Recent advances in diagnosing, managing, and understanding the pathophysiology of cluster headache

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Cluster headache, characterised by attacks of severe, recurrent, unilateral headache and ipsilateral cranial autonomic symptoms, remains a primary headache with an elusive pathophysiology. Recent advances have introduced effective treatments and broadened understanding of the clinical features of cluster headache. These features are similar in patients globally, but regional differences in prevalence and burden exist. International collaborations have led to identification of eight genetic loci associated with cluster headache. The pathophysiological mechanisms are still not fully understood but recent studies show that targeting the trigeminal autonomic reflex by neurostimulation, or targeting the neuropeptide calcitonin gene-related peptide (CGRP), might lessen the attack burden. The US Food and Drug Administration has approved galcanezumab, a monoclonal antibody targeting CGRP, as the first specific preventive treatment for episodic cluster headache. However, a preventive effect was not replicated in chronic cluster headache, and the European Medicines Agency did not approve galcanezumab, restricting its availability in Europe. Owing to the low prevalence of cluster headache, continued collaboration through multicentre clinical trials and data sharing will be imperative for further breakthroughs in understanding and management.

Introduction

Cluster headache is a primary headache disorder characterised by excruciating unilateral pain, predominately in the orbital region, accompanied by ipsilateral cranial autonomic symptoms, restlessness, or both.[1] The pain of a cluster headache attack is described as one of the most painful states known, surpassing giving birth, bone fractures, or gunshot wounds.[2] Therefore, it is important to recognise the clinical features of cluster headache to diagnose and alleviate these severe headache attacks.

Descriptions of cluster headache date back three centuries, with clear differentiation from migraine since 1926.[3] Thus, over the past century, cluster headache has been extensively studied as a distinct condition. Scientific advancements in the past 6 years have furthered our understanding of the clinical features of cluster headache, especially in east Asian and Indian populations, and the identification of eight genetic loci in cluster headache, only three of which have been implicated in migraine, offers hope for a comprehensive understanding of its pathophysiology. During this period, new treatments have emerged, targeting known elements of cluster headache pathophysiology.

This Review provides an updated perspective on the epidemiology, diagnosis, clinical features, genetics, and pathophysiology of cluster headache. Additionally, we propose a comprehensive approach to managing cluster headache that we believe can be applied globally.

Epidemiology

Epidemiological studies have found a cluster headache prevalence of 41–381 individuals per 100 000.[4–6] A meta-analysis found a lifetime prevalence of 124 individuals per 100 000 (95% CI 101–151),[4] whereas two later epidemiological studies found a lower lifetime prevalence of 41–87 individuals per 100 000.[5,6] Thus, the prevalence of cluster headache is similar to the age-standardised global prevalence of Parkinson's disease of 98 individuals (95% CI 90–107) per 100 000.[5,6] The clinical features of cluster headache should make the condition easily recognisable. However, cluster headache has a long diagnostic delay and patients are frequently misdiagnosed, so the prevalence might be underestimated.[7,8]

Cluster headache has a male predominance; the overall male-to-female ratio is reported to be 3–9:1 in East Asian and Indian populations, compared with 2–3:1 in European and North American populations.[9] As chronic cluster headache has a lower male to female ratio than episodic cluster headache, part of the observed disparity between the regions could be explained by the lower prevalence of chronic compared with episodic cluster headache in Asia.[10,11] Throughout the past four decades, the male-to-female ratio of people with cluster headache has gradually declined in studies in Europe and North America.[4,12] Changes in lifestyle have been suggested as a contributing factor to the declining ratio, but increased awareness of cluster headache in women might also have contributed.[12,13]

Classification and diagnosis

Diagnosis of cluster headache relies solely on carefully obtained clinical history. According to the third edition of the International Classification of Headache Disorders (ICHD-3), cluster headache is defined as recurrent unilateral, severe headaches in the orbital, supraorbital, or temporal regions lasting 15–180 min, and with cranial autonomic symptoms, restlessness, or both.[1] Cluster headache is divided into two subtypes: episodic, with attack periods (bouts) lasting 7 days to 1 year, separated by attack-free periods (remissions) lasting at least 3 months within the last year; and chronic, with attacks occurring either without a remission period or with remissions lasting less than 3 months within the last year (figure 1).

The duration of the remission period required for a diagnosis of episodic cluster headache was extended from 1 month in ICHD-2[14] to 3 consecutive months in ICHD-3;[1] with this elongation, 3–12% of people with episodic cluster headache had their diagnosis changed to chronic cluster headache.[15,16] The rationale for this remission duration is based on clinical expert opinion. In the future, the arbitrary distinction between chronic and episodic forms might be adjusted in light of an enhanced comprehension of the pathophysiology behind cluster headache.

In relation to differential diagnoses, secondary causes of headaches resembling cluster headache need to be excluded (panel 1). Patients might present to the emergency department owing to the extreme intensity of the pain. Eye pain with autonomic symptoms is classified as a red flag for a secondary cause,[17] and therefore further examination is needed. CT angiography can rule out a carotid artery dissection, and involvement of an ear, nose, and throat specialist or an ophthalmologist might be relevant if the clinical picture is unclear. According to the European Academy of Neurology guideline,[18] a new-onset headache resembling cluster headache should result in a brain MRI scan to exclude brain pathology. A study of 376 participants with cluster headache symptoms found that systematic screening for pituitary pathologies did not yield discernible benefits for any individual, but should be done when clinically relevant with visual or endocrinological symptoms or signs.[22]

Clinical features

The clinical characteristics of cluster headache have been widely described in studies from Europe, North America, the Middle East, and Asia.[9,23] The mean age of onset is consistently found to be in the second or third decade of life, but paediatric onset might be underreported, as approximately 22–39% of people with cluster headache report their initial cluster headache attack before the age of 20 years.[24] The paediatric clinical features are similar to those of adult-onset cluster headache.[25] Most clinical features are similar between sexes, but women have more comorbid migraine and nausea.[13,25]

Three phases of a cluster headache attack

The cluster headache attack has three phases, described in detail in a prospective study of 500 attacks: the preictal phase, the ictal headache phase, and the postictal phase.[26] In the preictal phase, 70–95% of all participants with cluster headache had at least one symptom.[26,27] Typically, general symptoms are restlessness or difficulties in concentration, and the prevailing localised symptom is a dull, painful sensation in and around the eye. The prospective data suggest the duration of the preictal phase to be 10–60 min.[26,27]

The ictal headache phase is well described. The pain intensity is very high, with a median rating of 9–10 out of 10 on the Numeric Rating Scale in retrospective studies. However, a prospective study concluded that attacks of lower intensity were common but less frequently reported.[26] Typically, pain is located in the orbital-temporal region, often with pain in the jaw, teeth, and neck.[26] The mean attack frequency is one to four per day, and the mean duration of a single untreated attack is 1–2 h.[26] Cluster headaches without autonomic symptoms are infrequent, as 97% of participants with cluster headache had at least one autonomic symptom during the attack, with a mean of four symptoms.[25,28] Lacrimation and conjunctival injection are the most frequent symptoms, occurring in 53–92% of people with cluster headache.[9,28] The prevalence of restlessness varies from 48–93%, with lower frequencies in studies in east Asia compared with studies in Europe and North America.[29]

The literature on the postictal phase is sparse. Nevertheless, a single prospective study on 500 cluster headache attacks revealed that 98% of participants reported symptoms such as a dull sensation in the attack area and reduced energy during the first hour after the end of the headache.[26] However, the symptoms of this phase might represent a true postictal phase, but could also be due to treatment side-effects.

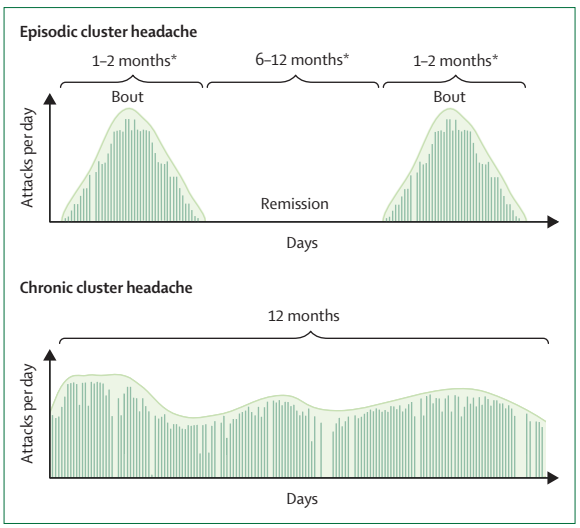

Figure 1: **Clinical spectrum of cluster headache**
Cluster headache occurs in two subtypes: episodic and chronic. In episodic cluster headache, the individual must have a remission lasting at least 3 months within the past year. In chronic cluster headache, the attacks occur without remission or with remissions lasting less than 3 months within the last year, although some variation over time can occur. Figure created with BioRender.com. *Numbers of months represent the average duration of bouts and remissions reported by people with episodic cluster headache, but can vary individually (the minimum is 3 months, but maximum could be several years).

Chronobiology

A striking feature of cluster headache attacks is their rhythmicity. A meta-analysis found that 3490 (70·5%) of 4953 participants across 16 studies showed a circadian pattern of attacks. The likelihood of an attack was highest between 0200 h and 0300 h.[30]

People with episodic cluster headache have attacks in bouts, which vary in duration and frequency for the

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Panel 1: Authors' recommendations for diagnosing and managing cluster headache

Diagnosing cluster headache*

- Exclude a secondary cause of headache
  - History: red flags such as new-onset headache, systemic fever, older age, and vision loss[17] can suggest a secondary cause
  - Neurological examination: focal neurological sign (apart from autonomic symptoms during the attack) or persistent autonomic symptoms between headache attacks[17] can suggest a secondary cause
  - Diagnostic investigations to consider if a secondary cause is suspected: CT angiogram, eye examinations, MRI
- Distinguish cluster headache from other primary headaches and facial pain
  - Some people have multiple primary headaches and each subtype needs to be described separately
- Features that can distinguish cluster headache from migraine:
  - Duration of the pain phase: 3 h or less for cluster headache, longer for migraine
    Pain behaviour: people with migraine often lie still, whereas many people with cluster headache move around (even when lying in bed, they are constantly restless or moving)
- Features that can distinguish cluster headache from other trigeminal autonomic cephalalgias (paroxysmal hemicrania, hemicrania continua, short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing [SUNCT], and short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms [SUNA]):
  - Duration of the pain phase: 15 min or longer for cluster headache, shorter for the other trigeminal autonomic cephalalgias
  - Treatment response to indomethacin: paroxysmal hemicrania and hemicrania continua is prevented by indomethacin, whereas cluster headache is not
- Features that can distinguish cluster headache from trigeminal neuralgia:
  - Duration of the pain phase: 15 min or longer for cluster headache, whereas trigeminal neuralgia last from a fraction of a second to 2 min
  - Pain of trigeminal neuralgia is provocable by external stimuli such as cold wind or tooth brushing
  - Autonomic symptoms are almost always present in cluster headache, whereas autonomic symptoms are uncommon in trigeminal neuralgia; if autonomic symptoms are present in trigeminal neuralgia, they are typically less severe compared with cluster headache
- Check whether the medical history fulfils the criteria for cluster headache according to the International Classification of Headache Disorders-3 criteria[1]

Managing cluster headache*

To provide sufficient pain relief, acute, transitional, and long-term preventive treatments are often combined. For many patients, all three types of treatment are initiated as soon as the bout arises. For short bout durations (≤14 days), long-term preventive treatment might be obsolete as uptitration might take a few weeks. These patients could be managed entirely by acute treatment and transitional prevention:

- Acute treatment
  - First line: oxygen and subcutaneous sumatriptan are preferably prescribed simultaneously, but initially the patient should use one treatment at a time to be able to differentiate the efficacy
  - Second line: nasal triptans—these are best suited for attacks lasting more than 30 min, and might be an option for people who are afraid of needles
- Preventive treatment
  - First line: typically combines long-term prevention verapamil (electrocardiogram-monitoring is needed) with add-on transitional preventive treatment (greater occipital nerve blocks)
  - Second line: lithium or galcanezumab (if available)

More details on managing cluster headache can be found in the appendix (pp 1–4).

*Based on published guidelines[1,17–21] and the expert opinion of the authors, who are all experienced headache clinicians and scientists.

See Online for appendix

individual. For most people with episodic cluster headache, bout duration is less than 2 months, and most studies report an annual occurrence of between one and two bouts. Precluster symptoms refer to the symptoms that individuals with cluster headache might have preceding a bout.[31] Retrospective studies have found that 35·3% and 57·0% of participants with episodic cluster headache could predict an impending bout. This ability for prediction could allow for early intervention and preventive treatment. However, precluster symptoms are not always followed by a bout, and for clinical usage the consistency and specificity of symptoms need to be verified. By contrast with migraine, episodic cluster headache is characterised by periods of spontaneous remission.[32] In remission, individuals with cluster headache do not have severe attacks, nor can their attacks be pharmacologically provoked by, for example, nitroglycerin[33] or calcitonin gene-related peptide (CGRP), whereas attacks can be provoked in this way during a bout.[33]

Studies in Taiwan, China, and South Korea have found fewer participants retrospectively reporting a circadian pattern of their attacks, a higher episodic-to-chronic ratio, shorter bout duration, and fewer attacks compared with studies in Europe and North America.[9] Overall, the data suggest disease burden might vary across the globe,

but better understanding of the role of latitude, culture, language, genetics, and environmental factors is needed.

Most attacks are nocturnal, and up to 320 (80%) of 400 people with cluster headache described sleep as a trigger.[34] Cluster headache attacks are not associated with a specific sleep stage.[34] Quality of sleep for people with cluster headache is lower than for people without the disorder, during both bouts and remission.[35] In bouts, patients with cluster headache have a longer sleep latency compared with age-matched and sex-matched controls, indicating signs of insomnia.[34,35] An altered chronobiology might not completely explain these sleep changes in people with cluster headache; psychological variables could theoretically contribute, owing to the anxiety of experiencing nocturnal attacks. Sleep apnoea has been proposed as a trigger for attacks, and in some case series treatment of sleep apnoea was postulated to provide relief, but a randomised clinical trial for chronic cluster headache in 2023 did not reproduce those findings.[36]

Prognosis

The natural history and prognosis of cluster headache are unclear, but an individual can have cluster headache for decades. A prospective study found that increasing age was associated with less frequent recurrence of bouts of episodic cluster headache,[37] which aligns with anecdotal reports of permanent remission over time.[38] People with episodic cluster headache have the potential to transition into a state of chronic cluster headache and, conversely, those with chronic cluster headache might revert to the episodic form. The prevalence of any transition in either direction is between 6% and 36%,[15] and predictive factors for transitions are unclear.

Disease burden

Cluster headache attacks themselves are extraordinarily painful, and people with episodic cluster headache are anxious about relapse, even between bouts when they do not have attacks.[39] Cluster headache is unfortunately also a long-term disease and quality-of-life measures are reduced compared with the general population and people with migraine.[39] All aspects of everyday life are affected by cluster headache. A high proportion of people with cluster headache are unemployed, and they have an increased risk of being on a disability pension compared with matched controls.[40] Consequently, the direct and indirect costs of cluster headache are high on both an individual and societal level,[39,41] and people with chronic cluster headache are more affected, in terms of both direct and indirect costs, than people with episodic cluster headache, possibly due to the more sustained attack burden. However, both cluster headache subtypes can affect crucial life choices, such as having children.[41] Even though remission lessens many symptoms,[42] the cyclical nature of cluster headache can be chronically disabling. Most quality-of-life investigations have been conducted with assessments or questionnaires developed for people with migraine, but two questionnaires specifically designed for cluster headache have been developed,[43,44] with the potential to improve the evaluation of treatment responses beyond the immediate effects of cluster headache.

Comorbidities

Multimorbidity is frequent in cluster headache,[45–47] and knowledge of comorbidities is important to optimise guidance and treatment. First-line therapies, such as triptans and verapamil, might affect the cardiovascular system, thus, electrocardiograms are essential before prescription to people with cluster headache.[18] Presence of cardiac or cerebrovascular disease sometimes contra-indicates first-line treatments but might, after careful consideration and discussion with the patient, be the only viable treatment. The potential treatment consequences underscore the need for education of people with cluster headache regarding cardiovascular risk factors and highlights the unmet need for new treatment options.

Psychiatric disorders such as depression and anxiety are more common among people with cluster headache compared with people without cluster headache.[45] Cluster headache is sometimes referred to as suicide headache, and a study in Norway found the odds of suicide attempt were higher (odds ratio 3·9, 95% CI 2·6–5·8) in people with cluster headache compared with the general population,[5] and suicidal ideation was more prevalent, even after adjusting for comorbid depression.[48] Consequently, it is imperative to assess patients with cluster headache for depression. A study from the Netherlands found that the use of illegal substances was higher among a cluster headache cohort than the general population, perhaps owing to an alleviatory effect, placebo effect, or pathophysiological traits towards more addictive behaviour among people with cluster headache.[49]

Genetics

Genetic studies of cluster headache can be categorised into those that explore heritability at the population level and those that aim to uncover the specific genes. Population studies have found the risk of developing cluster headache to be 5–18 times higher for first-degree relatives compared with the general population, but there is no clear hereditary pattern,[50] suggesting that the cause of cluster headache is either polygenic, influenced by environmental factors, or both. Candidate gene studies predominated until 2021, but findings were not always replicated.[51,52] In 2021, two hypothesis-free genome-wide association studies (GWASs) identified four loci associated with cluster headache in European cohorts.[53,54] Two of these loci were confirmed in a GWAS in a Han Chinese cohort, which additionally reported a new locus on chromosome 1,[55] suggesting the possibility of ethnicity-shared and ethnicity-specific genetic contributions to cluster headache.

Recently, these results were confirmed and expanded upon by the finding of three new loci associated with cluster headache in a meta-analysis by the International Consortium for Cluster Headache Genetics (table 1),[56] whereas none of the associations reported from candidate gene studies were replicated. 4777 people with cluster headache were included in the meta-analysis, which is a small number for a GWAS, but we consider the findings are robust as the effect size was large, the data quality was high, and the study design (including selection of healthy controls) was appropriate. The role of the identified genes in cluster headache is not yet fully understood and, so far, the results have not shown clinical relevance. Three of eight genetic loci are shared with migraine, indicating that although cluster headache and migraine are genetically distinct disorders, they have some similarities. The meta-analysis further showed that cluster headache is genetically correlated with traits such as cigarette smoking, pain disorders, and neuropsychiatric diagnoses, and mendelian randomisation analysis indicated a causal effect of cigarette smoking intensity.

Current or previous cigarette smoking is consistently found to be frequent among people with cluster headache, and 60–88% have a history of smoking.[57] Smoking is suggested to be a causative factor for cluster headache[57] and might also be an aggravating factor.[47,57] Cessation of smoking would be expected to alleviate cluster headache symptoms, but this was not the case in a retrospective study.[58] Given that the epigenetic changes caused by smoking can persist for more than 30 years,[56] any potential improvement to cluster headache symptoms from smoking cessation is probably too slow to be noticed in a prospective study or verified in a randomised clinical trial. In the International Consortium for Cluster Headache Genetics meta-analysis, five complementary methods were used to locate and prioritise candidate genes that could be causal for cluster headache. The analysis identified 20 potentially causal genes; four of the 20 genes prioritised by complementary methods in the meta-GWAS are among 1450 genes related to DNA methylation, at 2568 CpG sites associated with former smoking.[56]

Pathophysiology

Although understanding of cluster headache attacks has improved in the past 6 years, the cycling of both attacks and bouts remains poorly understood. The current understanding of cluster headache is based on human clinical and neuroimaging studies. Animal studies have contributed to mapping of the neuroanatomical pathways and effects of interventions;[59] however, no validated animal model of cluster headache encapsulates the chronobiologically activated unilateral pain and

	Chromosome	Reference	Function and possible involvement in cluster headache pathophysiology
DUSP10	1q41	Harder et al,[53] O'Connor et al,[54] and Winsvold et al[56]	A widely expressed phosphatase reported to be involved in inflammation
*CAPN2**	1q41	Chen et al[55] and Winsvold et al[56]	Calcium-activated cysteine protease that catalyses endopeptidase (eg, neprilysin); verapamil is reported to inhibit calpain activation
MERTK	2q13	Chen et al,[55] Harder et al,[53] O'Connor et al,[54] and Winsvold et al[56]	Highly expressed in microglia, with a role in neuroinflammation
FTCDNL1	2q33	Harder et al,[53] O'Connor et al,[54] and Winsvold et al[56]	Expressed in brain tissue and predicted to enable folic acid binding activity and transferase activity
FHL5†	6q16	Harder et al,[53] O'Connor et al,[54] and Winsvold et al[56]	Expressed in brain tissue and an activator of the transcription factor CREB; the CREB pathway is crucial for light entrainment of the circadian clock, contributes to sensitisation of nociceptive cells and meningeal pain hypersensitivity, and has a role in pain transmission evidenced by CREB activation in the trigeminal ganglion after stimulation of nociceptive neurons; triptans, used to treat cluster headache, reduce CREB activity within the trigeminal system
WNT2‡	7q31.2	Winsvold et al[56]	The WNT gene family consists of structurally related genes that encode secreted signalling proteins, but with an unknown involvement in cluster headache pathophysiology; these proteins have been implicated in oncogenesis and developmental processes, including regulation of cell fate and patterning during embryogenesis§
PLCE1†	10q23.33	Winsvold et al[56]	A phospholipase enzyme that catalyses the hydrolysis of phosphatidylinositol-4,5-bisphosphate to generate the second messengers inositol diacylglycerol and 1,4,5-triphosphate, which regulate processes affecting cell growth, differentiation, and gene expression§
LRP1†	12q13.3	Winsvold et al[56]	Expressed in the brain and vasculature, responsible for modulating synaptic transmission, and serves as an important sensor of the extracellular environment§

The roles of the genes identified in cluster headache are not yet fully understood, and the implication of these genes in cluster headache currently have no relevance for making the diagnosis in individual patients. The closest protein-coding gene to the locus is indicated. CAPN2=calpain 2. DUSP10=dual specificity phosphatase 10. FHL5=four and a half LIM domains 5. FTCDNL=formiminotransferase cyclodeaminase N-terminal-like. LRP1=LDL receptor related protein 1. MERTK=MER proto-oncogene tyrosine kinase. PLCE1=phospholipase C epsilon 1. WNT2=Wnt family member 2. *Locus identified in a trans-ancestry genome-wide association study. †Locus near risk loci previously identified for migraine. ‡Locus below significance in trans-ancestry genome-wide association study ($p=5{\cdot}91\times10^{-7}$). §The table includes functions for WNT2, PLCE1, and LRP1 obtained from GeneCards.

Table 1: **Summary of the eight loci associated with cluster headache in a genome-wide meta-analysis**

For more on **GeneCards** see https://www.genecards.org/

autonomic activation. Study of cluster headache is complicated by the short-lived nature of attacks. However, human provocation studies that include neuroimaging have provided insight into how attacks can be triggered pharmacologically,[60] offering hope that attacks might be investigated more extensively in the future. On the basis of currently available studies, three key neuroanatomical structures are proposed to explain the clinical features of cluster headache (figure 2).

First, altered activation of the trigeminovascular pathway might explain the severe unilateral pain located in the first branch of the trigeminal nerve.[61] The altered activation of this pathway seems to be shared with migraine, and is considered the final common pain pathway for transmitting pain signals for headache. Neuropeptides such as CGRP and pituitary adenylate cyclase-activating polypeptide (PACAP) 38 are released from trigeminal nerve endings when the pathway is activated[61,62]—CGRP and PACAP-38 can pharmacologically induce cluster headache attacks.[33,63] Plasma CGRP concentrations were thought to be persistently elevated in patients with cluster headache, but are now known to be lower between attacks compared with controls.[64] However, plasma CGRP concentration does increase during an attack or bouts compared with during remission.[64,65] Nitroglycerine and levcromakalim (a potassium channel opener) have also been found to induce cluster headache attacks.[60,66] Recently, vaccinations against COVID-19 were found to elicit cluster headache attacks.[67] Along with the fact that corticosteroids effectively reduce the frequency of attacks, that some of the loci identified in the GWAS are involved in inflammatory processes (table 1) might implicate a potential role of inflammation in activating the trigeminovascular pathway.[55,67]

Second, activation of the trigeminal–autonomic reflex is believed to cause ipsilateral cranial autonomic symptoms.[61] The trigeminal–autonomic reflex is composed of neurons originating from the trigemino-cervical complex that project to the superior salivatory nucleus (SSN). The outflow pathway from the SSN traverses the facial nerve to synapses in the sphenopalatine ganglion, with subsequent activation of post-ganglionic parasympathetic fibres responsible for stimulating the nasal and lacrimal glands. In a study of 80 side-locked (attacks always occur on the same side of the head) patients with episodic cluster headache in bout, the volume of the sphenopalatine ganglion increased on the symptomatic side compared with the volume of 40 matched controls without cluster headache.[68] Activation of the trigeminal–autonomic reflex elicits the secretion of neuropeptides, including PACAP-38, acetylcholine, and vasoactive intestinal peptide.[69] However, peripheral activation of the trigeminal–autonomic reflex cannot induce a cluster headache attack.[70,71] Currently available research thus supports the notion that the trigeminovascular pathway and the trigeminal–autonomic reflex are connected in a vicious circle that causes pain and autonomic symptoms during attacks, but the mechanisms underlying activation of this vicious circle in spontaneous attacks remain unknown.

Third, neuroanatomical connections, clinical characteristics, and neuroimaging studies indicate a modulatory function of the hypothalamus.[60,69,72,73] For example, in people with chronic cluster headache, a higher number of daily attacks was associated with a

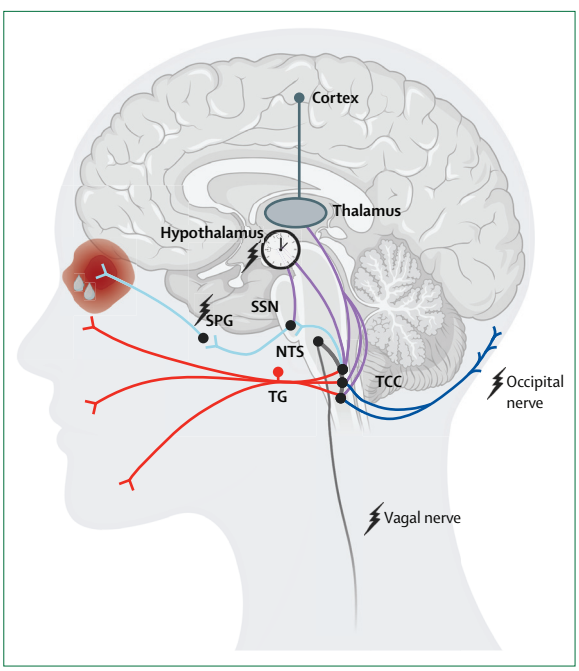

Figure 2: **Peripheral and central pathways of cluster headache pathophysiology**
The trigeminovascular pathway (shown in red) consists of bipolar neurons that have their cell bodies in the trigeminal ganglion and that have synapses centrally in the trigeminocervical complex and peripherally in the dura mater, cerebral vessels, and upper facial structures, including the orbital and supraorbital areas. Activation of the afferents is perceived as peripheral pain in humans. The trigemino–autonomic reflex (shown in light blue) is composed of neurons originating from the trigeminocervical complex that extend to the superior salivatory nucleus. These neuronal projections from the superior salivatory nucleus synapse in the sphenopalatine ganglion, which subsequently activates parasympathetic fibres responsible for stimulating the lacrimal glands. Connections from the trigeminocervical complex and superior salvatory nucleus to the hypothalamus and the thalamus (shown in purple): neuroanatomical connections, clinical characteristics, and neuroimaging studies indicate a modulatory function of the hypothalamus; the hypothalamus is visualised as the clock as it controls the circadian rhythm. The lightning icons indicate targets for neurostimulation that could have potential benefit in cluster headache; however, deep brain stimulation has not been approved for cluster headache. Neuroimaging studies during either spontaneous or induced cluster headache attacks have shown activation of the hypothalamus ipsilateral to the pain. The line from the thalamus to the cortex represents neuroimaging findings that suggest altered activation in the anterior cingulate cortex, insula, thalamus, ventral pons, prefrontal cortex, and primary sensory cortex are associated with cluster headache. Both the vagal nerve and the occipital nerve are neurostimulation targets for treating cluster headache; the proposed neuroanatomical pathways go directly from the occipital nerve to the trigeminocervical complex (dark blue) and from the vagal nerve to the trigeminocervical complex via the nucleus tractus solitarius (grey). Figure created with BioRender.com. NTS=nucleus tractus solitarius. SPG=sphenopalatine ganglion. SSN=superior salivatory nucleus. TCC=trigeminocervical complex. TG=trigeminal ganglion.

higher ratio of the volume of the anterior hypothalamus to the volume of the superior hypothalamus.[74] The functional connectivity between hypothalamus and medial frontal gyrus and occipital cuneus was changed both in bout and in remission compared with people without cluster headache.[75] Moreover, changes were found between the the hypothalamus and the medial frontal gyrus, precuneus, and cerebellar areas between patients in bout compared with patients in remission.[75] Lastly, a magnetic resonance spectroscopy study revealed that participants with episodic cluster headache have persistent biochemical changes in the hypothalamus compared with healthy controls or participants with chronic migraine.[76] The hypothalamus has anatomical pathways to both the trigeminovascular system and the trigeminal–autonomic reflex, with synapses in the trigeminocervical complex and the SSN.[69] The hypothalamus is a key regulating structure in the CNS and is important for homoeostasis in the neuroendocrine system, sleep, the circadian rhythm, and the autonomic nervous system.[69] This role aligns with the clinical features of cluster headache, such as the chrono-biological regulation, impaired sleep, and alterations in serum concentrations of hormones controlled by the hypothalamus, indicating involvement of the hypothalamus in cluster headache.[63,69,77]

Treatment

The two main types of treatment for cluster headache are those administered during an attack (acute treatment) and those administered in advance (preventive treatment), attempting to lessen both frequency and severity of future attacks. For patients with chronic cluster headache the preventive treatment is administered daily, and for those with episodic cluster headache the preventive treatment is administered during the bout. Preventive treatments have two subtypes: transitional treatments, which can be taken for only short periods but show effect rapidly; and long-term preventives, which are taken for longer periods but, in some cases, take time to taper up to an effective dose. Transitional and long-term preventive treatment can be combined to provide optimal attack reduction. Treatment guidelines for cluster headache have been published in several countries.[18,19–21] In the following sections, older studies are only briefly stated; more details and and our recommendations for treatment are in panel 1 and the appendix (pp 1–4).

Acute treatment

100% oxygen (flowrate 12 L/min) and sumatriptan 6 mg subcutaneously are first-line acute treatments. Effectiveness and safety for both treatments have been established in placebo-controlled trials, and both treatments relieved pain intensity by at least 50% in approximately three of four attacks within 15 min.[78,79] Oxygen treatment is not effective for all people with cluster headache, and response can depend on flowrate and inhalation modality. A randomised clinical trial found an equal effect between 7 L/min and 12 L/min, but before exluding the effect of oxygen a flowrate of 12–15 L/min should be tested—the effect might improve with optimised mask type;[80,81] non-breather masks are suggested to be the most appropriate.[20,21] Sumatriptan 6 mg subcutaneously might be associated with a faster response and a higher chance of achieving pain freedom compared with oxygen. Sumatriptan 6 mg subcutaneously is—like oxygen—a first-line treatment, and successfully treated 74% of attacks in 131 cluster headache patients within 15 min.[82] Real-world evidence shows that 73–90% of patients are 50% responders, meaning that they prospectively reported that the pain intensity was reduced by at least 50% compared with pretreament. Side-effects occurred in 34% of patients and included chest discomfort, nausea, and paraesthesia.[81] Triptans delivered by nasal spray (sumatriptan 20 mg or zolmitriptan 5 mg) are also effective in placebo-controlled trials, but are second-line treatments because the time to effect is longer (up to 30 min).[21,82] Oral triptans are generally considered too slow for acute treatment of cluster headache attacks, and a recent randomised clinical trial found oxygen treatment to be superior to oral zolmitriptan (5 mg).[83]

Neuromodulation of cluster headache attacks with non-invasive vagal nerve stimulation (nVNS) is a second-line acute treatment. nVNS has an effect as an acute treatment in episodic, but not chronic, cluster headache.[22] Pooling data from two randomised clinical trials, pain relief within 15 min was reported by 20 (39%) of 52 participants treated with nVNS, compared with 7 (12%) of 60 participants who received sham stimulation.[84] nVNS is costly, and is not reimbursed in many countries.[85] The proposed mechanism of action of nVNS is inhibition of the trigeminal autonomic reflex.[69] Invasive stimulation of the sphenopalatine ganglion proved effective in up to 62% of attacks in participants with chronic cluster headache in two randomised clinical trials,[86] but there are currently no providers for this treatment. Subcutaneous octreotide, nasal lidocaine, and sublingual ergotamine are potential third-line acute treatments (appendix p 1).

Transitional treatments

Steroids can be administered systemically or locally over the great occipital nerve. Oral corticosteroids have been used in cluster headache for more than 40 years, but only in 2021 was their efficacy supported by data from a randomised clinical trial.[85,87] A treatment plan of prednisone 100 mg orally for 5 days, followed by down-tapering by 20 mg every 3 days as an add-on to verapamil, reduced attack frequency by 2·4 attacks per week (95% CI 0·03–4·8) in participants with episodic cluster headache.[87] Moreover, 20 (35%) of 57 patients had complete attack cessation within the first week.[86] In

	Clinical trial identifier	Outcome	Stage	Study type	Comment
Botulinum toxin type A	NCT03944876	Preventive (chronic cluster headache)	Phase 3	RCT	Blockade of the sphenopalatine ganglion; phase 1 and 2 studies established safety and indicated efficacy[97]
Civamide nasal solution	NCT01341548	Preventive (episodic cluster headache)	Phase 3	RCT	A previous RCT reported efficacy[19]
Erenumab	NCT04970355	Preventive (chronic cluster headache)	Phase 2	RCT	Erenumab is a CGRP receptor monoclonal antibody, approved by FDA and EMA for migraine
High dose vitamin D3 and multivitamin	NCT04570475	Preventive (chronic and episodic cluster headache)	Phase 3	RCT	Case reports indicate decreased frequency, severity, and duration of headache with high-dose vitamin D3[98]
Ketamine and magnesium	NCT04814381	Preventive (chronic cluster headache)	Phase 4	RCT	A previous case series reported efficacy[99]
LSD	NCT03781128	Preventive (chronic and episodic cluster headache)	Phase 2	RCT	Case reports indicate that LSD might abort attacks and extend duration of the remission[85]
LSD (low dose)	NCT05477459	Preventive (chronic cluster headache)	Phase 2	RCT	Case reports indicate LSD might abort attacks and extend duration of the remission
Methylprednisolone	NCT05324748	Preventive (chronic cluster headache)	Phase 3	RCT	Repeated injection over the greater occipital nerve
ONS	NCT05023460	Preventive (chronic cluster headache)	Not provided	RCT	Burst stimulation allows for study masking because it is parastesia-free
ONS	NCT06124534	Safety (chronic cluster headache)	Not provided	Open label	ONS with new device technology (BliStim occipital nerve field stimulation therapy)
Rimegepant	NCT05264714	Preventive (chronic and episodic cluster headache)	Phase 2	Open label	Rimegepant is a CGRP receptor antagonist, approved by the FDA and EMA for migraine
Supraorbital nerve stimulation and ONS	NCT05868044	Safety (chronic cluster headache)	Not provided	Open label	ONS with new device technology (PRIMUS PNS System)

The ongoing trials have a notable emphasis on prevention of cluster headache attacks. The list of trials was obtained by searching Clinicaltrials.gov on March 15, 2024, with condition filtered for cluster headache, study type filtered for interventional, and study status filtered for not yet recruiting, recruiting, and active not recruiting. Multicentre trials with eptinezumab (NCT04688775 and NCT05064397) were completed in 2023, but the results have not yet been published. CGRP=calcitonin gene-related peptide. EMA=European Medicines Agency. FDA=US Food and Drug Administration. LSD=lysergic acid diethylamide. ONS=occipital nerve stimulation. RCT=randomised controlled trial.

Table 2: **Ongoing treatment trials in cluster headache**

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two randomised clinical trials, corticosteroid injections over the great occipital nerve were effective compared with injection of saline in 11 (85%) of 13 patients and 20 (95%) of 21 patients,[88] and 47–100% of people with cluster headache responded in a systematic review of real-world data (appendix p 2).[88] Oral corticosteroids are recommended only for short-term use as they can have severe long-term side-effects. The risk of side-effects is greater for people with chronic cluster headache than for people with episodic cluster headache, thus oral steroids should be used sparingly and only for severe exacerbations. Inhibition of nociceptive signals in the trigeminocervical complex were proposed to mediate the effect of great occipital nerve injections.[89]

Long-term preventive treatments

The first-line preventive verapamil is effective in reducing the frequency or intensity of cluster headache attacks in 50–94% of patients;[90] two randomised clinical trials (both n=30) from 1990 and 2000 found verapamil 360 mg to be superior to lithium and placebo, reporting a 50% and 80% response to verapamil (in the comparator trial of verapamil to lithium, there was no further specification of how this response was evaluated), leading to widespread acceptance of verapamil as the primary preventive treatment (appendix p 2).[18,19–21,90] Real-world data from 400 people with cluster headache suggest that only 41% of these individuals have 50% or greater reduction in either frequency or intensity of their attacks with verapamil.[91]

Whereas the efficacy of verapamil in cluster headache was discovered by chance,[90] CGRP monoclonal antibodies are the first targeted preventive medications to be applied to cluster headache. The proposed mechanism of action is by inhibition of CGRP during attacks, because plasma CGRP levels increase during an attack, and infusion of CGRP in patients with cluster headache can trigger an attack.[33,62] In a randomised clinical trial that included 109 participants with episodic cluster headache, the weekly frequency of cluster headache attacks was reduced by 3·5 (95% CI 0·2–6·7) by galcanezumab compared with placebo.[92] However, in a separate randomised clinical trial of chronic cluster headache, no difference was observed between galcanezumab and placebo (n=237).[93] In 2019, galcanezumab became the first preventive drug to be approved by the US Food and Drug Administration for episodic cluster headache, but was not approved by the European Medicines Agency as the identified efficacy was

Panel 2: **Future research directions and obstacles in cluster headache**

Clinical features

- The diagnostic delay for cluster headache remains long; can a reliable diagnostic biomarker discriminate between cluster headache and other headache disorders to prevent diagnostic delay?
- Short-term and long-term disease activity are both unpredictable; can markers of disease activity help to determine when or whether cluster headache will stop completely?
- Cluster headache can, for some people, transition from episodic to chronic, or vice versa; can clinical features or biomarkers be prognostic for transitions?
- How do genetic subtypes relate to clinical characteristics, bouts, and treatment responses?

Treatment

- Can new bouts and the eventual preventive effect of an early intervention be predicted? Longitudinal studies of participants with episodic cluster headache are needed
- Can identification of a therapeutic predictor allow for more personalised therapy that reduces side-effects and minimises delays in treatment?
- Can assays predict treatment response to, for example, antibodies that target the calcitonin gene-related peptide (CGRP) system? Such assays might also elucidate underlying possible pathophysiological differences in the features of cluster headache between affected individuals

Pathophysiology

- Diurnal and circannual rhythmicity are key features of cluster headache, but how are they regulated, and how do these common biological mechanisms alter the attack susceptibility?
- What are the roles and possible interactions of CGRP and pituitary adenylate cyclase-activating polypeptide 38 in cluster headache?
- What pathophysiological mechanism initiates and halts bouts? This information could could provide valuable insight into prevention of the bout itself, instead of treating attacks during bouts

judged to be too low compared with verapamil. Hence, availability is restricted outside the USA and Canada.[85] Other monoclonal antibodies targeting CGRP that have been tested for cluster headache are fremanezumab and eptinezumab: the two randomised clinical trials of fremenezumab (NCT02945046 and NCT02964338) were terminated after futility analysis[85] and two multicentre studies (one randomised clinical trial [NCT04688775] and one long-term observational study [NCT05064397]) of eptinezumab finished in 2023, but the results have not yet been published. Real-world evidence suggests that CGRP monoclonal antibodies are efficient in treating cluster headache; that this finding has not been shown in randomised clinical trials might be a result of trial methods, selection bias, placebo response, or potentially CGRP monoclonal antibodies being more effective for outcomes such as pain intensity than for the outcomes on attack frequency that were the primary endpoints in trials.

Preventive neuromodulation options include nVNS and invasive occipital nerve stimulation and deep brain stimulation. In an open-label observational study, nVNS as an add-on to the standard of care reduced the weekly frequency of cluster headache attacks by 3·9 (95% CI 0·5–7·2) compared with the standard of care alone.[94] In a randomised clinical trial for chronic cluster headache, occipital nerve stimulation was examined at 100% stimulation and 30% stimulation: half of the participants in both groups had a 50% reduction in attack frequency,[95] which was not considered to be mainly due to placebo effect since beneficial effects were sustained. Hardware-related re-operation (eg, battery replacement) was required in 44 (50%) of 88 participants. Consequently, occipital nerve stimulation might be a viable treatment option for medically refractory chronic cluster headache, but reimbursement varies among countries. Ventral tegmental area deep brain stimulation might be effective despite a paucity of evidence[96] and might be a last option for patients with the most refractory chronic cluster headache (appendix p 4). Lithium, topiramate, melatonin, and frovatriptan are recommended by the European Academy of Neurology if other preventives are insufficient, but they have either no evidence or a lower level of evidence than the other medications we have discussed (appendix p 3).[18]

Emerging treatments

Psilocybine has recently been explored as a treatment for cluster headache, and two ongoing phase 2 trials are currently examining the safety and efficacy of lysergic acid diethylamide (LSD; table 2). Many people with cluster headache report good effects of psychedelics on frequency or intensity of cluster headache attacks.[100] The pathophysiological rationale remains unknown, but both LSD and psilocybine have an acute effect on the pineal gland, which produces melatonin, and the psilocybine response seems to correlate with hypothalamic functional connectivity.[100] Both LSD and psilocybine are 5-HT2A serotonin receptor agonists, which might explain their similar effects.[101] The psychedelic effect might compromise the masking of these treatments in future studies. The effectiveness of LSD and psilocybine is still unknown, as recent studies have been too underpowered to draw a firm conclusion.[100,102] PACAP-38 is an interesting target that could be tested for the treatment of cluster headache. PACAP-38 is expressed in parasympathetic neurons, such as those within the sphenopalatine ganglion, and animal models have shown CGRP and PACAP-38 are both involved in vasodilation, neurogenic inflammation, and nociception.[103] A recent phase 2 trial testing a monoclonal antibody (Lu AG099222) directed against PACAP-38 for treatment of migraine (NCT0513323) reported a reduction in migraine days per month.[104]

Conclusions and future directions

Cluster headache is a devastating disorder, and early recognition is important as several treatment choices are available. Over the past 6 years, research on cluster

headache has revealed new effective treatments, eight genetic loci associated with cluster headache, smoking as a modifiable risk factor, and increased knowledge of regional differences in clinical features.

Cluster headache is a dynamic but chronic disorder, evolving over decades, if not lifelong. The clinical characteristics of cluster headache are well described, but our understanding of the cluster headache cycle and prognosis remain incomplete. The disparity in how chronic and episodic cluster headache respond to treatment suggests that the underlying pathophysiology might be different. Our recommendations for future research directions are shown in panel 2.

One of the most crucial obstacles faced by doctors and patients is the scarcity of affordable acute and efficacious preventive treatments for cluster headache. Large randomised clinical trials have shown the feasibility of conducting such trials for cluster headache and targeting key elements of its pathophysiology. Galcanezumab has shown efficacy compared with placebo and received approval from the FDA, but not from the European Medicines Agency. Acute treatment using neurostimulation of the sphenopalatine ganglion was promising but is no longer available. Other neuromodulation treatments, such as occipital nerve stimulation and nVNS, are safe but not reimbursed in many countries. Thus, despite recent progress, the therapeutic spectrum for most individuals with cluster headache remains largely unchanged. Therefore, an urgent imperative exists for both improving the availability of existing treatments and conducting confirmatory studies and head-to-head trials. The past few years have shown that multicentre collaborations are possible and effective in advancing cluster headache research, so the major obstacle to moving forward is a shortage of funding. Exploring the pathophysiological mechanisms underlying cluster headache, its remission, and the potential genetic influences on disease cycles might provide valuable insights into the internal regulation of cluster headache and open new avenues for therapeutic interventions.

Search strategy and selection criteria

We searched PubMed and Embase on March 15, 2024, for articles published between July 1, 2017 (the final date of the literature search in the previous Review on cluster headache in *The Lancet Neurology*), and March 15, 2024, with no language restrictions. For PubMed, the following search was applied: ("Trigeminal Autonomic Cephalalgias"[Mesh:NoExp]) or "Cluster Headache"[Mesh] or "Cluster Headache" or "Trigeminal Autonomic Cephalalgias". For Embase, the following search was applied: exp cluster headache/ or exp trigeminal autonomic cephalalgia/. Manuscripts were screened in two stages—an abstract screening, and a full text screening—by two assessors (ASP and NL) who selected original research articles and review papers on epidemiology, diagnosis, clinical features, genetics, pathophysiology, and treatment. Papers were selected on the basis of originality, level of evidence, and relevance to this Review. The Covidence tool for scoping reviews was applied to enhance transparency and accuracy of the screening process.

Contributors

ASP and RHJ conceptualised the manuscript. ASP and NL searched and selected the references. ASP wrote the first draft, which was subsequently reviewed and refined by NL and RHJ. S-JW translated, interpreted, and incorporated the guidelines from Taiwan and China. All authors supplemented and revised the draft for critical content, and approved the final version of the manuscript.

Declaration of interests

ASP has received a restricted research grant (payment to their institution) and conference attendance from Lundbeck Pharma, and personal fees from Pfizer for teaching activities. NL has received a restricted research grant from Lundbeck Pharma (payment to their institution), a research grant from the Capital Region Research Foundation, support for conference attendance from Pfizer, and personal fees from teaching activities for general practitioners from Dagens Medicin and Pfizer (personal). PJG reports, over the past 36 months: grants from Celgene and Kallyope; personal fees from Aeon Biopharma, AbbVie, Amgen, eNeura, CoolTech, Dr Reddys, Eli Lilly, Epalex, Linpharma, Lundbeck, Novartis, Pfizer, Sanofi, Satsuma, Shiratronics, and Teva Pharmaceuticals; participation on a data and safety monitoring board for Aeon Biopharma and Man & Science; personal fees for advice through Gerson Lehrman Group, Guidepoint, SAI Med Partners, and Vector Metric; fees for educational materials from CME Outfitters; publishing royalties or fees from Massachusetts Medical Society, Oxford University Press, UptoDate, and Wolters Kluwer; and a patent for magnetic stimulation for headache (WO2016090333 A1) assigned to eNeura, without fee. PJG is a board member of the American Headache Society, Migraine Trust, and Organisation for Understanding Cluster Headache. ACB reports honoraria for presentations from Novartis, Teva, and Lundbeck; and research funding from the Swedish Brain Foundation and the Mellby Gård Foundation. S-JW has received honoraria as a moderator from AbbVie, Biogen, Eli Lilly, Hava Biopharma, and Pfizer; has received consulting fees from AbbVie, Eli Lilly Taiwan, Percept, and Pfizer Taiwan; and has received research grants from the Taiwan branches of Eli Lilly, Lundbeck, Novartis, and Orient Europharma. RF reports research grants from Bioprojet, Jazz Pharmaceuticals, Netherlands Brain Foundation, and ZonMW (fee for institution); educational honoraria from Novartis (fee for institution), Teva Pharmaceutical Industries, Bioprojet, and Lundbeck Pharma (personal fees); consultancy for AbbVie, Eli Lilly, and Takeda (fee for institution); and is a member of the cluster headache section of the Dutch Headache guidelines (unpaid). MB reports grant funding from the Will Erwin Headache Research Foundation; travel support for attending meetings from the American Headache Society; has served as a consultant for Lundbeck, Beckley Psytech, Praxis Precision Medicines, and PureTech Health; is a site investigator for a cluster headache clinical trial funded by Lundbeck; was a paid guest for a video podcast by the American Academy of Neurology, is a paid survey respondent for Doximetry, and is an unpaid member of the medical advisory board of Clusterbusters. S-JC was involved as a site investigator of a multicentre trial sponsored by Allergan, AbbVie, Hyundai Pharmaceutical, Ildong Pharmaceutical, Eli Lilly, Pfizer, and Lundbeck; and has received lecture fees or advisory honoraria from AbbVie Korea, Lundbeck, Eli Lilly Korea, SK Chemicals, Teva Pharmaceutical Industries, and Pfizer. MFPP reports consulting fees for AbbVie–Allergan, Ache, Eli Lilly, Eurofarma, Libbs, Lundbeck, Kenvue, Pfizer, Sanofi-Aventis, and Teva Pharmaceutical Industries; travel support from Teva; participation in advisory boards for AbbVie-Allergan, Eli Lilly, Pfizer, Kenvue, Eurofarma, and Sonofi-Aventis; and is president of the Brazilian Association for Cluster Headache and Migraine (unpaid). RHJ received a restricted research grant (for institution) for work on cluster headache from Lundbeck Pharma; received a research grant for treatment trial for idiopathic intracranial hypertension (for institution) from Novo Nordisk Foundation; is on an

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advisory board for Lundbeck Pharma and has received fees for participation on an advisory board (for institution); has received personal fees for educational and teaching activities from Pfizer, Teva Pharmaceutical Industries, Novartis, AbbVie, Lundbeck, and Eli Lilly; is chair of the Master of Headache Disorders at the University of Copenhagen, a director of the Danish Headache Center, and undertakes unpaid activities as a director of Lifting The Burden.

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