for CH prevention in youth [18]. Verapamil can be titrated until the target dose of 3–10 mg/kg/day, monitoring the electrocardiogram P-R interval. It is considered as the most effective drug for CH prevention in children and adolescents [470]. Hypotension, fatigue, bradycardia, and atrio-ventricular block are the main side effects. Topiramate has lower evidence of efficacy, compared to verapamil [470]. In paediatric age, it is used at the dose of 1–2 mg/kg/day. Decreased serum bicarbonate, hyperammonaemia, dizziness, and Weight loss are the main side effects. In the literature, lithium was used only in 3 Young patients, among whom only one 13-year-old boy had a positive outcome. Melatonin, whose use in youth should be considered due to the lack of serious adverse events, has no solid evidence of efficacy in children and adolescents [478]. The dose to be used is of 0.1–0.2 mg/kg/day. The use of valproate, gabapentin, indomethacin, propranolol, methysergide, and pizotifen has been anecdotally reported in the literature [470, 477, 478, 481–483].

Transitional treatment

Transitional therapies are started along with preventive medications and should lead to a quick improvement, before the preventive drugs may become effective, which may take days or weeks [342]. The typical transitional medication is represented by corticosteroids whose use for short periods has been suggested in children [484]. Indeed, there are case series showing both efficacy and safety of oral and intravenous prednisone [478, 482, 485]. The commonly used dose of oral prednisone is 1–2 mg/Kg/day.

GONB has not been studied adequately in Young CH patients. Unilateral injection with 30 mg of 1% Lidocaine and 40 mg of methylprednisolone has been shown effective on both intensity and frequency of the attacks in 3 adolescents with CH [486].

Other recommendations

CH has been found associated to tobacco exposure also in paediatric patients [372, 472]. Therefore, smoking cessation in the household is recommendable. Alcohol and recreational drugs might trigger the attacks; thus, they should be avoided. In conclusion, educational therapy regarding alcohol, tobacco and substance abuse should be an important part of CH treatment in adolescents.

CH in pregnancy and lactation

Compared to migraine, CH is a relatively uncommon condition primarily affecting males. Consequently, there is less knowledge regarding its epidemiology during pregnancy and breastfeeding. Bouts of CH are rare during pregnancy. This is attributable to various potential factors. In the reproductive years, specifically under the age of 50, the male-to-female ratio is 7.2:1 for episodic CH and 11:1 for chronic CH [487]; these ratios become lower after the age of 50. Moreover, data indicates relative hypofertility in women with CH [29, 488], particularly when the disease begins prior to the first pregnancy [489]. Women who suffer their initial attack prior to their first pregnancy typically have fewer offspring than those who were already mothers at the time of clinical onset [488, 489]. In a particular study, almost 60% of female patients diagnosed with CH remained childless. Of these women, 8% expressed concern that the attacks would

hinder their ability to care for a child, while 4% feared transmitting the disorder [37].

Burish et al. [490] conducted a retrospective study in which CH patients were interviewed about their experiences of similar pain, in order to compare them with CH attack pain. Labour pain (childbirth), pancreatitis and nephrolithiasis were then examined; the pain experienced during CH attacks was found to have an average value of 9.7 on a numerical rating scale from 0 to 10. This was significantly higher than the score of 7.2 found for labour pain [490]. Sharaf & Ali [491] reported two patients who experienced both CH and labour pain in rapid succession. Both patients articulated their preference for labour pain over the pain associated with CH.

The data are inconclusive about whether CH improves throughout pregnancy or remains stable, and most research is constrained by restricted sample sizes and retrospective methodologies. A survey of 249 individuals with CH revealed that 34 were female, of whom only eight had experienced pregnancy since the onset of CH; six of these eight reported a remission of clusters during pregnancy [488]. A retrospective questionnaire-based investigation was undertaken involving 196 women with CH, compared to migraine sufferers and healthy controls. Among the women with CH, 143 patients who had undergone at least one pregnancy experienced their initial CH attacks postpartum; only 19 of these patients indicated experiencing CH attacks during pregnancy, and the majority did not report an escalation in the severity or frequency of these attacks relative to those occurring outside of pregnancy [489]. Out of 111 patients with episodic CH who had been pregnant, 23% stated that a "predicted" cluster phase did not manifest during pregnancy. In eight cases, the cluster phase commenced within one month of delivery. Bahra et al. [18] showed that merely 5% of women with CH experienced attacks during pregnancy, and their seasonal pattern altered at conception, meaning that anticipated attacks did not occur. Manzoni and colleagues [29] reported that CH was unaffected by menstruation, pregnancy, and the postpartum period in 82 patients.

Certain therapeutic recommendations and clinical studies concentrate explicitly on TACs in the context of pregnancy and lactation [482, 492–494].

In the context of pregnancy and lactation, high-flow oxygen therapy at 100% administered using a non-rebreather mask, subcutaneous sumatriptan or nasal spray, and zolmitriptan nasal spray should be employed with caution and under medical supervision as the primary acute interventions [492]. These medications do not seem to elevate the risk of congenital anomalies in babies, and sumatriptan appears to be safe for use during nursing [482]. Evidence supporting the efficacy of intranasal lidocaine and transcutaneous vagal nerve stimulation is limited. In the absence of comprehensive research, verapamil and short-term oral prednisone/occipital nerve block are regarded as likely safe during pregnancy and nursing, as they do not elevate the teratogenic risk to the foetus [495, 496]. Steroids can elicit moderate and transitory reduction of adrenocortical function in the baby only when taken during late pregnancy [497]. Particular attention must be directed towards patients administered high dosages of verapamil, as it is detectable in breast milk; however, it is improbable to induce harmful effects in breastfed newborns [497]. Lithium medication is contraindicated during pregnancy and nursing due to potential foetal and maternal problems. Generally, the same contraindications are applicable to topiramate and valproate, although they are deemed compatible with breastfeeding healthy full-term infants post-neonatal period [498, 499]. There is no conclusive evidence endorsing the use of galcanezumab during pregnancy and lactation. Coupled with the fact that immunoglobulins can cross the placental barrier, the technical drug data sheet states that galcanezumab administration is contraindicated during pregnancy [500].

In summary, CH attacks during pregnancy are infrequent; however, when they manifest, they typically retain their original characteristics and severity. Although some women may observe a modification in the seasonal rhythm of their CH during pregnancy, many do not. Options for treating CH during pregnancy are restricted due to safety concerns associated with drugs, making management of these headaches difficult.

The crossroad between CH and other primary headaches

Primary headache disorders are characterized by the absence of underlying cranial or cerebral lesions that could explain the pain, distinguishing them from secondary headaches [501]. However, this lack of structural pathology does not imply a shared pathophysiological mechanism. While all primary headaches ultimately activate central nociceptive networks - particularly within the trigeminovascular and brainstem systems, the initiating mechanisms vary substantially.

Most disorders in the 'other primary headaches' category [502] are rare and fall into distinct groups, some with overlapping mechanisms. Hypnic headache (HH) [503] and CH share a circadian pattern and nocturnal onset, suggesting hypothalamic dysfunction as a common pathophysiological mechanism. Imaging studies show reduced posterior hypothalamic volume in HH, like CH, supporting the role of a disrupted circadian pacemaker. Despite shared chronobiological features, the clinical presentation is quite distinct, and reports of overlap between the two disorders are scarce.

Exertional headaches [502], such as sexual, exercise, cough, and primary thunderclap headaches, are linked to impaired cerebrovascular autoregulation or transient venous pressure changes. Epicranial headaches, including primary stabbing headache, epicrania fugax, and nummular headache, are thought to arise from hyperexcitability or dysfunction of terminal pericranial nerve branches, though central mechanisms involving the trigemino-cervical and trigemino-parasympathetic reflexes may also contribute. Peripheral sensitization of myofascial nociceptors and central sensitization at spinal and supraspinal levels are also key mechanisms in tension-type headache [504], a very common primary headache. Despite its prevalence, tension-type headache shares little clinical or pathophysiological overlap with CH, and comorbidity between the two is not reported.

In contrast to the abovementioned primary headaches, cluster headache shares similarities with TACs, particularly in their stereotyped lateralization, prominent cranial autonomic features, hypothalamic activation and neuroanatomical substrates, and in response to overlapping pharmacological treatments and/or neuromodulation. While the overlap with other TACs is common and significant, it will be addressed separately. In the next paragraphs we will focus on the clinical, pathophysiological, and therapeutic intersections between cluster headache and migraine, emphasizing points of convergence relevant to clinical practice.

Epidemiology and clinical characteristics

In early medical literature, both migraine and what is now recognized as CH were classified as 'vascular headaches', based on the belief that cerebral vasodilation was the primary driver of pain. CH was initially considered a migraine variant, with its severe, unilateral pain attributed to distension of cephalic vessels. This view began to change in 1939 when Horton and colleagues described the condition as 'histaminic cephalalgia', identifying its unique clinical profile. By 1952, Horton had further characterized its cyclical nature and response to vasodilators, laying the groundwork for CH to be recognized as a distinct syndrome [505]. Still, due to its rarity, CH remained underrecognized for years and was often referred to as 'cluster migraine' [506].

The differences between the two disorders are evident in their prevalence: migraine affects about 14% of the global population, while cluster headache is much rarer, affecting around 0.1%. Both typically start between the ages of 20 and 30, but the gender ratio differs: cluster headache is more common in men (4:1), while migraine is more common in women (1:3).

Migraine and CH are polygenic and multifactorial, with both showing a positive family history. CH family history varies from 0 to 22%, while migraine familial risk is 35%–60% [507]. First-degree relatives of CH patients have a 5 to18 times higher risk, compared to 1.5 to4 times higher for migraine. Monozygotic twin concordance is 5.4% for CH, and 36–48% for migraine [50, 508, 509]. Furthermore, comorbid migraine is present in 10-16.7% of CH patients [510].

The duration of attacks also differs, with migraine attacks lasting 4 to 72 h, while CH attacks last 15 to 180 min. Although pain is Often localized to the ophthalmic nerve territory in both conditions, in CH, the most intense pain is typically found in the orbital, supraorbital, or temporal regions, whereas migraine pain can occur anywhere on the head. Migraine is unilateral in approximately 55–67% [511, 512] of cases, while CH is almost always unilateral [465], with nearly 100% of cases being 'side-locked' - consistently affecting the same side. Interestingly, although side-locked headaches are rare in migraine, they occur in about 26% of patients [513]. Pain intensity is typically higher in CH, with one Hospital-based study reporting a mean VAS score of 9.0 for trigeminal autonomic cephalalgias (mostly CH) and 7.0 for migraine [514]. Another key difference is in behavior during attacks: migraine patients tend to avoid movement, as physical activity worsens the pain, whereas CH patients often exhibit restlessness.

CAS are a hallmark of cluster headache but are also observed in migraine. At least one CAS has been reported in 26–74% of migraine patients, with an average of two symptoms per patient [515, 516]—about half the number typically seen in CH [517]. The most reported CAS in both conditions include lacrimation, nasal congestion, and conjunctival injection [465, 515, 516]. Interestingly, migraine patients who experience CAS tend to have more severe and strict unilateral pain, echoing features of CH [515]. Conversely, symptoms traditionally associated with migraine, such as photophobia, phonophobia, and aura, have also been observed in CH. One study reported photophobia or phonophobia in about 50% of CH patients [465], and another found rates of approximately 90% during a cluster period and 50% outside of it [518]. Nausea and vomiting have also been reported in 28% of CH cases [465].

Both migraine and CH are episodic disorders with pain-free intervals. However, CH derives its name from the typical 'cluster periods' or bouts, during which attacks occur daily for weeks or months, followed by a pain-free remission phase. In contrast, migraine attacks typically occur throughout the year without a clearly defined pattern of bouts. Timing also differs: CH attacks are most frequent between 2:00 and 4:00 AM and are more common from September to November [31], whereas migraine attacks are most frequent in the early morning [519].

Both conditions have identifiable triggers. Common migraine triggers include stress, sleep disturbance, and emotional factors [520], while the most frequent CH triggers during a bout are alcohol and stress [31]. Alcohol is also a trigger for migraine, but it is a much more potent trigger for CH (during a bout) than for migraine.

The overlapping biology: current view of shared mechanisms

GWAS for migraine identified 123 risk loci [71], providing more extensive data compared to the 9 loci identified for CH [15]. Migraine risk loci span a broad range of tissues—cardiovascular, cerebrovascular, neuronal, digestive, and ovarian—with recently identified variants linked to therapeutic targets such as CGRP and serotonin receptors [71]. CH loci are primarily associated with brain and arterial tissues; three of them (FHL5, PLCE1, and LRP1) overlap between migraine and CH, being implicated in vascular smooth muscle function, signal transduction, and immune response. Notably, effect sizes for these loci were greater in CH, suggesting stronger or more specific genetic contributions than to migraine [15]. CH is genetically associated with smoking, ADHD, depression, and musculoskeletal pain [15], whereas migraine is linked to a broader spectrum of comorbidities, including psychiatric disorders, cerebrocardiovascular diseases (stroke, hypertension, coronary artery disease, fibromuscular dysplasia), metabolic conditions (type 2 diabetes, hyperlipidemia), autoimmune and respiratory diseases, endometriosis and sleep disorders [71].

The hypothalamus is a critical hub in the pathophysiology of both migraine and CH, with neuroimaging studies demonstrating both overlapping and distinct patterns of hypothalamic involvement in each disorder. In migraine, the hypothalamus shows sustained activation during both the prodromal and ictal phases, suggesting a role in initiating attacks and potentially mediating prodromal symptoms. Conversely, in CH, increased posterior hypothalamic activity is consistently observed during the ictal phase, with recent findings even indicating its activation during remission in response to trigeminonociceptive stimuli, implying a persistent state of sensitization. Both disorders exhibit anterior hypothalamic activation in chronic forms and involve abnormalities in multisensory processing regions, yet CH patients show unique bilateral hypothalamic enlargement and increased functional activity in cognitive brain networks compared to migraine [517, 521, 522].

A supervised machine learning approach identified hypothalamus and PAG connectivity as key MRI patterns distinguishing migraine and CH from controls. The best marker differentiating the two disorders was reduced functional connectivity between the left thalamus and parietal regions (precuneus, angular gyrus) in CH, possibly reflecting altered processing of internal sensory signals linked to agitation and restlessness [521].

The hypothalamus modulates trigeminal pain processing via functional connections with the TNC, PAG, and higher-order cortical regions, including the PFC and anterior cingulate cortex [522]. Beyond its role in pain processing, it is the central integrator of environmental, sensory, and peripheral inputs, having extensive bidirectional connections with behavioral, autonomic, and endocrine systems; it regulates homeostasis, circadian rhythms, stress responses, feeding, thermoregulation, and energy balance [523].

Functionally, the hypothalamus is anatomically compartmentalized. The posterior hypothalamus, implicated in the modulation of descending pain pathways, maintains reciprocal connectivity with key trigeminal nociceptive regions [522]. The hypothalamic SCN is the master circadian pacemaker and may be involved in chronobiological factors central to both CH and migraine. In CH, robust but individually variable circadian and circannual patterns are observed, with genetic associations involving core clock genes like CLOCK, REV-ERBα, and CRY1. Treatments such as melatonin, corticosteroids, and lithium target circadian regulatory mechanisms, and verapamil alter circadian gene expression in animal studies. Similarly, around 50% of migraine patients report circadian attack patterns, typically peaking in the late morning. While circannual trends are weaker, genetic links include CK1δ, RORα and, to a lesser extent, CLOCK. Migraine is influenced by zeitgebers -external cues such as light, physical activity, meal timing, and sleep-wake changes, all of which can act as attack triggers [35].

Sleep has a strong but complex association with the clinical features of CH and migraine, both showing a high prevalence of sleep disturbances. Hypothalamic circadian entrainment to light is mediated by PACAP-containing retinal ganglion cells projecting to the SCN, a pathway increasingly implicated in headache pathophysiology. Peripheral PACAP reliably triggers migraine and CH attacks, and anti-PACAP monoclonal antibodies are now in clinical trials as preventive therapies [98, 524].

Additionally, other common triggers like stress responses may also be mediated through hypothalamic mechanisms, as the anterior hypothalamus contains corticotropin-releasing hormone (CRH)–secreting neurons, central to the hypothalamic-pituitary-adrenal (HPA) axis and stress regulation, including pain-related responses [522]. The lateral hypothalamus houses orexin-producing neurons, classically linked to arousal and energy homeostasis.

Additionally, sexually dimorphic circuits within the hypothalamus influence reproductive behavior and energy regulation in a sex-specific manner [523]. While migraine is more common in women and clearly

influenced by fluctuations in female sex hormones, CH tends to affect men more frequently, though both conditions show hormonal involvement. In CH, low testosterone levels (observed in both sexes) may play a role, possibly linked to disrupted REM sleep. Hormonal interventions like contraception or estrogenic therapy can modulate migraine severity, while testosterone supplementation has shown potential in reducing CH attacks, suggesting that sexual hormonal balance may be a shared, though differently expressed, factor in both disorders [525].

Other hormonal patterns differ between migraine and CH, like melatonin and cortisol. Recently, glial-derived neurosteroids have been shown to modulate neuronal excitability and influence the course of both disorders. These effects may be genetically driven or triggered by stressors, potentially explaining attack triggers and shared comorbidities [526].

The cellular heterogeneity of the hypothalamus is notable. Peptidergic neurons vary by neurotransmitter expression: some neuropeptides, such as oxytocin, are predominantly found in glutamatergic neurons, while others like neuropeptide Y localize to GABAergic populations. Pain modulation and autonomic control are further shaped by serotonergic and melanin-concentrating hormone (MCH) pathways. Glial cells (astrocytes, microglia, and ependymal cells) play active regulatory roles, contributing to circadian rhythm generation, neuroendocrine signalling, metabolic sensing, and social and reproductive behaviours [523].

Beyond the hypothalamus, CH and migraine pathophysiology also involve the trigeminovascular system and the trigeminal-autonomic reflex. Activation of the trigeminovascular system leads to the release of neuropeptides like CGRP, substance P, and neurokinin A. This system engages parasympathetic pathways via the sphenopalatine ganglion, releasing vasoactive mediators such as NO, VIP, CGRP, and PACAP-38, which likely contribute to pain and autonomic symptoms in both migraine and CH, albeit with distinct expression patterns [527]. These peptides and others have been investigated as biomarkers. While elevated levels of CGRP and serotonin are consistently observed in migraine, no significant differences in blood levels of CGRP, PACAP-38, or substance P have been found between migraine and cluster headache patients during ictal or interictal phases [528]. Human provocation studies further support shared mechanisms, as agents like histamine, nitroglycerin, sildenafil, CGRP, PACAP-38, and VIP can induce attacks in both conditions, despite variable response consistency and latency [527]. Although no direct comparisons have been made, the group at the Danish Headache Center has reported that CGRP induced migraine in 65% of patients [529], whereas it induced attacks in 89% of patients with episodic CH during a bout and 50% of those with chronic CH [85]. PACAP38 induced migraine in 58% of patients [530], and induced attacks in 43% of patients with episodic CH during a bout and 47% with chronic CH [97]. Interestingly, neither CGRP nor PACAP38 induced CH attacks in patients outside of bout periods [85, 97]. The time to onset of migraine attacks was longer than that of CH attacks [517] possibly suggesting the difference in cascade from CGRP/PACAP-38 to pain in two diseases.

Similarities and differences in treatment options

Modulation of the serotonergic system has proven effective as an acute treatment strategy for both migraine and CH, primarily via triptans, which act as 5-HT_1B/1D receptor agonists. While oral triptans are commonly used for migraine, they are usually ineffective for cluster headache, which typically requires subcutaneous injection. Interestingly, while 100% oxygen inhalation remains a mainstay of CH attack management, emerging evidence suggests that up to 46% of migraine patients may also derive benefit. The proposed mechanism involves oxygen-induced hyperoxia, which may inhibit dural plasma protein extravasation and modulate neuropeptide release within the trigemino-autonomic reflex arc. This overlap suggests shared downstream pathways in both disorders, particularly involving the trigeminal-autonomic system [517, 527].

In contrast, prophylactic treatments show more condition-specific responses. Agents such as topiramate, valproic acid, and CGRP pathway inhibitors clearly demonstrate superior efficacy in migraine prevention. Conversely, verapamil, steroids and melatonin are more reliably effective in CH. Interventional therapies further highlight this divergence: GONB, SPG interventions, and ONS show benefit primarily in CH, transcranial magnetic and supraorbital stimulation in migraine, whereas noninvasive VNS appears to have therapeutic value in both conditions. These findings underscore both the overlapping and distinct neurobiological mechanisms underlying migraine and CH, with implications for individualized treatment strategies [517, 527]. CGRP monoclonal antibodies are widely used for migraine prevention, and galcanezumab has been approved by the FDA for the treatment of episodic CH. As of 2025, clinical trials of PACAP monoclonal antibodies for migraine have been conducted [100], but no such trials had yet been conducted for CH.

The subtle overlapping of TACs and other orofacial pain conditions

Despite being considered distinct disorders, emerging clinical and radiological evidence supports a broader nosographic concept of SUNCT, SUNA, and trigeminal neuralgia, involving common neurobiological mechanisms

[531]. These syndromes may co-exist or switch from one type to another in the same patient, thus suggesting a possible pathophysiological relationship [532–534]. Trigeminal neuralgia, traditionally called tic douloureux, is a neuropathic facial pain condition characterized by spontaneous and elicited paroxysms of electric shock–like or stabbing pain in the distribution territory of one or more trigeminal division. The pain in trigeminal neuralgia most frequently affects the distribution of the second (maxillary) or third (mandibular) division of the trigeminal nerve, with the right side of the face affected more often than the left side [535]. Trigeminal neuralgia exhibits a remarkable clinical overlap with SUNCT and SUNA, including the neuralgiform character of the pain, short duration, high daily frequency of attacks and presence of trigger factors: moreover, the presence of trigger factors, considered the hallmark sign of trigeminal neuralgia [536], was reported in up 80% of patients with SUNCT [537, 538]. The characteristics distinguishing SUNCT from trigeminal neuralgia, such as the primary involvement of the ophthalmic division, the presence of pronounced CAS, the absence of a refractory period following paroxysmal attacks and the absence of a background pain between the paroxysmal attacks, seem to suggest a continuum of symptoms rather than neurobiological differences [531].

In a large, published SUNA series, a high proportion of patients reported pain in V2 and V3, the most frequently affected divisions in trigeminal neuralgia, thus supporting the hypothesis of continuum with this facial pain condition [539].

Trigeminal neuralgia is typically characterized by remission periods, lasting from weeks to years. Similarly, remission periods lasting for several months have been also described in SUNCT [540].

Triggered paroxysmal pain in trigeminal neuralgia is usually followed by a refractory period. Refractory periods have rarely been reported in TACs. The lack of refractory periods in SUNCT and SUNA should be explained by a central disinhibition of the trigeminal nucleus caudalis [541].

Trigeminal neuralgia is characterized by electric shock-like sensation lasting from fraction of second up to 2 min. The cutoff at 2 min has not been thoroughly validated but is based on patient reports. Patients may report multiple overlapping attacks that may feel as one longer attack; this phenomenon, however, seems to be an unlikely occurrence in the presence of a refractory period. It has been suggested that patients with paroxysmal attacks of long duration may form part of a spectrum with SUNCT and SUNA [541].

Autonomic symptoms, key signs of SUNCT and SUNA, are reported from 31 to 67% of patients with a definite diagnosis of trigeminal neuralgia [542, 543]. This observation raises the possibility that the different degree in cranial autonomic activation, possibly related to the different duration of attacks, may reflect a different degree of involvement of similar pathophysiological mechanisms between these conditions [531]. These symptoms are considered mediated by a parasympathetic reflex via trigeminal nerve activation, the trigemino-parasympathetic reflex. In SUNCT and SUNA, the activation of trigemino-parasympathetic reflex also involves the activation of the posterior hypothalamus. A similar brain area seems to be activated in patients with classical trigeminal neuralgia [544].

The partial overlap among these facial pain conditions is also supported by the evidence of patients with trigeminal neuralgia and concomitant continuous pain reporting a higher occurrence of CAS, less frequent cutaneous trigger, waking from sleep and poor response to both pharmacologic and surgical treatments [541, 545].

Nocturnal attacks are common in TACs and are considered not typical of trigeminal neuralgia. Pain-related awakening has been described in a significantly higher proportion of patients with trigeminal neuralgia with long attack duration than in those with short attacks [546].

Although the majority of SUNCT forms are idiopathic, secondary forms related to posterior fossa abnormalities have been described [537]. In addition, neurovascular compression, the recognized etiological factor of classical trigeminal neuralgia, was detected in 88% of patients with SUNA/SUNCT [547]. These data, requiring confirmation in a larger sample of patients, seem to support an aetiological overlap between SUNA/SUNCT and trigeminal neuralgia.

Partial overlaps are also recognized in the pharmacological and surgical treatment options of these forms of facial pain. Lamotrigine, the preventive treatment of SUNA/SUNCT, is recommended as second-line treatment in patients with trigeminal neuralgia, when carbamazepine and oxcarbazepine are ineffective or contraindicated [548]. In addition, emerging evidence supports the efficacy of oxcarbazepine in the treatment of SUNCT [549, 550]. Regarding the surgical strategy, microvascular decompression, the recommended surgical option in classical trigeminal neuralgia, relieved pain in 63% of selected cases of SUNA/SUNCT at a mean follow-up period of 14 months [551]. This finding suggests the possible role of trigeminal sensory root damage in the pathogenesis of these conditions.

These observations, taken together, support the hypothesis of common underlying pathophysiological mechanisms. These facial pain conditions may represent a spectrum disorder, characterized by unilateral short-lasting neuralgiform attacks with different degree of cranial autonomic activation, reflecting the different degree

of involvement of central and peripheral mechanisms, namely the posterior hypothalamic dysfunction and the trigeminal sensory root damage.

The burdens attributable to CH

Headache disability means limitations in daily life. This includes work, school, and social time. It is a major part of the total burden. Burden also includes cost, distress, and social impact. Global Burden of Disease studies use attack rate and severity to measure it. Migraine Disability Assessment Score Questionnaire (MIDAS) and Headache Impact Test (HIT-6) are tools commonly used in clinics to measure the disability caused by migraine. The burden of CH is difficult to measure [552]. It affects many aspects of life, from daily function and mental health to financial cost and even suicide risk. There are four main challenges in assessing this burden. First, there are no tools made specifically for CH. Most studies rely on migraine tools instead. Second, the timing and pattern of CH attacks, especially in episodic form, make it hard to assess symptoms clearly. Third, many studies involve small groups, Often those with the more severe chronic form. Fourth, there is a major lack of data from low- and middle-income countries, where nearly 90% of the world's population lives [10, 553].

Quality of life (QoL) in CH is low. Studies used SF-36, SF-12, and EuroQoL-VAS—all general tools to assess QoL. CH patients reported worse QoL than healthy subjects and even migraine patients. Invasive treatments may reduce attacks but often do not improve QoL [553–557]. CH affects QoL even between attacks. Worry about future attacks adds stress. Patients avoid triggers, which limits daily life. These emotional effects add to the total burden [10, 558, 559].

Disability in CH is often underestimated. Studies using MIDAS and HIT-6 tools showed high scores on HIT-6 (Often over 60) and MIDAS (over 21). Even after major treatments like nerve blocks or brain stimulation, disability stays high. This shows that the real impact of CH is deeper than what current tools can capture [10, 553, 560, 561]. A recent study by Göbel et al. used the WHO Disability Assessment Schedule (WHODAS 2.0) in nearly 200 CH patients. They showed that 92.7% had severe limits in daily function and major impairment [562].

The socioeconomic burden of CH is heavy. Few studies cover this aspect, but findings are clear. Many patients lose workdays, miss chances for promotion, or leave jobs entirely. Daily life is limited, even outside attack periods. Some lose their jobs due to the headache impact [10, 553]563– [565]. CH leads to high healthcare use and costs. CH patients see more doctors and use more treatments than the general population. A German 6-month study showed average costs of €5,963 per patient. Costs were higher for chronic CH (€10,985) than episodic CH (€2,583), mostly from acute treatments. A Danish study reported similar findings, with annual direct costs of €9,158 for chronic CH and €2,763 for episodic CH [10, 553, 563–565].

Suicide risk in CH is high. CH is often called the 'suicide headache' due to the extreme pain it causes, despite large studies on actual suicide rates in this group are still lacking [10]. Anyway, a U.S. survey found that 55% of CH patients had an increased risk of suicide. Another study showed high rates of suicidal thoughts, often linked to demoralization. This highlights the urgent need for better support and care [37, 452, 566]. A Korean study examined suicide risk in CH. During attacks, 64% reported passive suicidal thoughts, 36% had active thoughts, 6% made plans, and 2% attempted suicide. These risks dropped significantly between attacks. This shows suicide risk is closely tied to the pain. Effective treatment of attacks may lower this risk [451]. Other conditions like personality disorders, insomnia, and substance abuse may raise suicide risk in CH.

Advocacy in CH

In contrast to other more common forms of headache, such as migraine, this condition, precisely because of its lower prevalence, is little known among laypeople and often among physicians too, leading to frustrating clinical and diagnostic experiences for patients [567, 568]. To achieve significant improvements in care systems, foster research, diminish stigma, and promote health equity, advocacy for patients with CH is essential (Fig. 4). Below are several key issues that should be addressed through advocacy.

As mentioned above, one of the major challenges of CH is its rarity, which results in limited knowledge and awareness of the disease [569]. Even in countries with well-developed health care systems, patients with CH often receive a delayed diagnosis or face misdiagnosis and clinical mismanagement. Delays in diagnosis may be due to the patient delaying seeking medical care or the physician struggling to make the correct diagnosis [568]. Therefore, advocacy should focus on educating and raising awareness among laypeople and physicians by providing precise and accessible information about the condition, its severity, and the need for timely professional intervention [570]. The creation and dissemination of educational materials, involvement in awareness campaigns, and collaboration with patient advocacy groups can help bridge this knowledge gap [570].

The highly disabling nature of CH attacks is another critical aspect that requires advocacy [571]. Attacks are so intense that they are often described as the most excruciating pain imaginable, and they have a profound impact on patients' daily lives and their ability to work, maintain social relationships, and carry out everyday

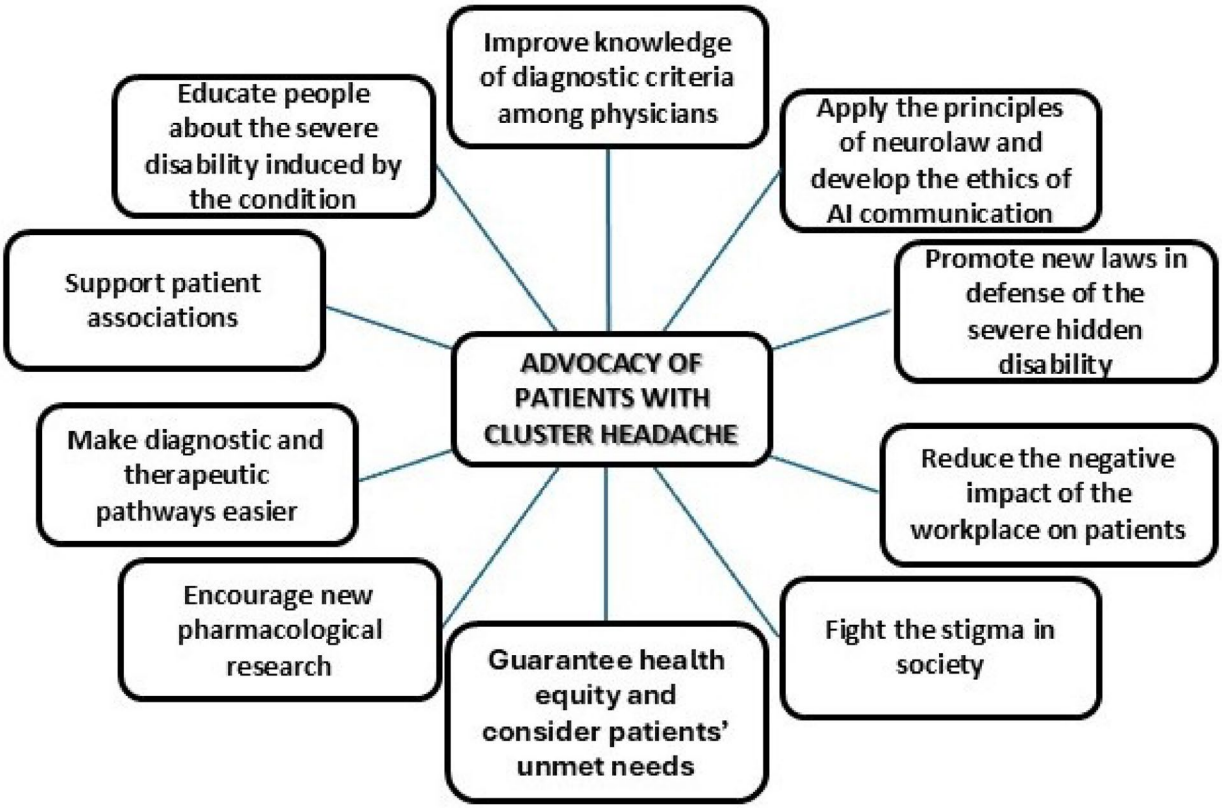

Fig. 4 Factors involved in advocacy for cluster headache patients

activities [569]. Advocacy should aim to make individuals, society, and policymakers aware of the real disabling effects of CH [572], in order to gain social recognition of the condition and concrete responses, such as the promotion of policies that ensure patients' access to adequate sick leave, workplace accommodations, and support for disability claims [573, 574]. The lack of formal recognition of CH as a disabling condition in disability assessment systems is a shortcoming that needs to be overcome at global level [575], in line with what has already happened in Italy [576], thanks in part to the efforts of local patient associations. In Italy, this recognition has made it possible to reach a consensus statement between health professionals, forensic experts, and representatives of patient associations, precisely to help physicians ensure recognition of their patients' social rights as people living with disabilities [577]. As mentioned, this achievement, enabling patients with chronic headaches (including chronic CH) to lead more dignified and sustainable lives, needs to be extended globally.

Although the stigma associated with headache has been extensively studied in migraine [578, 579], it does not spare patients with CH [557, 580]. Lack of knowledge about the disorder among the general public can lead to skepticism and minimization of patients' suffering [557]. This stigma can be internalized by patients themselves, who may develop feelings of shame, isolation, and reluctance to speak openly about their condition [579]. Advocacy must actively counteract this stigma through awareness campaigns that promote accurate and non-stigmatizing portrayals of headache [567], including CH. This can entail the use of patient-friendly language, for example, where the focus is on the disorder rather than the person ("person with cluster headache" rather than "cluster headache patient") [581]. The process of destigmatization [570] must also extend to the workplace, which must be rethought so that it becomes an inclusive environment where the invisible nature of the disorder is recognized, environmental triggers are reduced, awareness among colleagues is encouraged, and organizational policies based on the principles of diversity, inclusion, and accessibility are adopted, thus helping to improve the quality of life and productivity of patients with the disorder [582].

In terms of access to care, patients with CH often face challenges due to a lack of specialists with experience in managing this rare condition [570]. The concentration of the relevant expertise in specialized centers can create geographic and time barriers for patients, especially in rural areas or areas with limited health care resources [583, 584]. Advocacy can promote the development and strengthening of networks of centers specializing in

headache care to ensure a more equitable distribution of services and facilitate access to specialized consultations through tools such as telemedicine [567, 580]. In addition, it is crucial to support the training of primary care physicians to recognize the signs and symptoms of CH at an early stage. This area may also include the use of artificial intelligence to provide specific tools to support the clinician [585] and ensure that patients are promptly referred to specialists [570, 586]. Collaboration among patient advocacy groups, scientific societies, and healthcare institutions is essential to define and implement structured care models that address the specific needs of patients with CH [580].

Although research on CH is progressing, more scientific effort and more financial support are needed to fully understand the pathophysiological mechanisms of the disease, identify new therapeutic targets, and develop more effective and targeted treatments [11, 587]. The funding of migraine research has been considered disproportionately low compared with the burden of the disease [575], and it is likely that CH research, due to the rarity of the condition, will receive even less attention. Therefore, advocacy groups must approach national and international funding agencies to urge increased investment in CH research [570, 584]. This includes support for epidemiologic studies, basic research into disease mechanisms, and clinical trials to evaluate the efficacy and safety of new therapies. Notably, CH treatment has not seen the level of research activity that has been devoted to new therapies for migraine, and there is no consensus on whether new therapies developed for migraine can be applied to CH, despite a considerable pathophysiological overlap between the conditions [11]. As a result, many patients are driven by frustration at the limited range of treatment options and difficulty accessing treatment to seek alternative, not always licit, routes [372, 375], sometimes with the support of associations [588]. These problems are also found in countries with greater healthcare resources.

Patient empowerment is a central element of advocacy in CH: providing patients with accurate and understandable information about their condition, available treatment options, and their rights can help them to become active participants in treatment decisions and advocates for themselves [570]. Patient associations are essential in creating supportive communities where patients can share experiences, obtain information, and feel less isolated [570]. Therefore, it is crucial to support and strengthen these organizations by providing them with resources and platforms to make their voices heard [572].

Finally, there are new challenges on the horizon that should be considered when advocating for patients with CH. Given the increasing pathophysiological knowledge of the disease and the growing possibility of monitoring and modulating brain activity [589], patients with CH are exposed to the risk of manipulation and control of this activity. This aspect is being studied within the field of "neurorights" [590] with the aim of ensuring preservation of patients' mental integrity and cognitive freedom, crucial for safeguarding their mental autonomy and protecting them against non-consensual interference with their brain activity. This ethical issue, still little discussed, is highly relevant to patients suffering from CH, and represents an evolution of the similar one already raised in psychiatry concerning the impact of drugs on the autonomy, privacy, and integrity of patients receiving neuropsychopharmacological treatments [591]. Moreover, as artificial intelligence becomes more widespread in health care and the field of headache [585], it will be crucial to monitor its ethical aspects to ensure fairness, transparency, and protection of the rights of patients, especially those who, like individuals with CH, are at risk of being marginalized by algorithmic systems that are opaque or inadequately calibrated to the specific needs of those affected by rare diseases [592].

In conclusion, advocacy in CH is an ethical obligation and a practical necessity. The objectives of addressing the unmet needs of patients, combating stigma, improving access to care, and promoting research are attainable goals that can be achieved through the collaborative efforts of patients, family members, physicians, researchers, associations, and policymakers. By following the advocacy models developed for migraine and adapting them to the specificities of CH, it is possible to bring about change and significantly improve the lives of those living with this painful and disabling condition [575, 584]. All efforts must be directed towards addressing the hidden disabilities of patients with CH, whose quality of life is severely impacted by the severity of their acute attacks and the discomfort experienced during the intercritical phases. Like those with migraine [593], patients with CH have to cope with anticipatory anxiety, social and work restrictions, and a severe emotional impact of their condition, which is completely underestimated by those around them and by those who should be caring for them.

Conclusions

CH is characterized by several key clinical factors, including the severe unilateral pain associated with autonomic symptoms and notable agitation, the higher prevalence in males, and specific circadian and circannual patterns of recurrence.

Despite the extensive previous efforts, our therapeutic arsenal remains constrained to medications targeting non-specific pathways. This is attributable to both the rarity of the disease and the stagnation in pathophysiological knowledge. Indeed, the pathophysiological

evidence for CH closely mirrors that of migraine, including significant involvement of the trigeminal-autonomic system and hypothalamic activation. In particular, hypothalamic dysfunction, likely in the suprachiasmatic nucleus, seems to play a major role in determining the circadian recurrence of attacks, influencing the temporal aspects of the attacks. Several other cerebral regions, including the brainstem and mesocorticolimbic networks, play an additional role, particularly in cases of chronic CH. Nonetheless, when these neurolimbic structures are suppressed using invasive techniques like DBS, the positive effects do not manifest instantaneously, but rather with a delay of several months, suggesting that they are not the locus of the primary dysfunction.

Several molecules with a pivotal role in migraine pathophysiology, including CGRP, PACAP, VIP, and nitric oxide, seem to influence the modulation of pain and autonomic symptoms also in CH. However, the evidence that their plasma levels do not correlate with attack frequency and the discouraging outcomes obtained with the administration of CGRP-blocking antibodies suggest that some crucial biological differences exist between these two primary headache disorders. While CH and other primary headaches, especially migraine, exhibit shared genetic and pathophysiological pathways, they possess distinct clinical features and treatment responses, which makes it impossible to consider them as a continuum. Consequently, we should change our perspective by refraining from directly translating the insights gained from the research of other main types of primary headaches into CH pathophysiology. Additional research is required to ascertain not only which brain structure(s) initiates the attack, but also which one(s) is in charge of stopping it, and what the relationships are with the hypothalamic master clock and the subordinate clocks distributed throughout the human body. Then, further efforts should be made by all the researchers worldwide, focusing also on the distinct nature of pain associated with a CH attack compared to other primary headaches. This includes understanding the pathophysiological reasons for its severity, as well as its strict lateralisation, the biology under the higher male prevalence, or the loss of certain clinical and pathophysiological characteristics when CH becomes chronic. Comprehending these pathophysiological elements may facilitate the identification of novel molecular and structural targets, which may fuel the development of drugs that operate more rapidly and effectively.

In conclusion, CH is characterised by a complex, multifactorial, and yet inadequately understood pathophysiology. Precise diagnosis, additional research studies, and robust psychosocial and institutional support are necessary to improve the quality of life for individuals affected by this debilitating condition.

And here, where the *Hallmarks of Primary Headache Disorders* trilogy appears to reach its conclusion with Cluster Headache, the project evolves instead, leaving a deliberate opening for the completion into a five-act masterpiece. We're all set to appreciate the final two acts.

Abbreviations

5-HT	5-hydroxytryptamine
5-HTTLPR	5-HT transporter gene-linked polymorphic region
ADH4	Alcohol dehydrogenase 4
ADHD	Attention deficit hyperactivity disorder
AMY1	Amylin subtype 1 receptor
BBB	Blood-brain barrier
CAS	Cranial autonomic symptoms
CaV	Voltage-gated calcium channels
CCBs	Calcium channel blockers
CGRP	Calcitonin gene-related peptide
CH	Cluster headache
CLR	Calcitonin-like receptor
DBS	Deep brain stimulation
DHE	Dihydroergotamine
DMN	Default mode network
DMT	Dimethyltryptamine
fMRI	Functional magnetic resonance imaging
GONB	Great occipital nerve block
GWAS	Genome wide association study
HCRTR2	Hypocretin Receptor 2 gene
HF	High-frequency
HH	Hypnic headache
HIT	Headache Impact Test
K_{ATP}	Adenosine triphosphate (ATP)-sensitive potassium
LEPs	laser-evoked potentials
LF	Low-frequency
LSA	Lysergic acid amide
LSD	Lysergic acid diethylamide
MERKT	Mer tyrosine kinase protooncogene
MIDAS	Migraine Disability Assessment Score Questionnaire
MrgprB2	Mas-related G-protein coupled receptor member B2
nBR	Nociceptive blink reflex
NMDA	N-methyl-D-aspartate
NNT	Numbers needed to treat
NO	Nitric oxide
NOS	Nitric oxide synthases
nNOS	Neuronal NOS
ONS	Occipital nerve stimulation
PACAP	Pituitary adenylate cyclase-activating polypeptide
PAG	Periaqueductal grey area
PET	Positron emission tomography
PREP	Pain-related evoked potentials
QoL	Quality of life
RAMP1	Receptor activity-modifying protein 1 gene
rCCH	Refractory chronic cluster headache
RCP	Receptor component protein
RCTs	Controlled clinical trials
REM	Rapid-Eye-Movement
rs2653349	G1246A polymorphism
SCN	Suprachiasmatic nucleus
SNP	Single Nucleotide Polymorphism
SoC	Standard of care
SPG	Sphenopalatine ganglion
SPGb	Sphenopalatine ganglion block
SSN	Superior salivatory nucleus
TACs	trigeminal autonomic cephalalgias
TCC	Trigemino-cervical complex
tDCS	Transcranial direct current stimulation
TEAE	Treatment-emergent adverse effects
TENS	Transcutaneous electrical nerve stimulation
TG	Trigeminal ganglia
TMS	Transcranial magnetic stimulation
TNC	Trigeminal nucleus caudalis

t-VNS	Transcutaneous vagus nerve stimulation
VIP	Vasoactive intestinal polypeptide
VNS	Vagus nerve stimulation
VTA	Ventral tegmental area
WGS	Whole genome sequencing

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Gianluca Coppola planned the study, collected the entire body of the manuscript, and drafted Introduction and Discussion section. Paolo Martelletti planned the study, drafted discussion section, and supervised the whole manuscript. The remaining authors drafted sections of the manuscript, in detail: Li-Ling Hope Pan and Shuu Jiun Wang (Clinical features of episodic and chronic CH), Andrea Carmine Belin and Innocenzo Rainero (Genetic basis), Peter J Goadsby and Marta Vila-Pueyo (Molecular pathways), Messoud Ashina and Doga Vuralli (The trigeminal autonomic reflex), Kuan-Po Peng and Igor Petrušić (Hypothalamic mechanism in CH), Stefania Ferraro and Yonggang Wang (Central mechanisms other than hypothalamus), Marco Lisicki and Gabriele Sebastianelli (Electrophysiological aspects of CH), Mads Barloese and Rolf Fronczek (The chronobiology of CH), Mario Peres and Sara Bottiroli (Personality traits of patients with CH), Jacob C. A. Edvinsson and David García-Azorín (Old and new pharmacological targets), Mark Obermann and Cristina Tassorelli (Acute and bridge pharmacological treatments of CH), Teshamae Monteith and Dagny Holle (Preventive treatments), Julia Jansen and Licia Grazzi (Alternative medical approaches on CH treatment), Giorgio Lambru and Stefan Evers (Non-invasive neuromodulation), Alberto Proietti Cecchini and Michel Lanteri-Minet (Invasive neuromodulation), Roberto De Icco and Debashish Chowdhury (Nerve blocks), Alberto Raggi and Marta Waliszewska (Cluster headache prognosis), Dimos D Mitsikostas and Surat Tanprawate (Definition and management of refractory CH), Marco Antônio Arruda and Massimiliano Valeriani (Cluster headache in children and adolescents), Raquel Gil-Gouveia and Tsubasa Takizawa (The crossroad between CH and other primary headaches), Giulia Di Stefano and Andrea Truini (The subtle overlapping of trigeminal autonomic cephalalgias and other orofacial pain conditions), Tissa Wijeratne and Danilo Antonio Montisano (The burdens attributable to CH), Cherubino Di Lorenzo and Giorgio Sandrini (Patients' advocacy).

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Competing interests
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