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Chronic cluster headache is a rare disease: Implications for diagnosis, treatment and public health

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Abstract

Cluster headache (CH) is a rare and painful primary headache disorder characterized by severe unilateral pain and cranial autonomic symptoms. This perspective examines the epidemiological evidence supporting the classification of chronic cluster headache (CCH) as a rare disease, noting a prevalence of CH of approximately 124 per 100,000 individuals, with only 3.5–13.7% manifesting CCH. This prevalence meets criteria established by both the US Food and Drug Administration and European Medicines Agency for rare disease designation. The rarity of CCH creates substantial clinical and research challenges, including prolonged diagnostic delays, limited research funding and a dearth of approved treatments. The economic burden is particularly notable, with annual costs exceeding €20,000 per patient. Addressing these challenges requires a coordinated approach focusing on increased research funding, enhanced policy advocacy, improved diagnostic training and the development of comprehensive disease registries to advance both patient care and scientific understanding of this devastating neurological condition.

Keywords

chronic disease, cluster headache, health care costs, public health, rare disease

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Introduction

Cluster headache (CH) is one of the most debilitating primary headache disorders, characterized by excruciating unilateral pain predominantly in the orbital region, accompanied by ipsilateral cranial autonomic symptoms and/or restlessness (1). The pain intensity of CH attacks is considered among the most severe known to humans, surpassing that of childbirth, bone fractures and gunshot wounds (2). Despite its relatively low prevalence, estimated at overall 124 (confidence interval 101–151) per 100,000 individuals (3), CH imposes a substantial burden on both patients and healthcare systems.

CH imposes devastating health burdens on affected individuals, causing excruciating pain that significantly impairs quality of life and psychological well-being. Studies consistently demonstrate that CH patients exhibit substantially elevated rates of depression, anxiety and suicidal ideation, with reports indicating that 47–55% experience suicidal thoughts and 1.3–2% attempt suicide (4). The condition's debilitating nature prevents normal functioning during attacks, necessitating complete cessation of activities and often resulting in occupational disability, with patients twice as likely to receive disability pensions compared to the general population (5). Even between attacks, patients report reduced quality of life, with persistent anxiety

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about the next attack and sleep disturbances that continue even during remission periods (6).

The socioeconomic consequences of CH extend beyond individual suffering to create substantial healthcare and societal costs. Studies show that CH patients have significantly higher healthcare utilization compared to controls, with two to three times more outpatient visits (26.5 vs. 12.4), hospital admissions (0.2 vs. 0.1) and emergency department visits (1.0 vs. 0.3) (all $p < 0.001$) (7). The economic impact is particularly pronounced in chronic CH (CCH) patients, with mean annual direct costs of €9158 and indirect costs of €11,809 per CCH patient (total annual cost more than €20,000), placing it among the most costly neurological disorders (8,9).

Cluster headache prevalence

Epidemiological studies have found an overall CH prevalence of 41–381 individuals per 100,000. A meta-analysis by Fischera et al. (3) found a lifetime prevalence of 124 individuals per 100,000 (95% confidence interval = 101–151), whereas more recent epidemiological studies found a lower lifetime prevalence of 41–87 individuals per 100,000 (10,11). The Veterans Health Administration cohort study showed 1 1-year prevalence of CH diagnosis ranging from 0.08% to 0.10% for women and 0.10% to 0.18% for men (12). This prevalence is similar to the age-standardized global prevalence of Parkinson's disease of 98 individuals per 100,000. Compared with other trigeminal autonomic cephalalgias in a Norwegian registry study, the one-year prevalences were 14.6/100,000 (CH), 2.2/100,000 (hemicrania continua), 1.4/100,000 (paroxysmal hemicrania) and 1.2/100,000 (SUNCT/SUNA; i.e. short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing/short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms) (13).

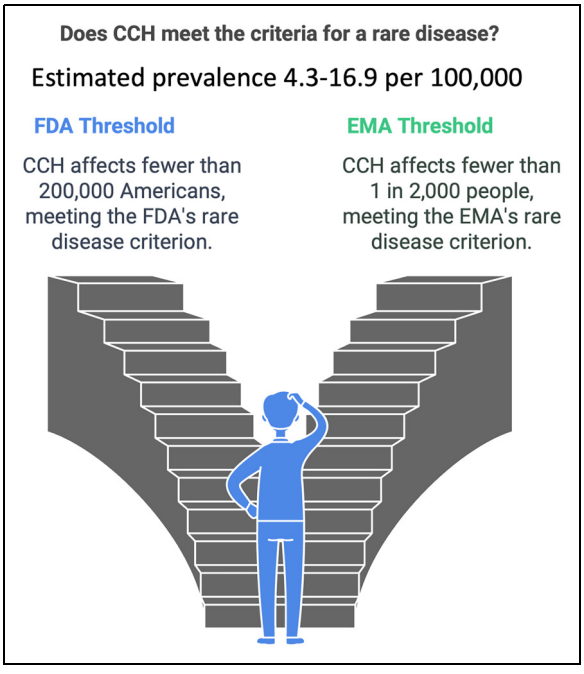

Figure 1. Chronic cluster headache (CCH) meets US Food and Drug Administration (FDA) and European Medicines Agency (EMA) thresholds for rare disease. Created using Napkin AI.

The exact prevalence of CCH is challenging to determine due to its rarity, diagnostic complexities and reporting limitations (14–17). A notable East–West disparity exists in the prevalence of CCH. Studies in Eastern populations have found that CCH is relatively rare compared to Western populations. The proportion of CCH in Eastern countries varied between 0% and 7.5% of all CH patients (18). For example, a study in Japan found that only 3.5% of CH patients were diagnosed with the chronic form (19), while a recent study in China reported a prevalence of CCH at 2.33% among CH patients (20). In contrast, Western studies have reported higher proportions of chronic cases, ranging from 3.8% to 13.7% of CH patients (3). Based on the maximal ratios (13.7%), the estimated CCH patients in the USA (calculated at 381 per 100,000) fall below both the US Food and Drug Administration (FDA) threshold of 200,000 affected Americans (total diagnosed population) and the European Medicines Agency (EMA) criterion of fewer than one in 2000 people (Figure 1) (21,22). There is no doubt that CCH is a rare disease, but, in some countries, even all CH can also be considered rare. As an example, the prevalence of CH in Brazil is 41 per 100.000 inhabitants, below the FDA and EMA threshold, as well as the local Brazilian threshold considered (65 per 100.000).

As with other rare diseases, CCH patients experience diagnostic delay, a lack of understanding among the public and medical community, and higher costs for disease-specific treatments (23). Clinical trial recruitment for rare disorders is challenging, and effective treatments are typically described in open-label studies or case series, or by patient report, before their effectiveness is established with placebo-controlled clinical trials (24). Formally classifying CCH as a rare disease carries significant implications for patient care, research funding and therapeutic development. Given the extreme disability associated with CCH and the limited therapeutic options currently available, securing a rare disease designation represents a crucial step toward improving care for this severely affected patient population.

CCH warrants recognition as a distinct rare disease separate from episodic cluster headache (ECH) based on fundamental differences in pathophysiology, treatment response and disease behavior patterns, despite being often viewed as merely a continuum of the same condition, similar to episodic and chronic migraine. Unlike migraine, where the episodic–chronic distinction is based primarily

on attack frequency, ECH and CCH represent fundamentally different disease patterns, with ECH characterized by prolonged attack-free remission periods lasting months to years, while CCH patients experience constant symptoms with remissions lasting less than three months (1). Treatment responses diverge significantly between the subtypes, with galcanezumab showing efficacy in ECH but failing in CCH (25,26), and non-invasive vagus nerve stimulation demonstrating effectiveness only in episodic patients (27). Furthermore, calcitonin gene-related peptide (CGRP) provocation studies reveal distinct patterns: 89% of episodic patients were susceptible to CGRP-induced attacks during active phases but 0% during remission, while chronic patients showed persistent but reduced susceptibility (50% of patients) (28). These fundamental distinctions reflect deeper pathophysiological differences rather than simply representing varying degrees of the same condition. Recognizing this distinction has important implications for patient management, treatment selection, and future research directions in CH care.

Implications for diagnosis, research and treatment

The low prevalence of CH has far-reaching implications across diagnosis, research and treatment domains (Figure 2). Diagnostic delay remains a substantial challenge, with studies documenting average delays of 5.7 years before correct diagnosis (29). This prolonged diagnostic journey is attributable to several factors, including limited healthcare provider exposure to and experience with CH, symptom overlap with more common conditions such as migraine or sinusitis, and insufficient awareness of distinctive clinical features among primary care physicians (15). The diagnostic challenge disproportionately affects certain populations, with women and those with early-onset disease experiencing significantly longer delays, further exacerbating health disparities (30). These implications are even more aggravated in CCH, where the extreme rarity and continuous nature of symptoms create additional barriers to recognition and appropriate management. These diagnostic hurdles are particularly concerning given CH's status as one of the most painful conditions known to medicine, with substantial impacts on quality of life and elevated suicide risk (8). Suicidal thoughts are reported by 47–55% and attempts by 1.3–2% of people with CH (4).

The rarity of CH presents formidable methodological challenges for conducting adequately powered clinical trials, resulting in a limited evidence base for treatment decisions. Out of 27 unique placebo-controlled prevention trials for ECH and CCH, five were terminated early, and seven of the 10 completed trials enrolled fewer patients than planned or failed to report the planned sample size (31). Due to the low prevalence, CH trials often require multiple centers across different regions or countries to recruit sufficient participants, which adds complexity to trial management and increases variability. Consequently, statistical power limitations have contributed to the scarcity of medications approved specifically for CH prevention, with most current treatments being used off-label and based on limited evidence (32). This restricted evidence base has contributed to regulatory divergence, exemplified by the FDA approving galcanezumab for ECH prevention, while the EMA declined approval for both ECH and CCH (4).

The low prevalence of CH creates substantial barriers for research funding and pharmaceutical development, resulting in significant treatment gaps for this severely painful condition. Given the small patient population, pharmaceutical companies may have reduced financial incentives to develop CH-specific treatments (32,33). This economic reality creates a detrimental cycle wherein inadequate research funding yields fewer clinical trials, thereby limiting the evidence base for informed treatment decisions. Further complicating this landscape is the inherent difficulty in recruiting participants for placebo-controlled CH trials, as patients suffering from this excruciating condition are understandably reluctant to risk receiving a placebo (31). Adding the inherent risk of a negative trial outcome and the pricing uncertainty, even if a trial would be positive, leads to a situation in which CH trials are rarely conducted despite the limited availability of approved preventive treatment options in ECH and no approved preventive treatment option in CCH. The current research landscape inadequately addresses the clinical needs of patients suffering from this severe neurological disorder.

Addressing the challenges presented by the rarity of CH demands a coordinated, multi-stakeholder response involving medical professionals, researchers, pharmaceutical companies and regulatory authorities. While understanding CH pathophysiology has progressed in recent years, substantial unmet patient needs persist, necessitating innovative approaches to evidence generation and therapeutic development tailored to rare disease contexts (8). Future advances will likely depend on methodological innovations that accommodate the unique challenges of studying rare diseases, including adaptive trial designs, enriched enrollment strategies and novel statistical approaches that maximize information from limited patient populations. Additionally, integrating real-world evidence into regulatory decision-making frameworks represents a promising pathway for advancing therapeutic options for this severely debilitating condition, potentially offering a more flexible route to treatment approval while maintaining rigorous efficacy and safety standards (34).

Public health implications

CCH warrants classification as a rare disease due to its low prevalence and the significant impact on patients' quality of life. Several strategies can be implemented to improve the

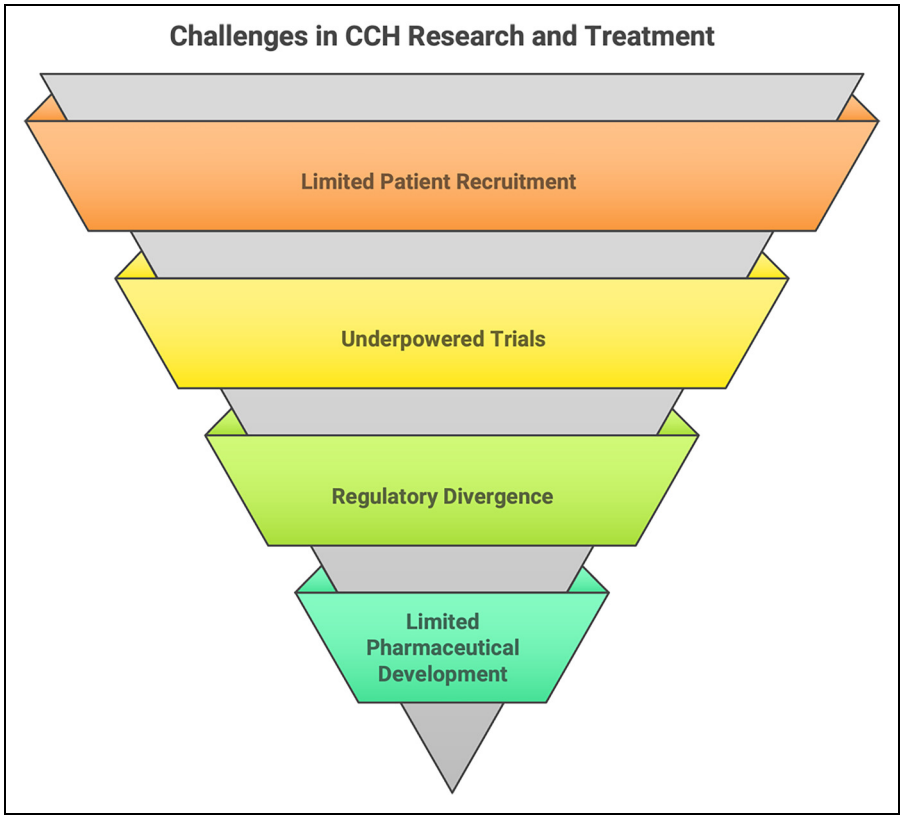

Figure 2. Challenges in chronic cluster headache (CCH) research and treatment. Created using Napkin AI.

care of patients with CCH, considering the substantial economic burden, the lack of FDA-approved treatments specifically for this condition and the current treatment options available. A comprehensive public health approach to CCH should encompass four interconnected strategies: enhanced research funding, strategic policy advocacy, improved clinical training and robust disease registry development.

Research funding

Developing evidence-based interventions for CCH requires substantial increases in targeted research funding. National funding bodies, including the National Institutes of Health, should prioritize CCH research to advance understanding of its pathophysiology and identify effective treatments. Multi-institutional collaborative efforts are crucial for rare diseases like CCH, where patient recruitment challenges necessitate coordinated research networks. Such collaborative frameworks facilitate larger sample sizes for clinical trials and support mechanistic studies that may lead to targeted therapeutic approaches (35).

Policy advocacy

Strengthening patient advocacy groups can help raise awareness and influence health policy decisions. Advocacy organizations are pivotal in lobbying for better healthcare policies, insurance coverage for treatments, and increased research funding for rare disorders. A key advocacy goal should include pursuing orphan designation for CCH, which would provide regulatory incentives for pharmaceutical companies to develop targeted treatments and could facilitate expedited approval pathways. The collaborative partnership between patient advocacy groups, scientists and government officials has been instrumental in adopting public policies and the Orphan Drug Act, significantly impacting rare disease research and treatment (36,37).

Improved diagnostic criteria and training

Reducing the substantial diagnostic delay in CCH requires enhanced education among healthcare providers. Targeted training programs should focus on specific CCH diagnostic criteria and evidence-based treatment protocols for primary care physicians, general neurologists, otolaryngologists and dentists (17). These educational initiatives should emphasize recognition of CCH's distinctive clinical presentation and appropriate medical management strategies to prevent misdiagnosis and inappropriate treatments. Continuing medical education on CCH would significantly reduce the diagnostic delay currently experienced by patients,

thereby decreasing unnecessary suffering and economic burden (38).

Disease registries

National and international CCH registries represent critical infrastructure for advancing understanding of this rare disease. Comprehensive registries facilitate systematic data collection on epidemiology, treatment outcomes and natural disease course (34). The RegistRare Network in Italy provides an exemplary model, having established a specialized registry for rare primary headaches, including CCH, across multiple tertiary headache centers (14). Such registries bridge knowledge gaps regarding rare headache disorders through standardized data collection protocols and enable cross-institutional research collaboration while providing essential metrics for healthcare resource allocation and policy development.

Conclusions

CCH merits formal recognition as a rare disease, with prevalence rates well below established thresholds set by regulatory agencies. This designation would acknowledge patients' exceptional challenges, including significant diagnostic delays, limited treatment options and substantial economic burdens. A coordinated approach integrating enhanced research funding, strategic policy advocacy, improved clinical training and comprehensive disease registries represents the most promising strategy for addressing these challenges. By formally recognizing the status of CCH as a rare disease and mobilizing coordinated efforts among all stakeholders, the medical community can work toward alleviating the profound suffering experienced by individuals with this excruciating and debilitating condition while potentially reducing its considerable socioeconomic impact.

Clinical implications

- Chronic cluster headache affects only 3.5–13.7% of cluster headache patients but lacks formal rare disease recognition, creating barriers to research funding and treatment development despite meeting FDA and EMA prevalence thresholds.
- Patients experience devastating diagnostic delays averaging 5.7 years and substantial economic burden exceeding €20,000 annually per patient, reflecting the urgent need for improved clinical awareness and training.
- Current treatment options remain limited, with no FDA-approved preventive therapies specifically for chronic cluster headache, leaving patients with this excruciating condition inadequately managed.
- Formal rare disease designation could facilitate orphan drug development, enhance research funding and improve patient access to specialized care through coordinated public health initiatives.

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