Cluster Headache: The Master Reference

Important — please read before using this document.

This is not medical advice. It is an independent, privately maintained research summary, revised continuously, and it may contain errors, omissions or findings that have since been superseded. Nothing in it is a recommendation. Treatment decisions belong with a qualified clinician who knows your history.

Several treatments described here carry serious documented risks, and the legal status and availability of others differ by country. Descriptions are included for completeness, not as encouragement.

This copy is a snapshot. The document is revised monthly; this file was generated on 2026-08-15. The current version is always at https://clusterfuk.world. If you pass this file on, please keep this notice attached — a stale copy presented as current is how good information becomes bad information.

If you are in crisis, please reach a person now: Lifeline 13 11 14 (Australia) · Samaritans 116 123 (UK) · 988 (US & Canada) · or find a service in your country at findahelpline.com.

Full notice: https://clusterfuk.world/disclaimer/

Cluster Headache: The Master Reference

Assembled from five research chapters: history & nature · mechanism · epidemiology · types & diagnosis · treatment · citizen science & community knowledge · the research frontier

Version 1.0 — assembled 13 August 2026 Compiled as a personal reference document. Owner: Ben.

About this document

This document is an editorial assembly of five separately researched chapters. Nothing factual has been added, altered or resolved during assembly: the editor's job was confined to rearranging, deduplicating and smoothing. Where chapters repeat material, the fullest version was kept in its best home and the duplicate replaced with a cross-reference; where chapters *contradict* each other, both claims were kept and the conflict is flagged in the dedicated **Unresolved Conflicts** section rather than adjudicated. Anything that looked like a research error was left as found and listed under **Editor's Queries**.

Conventions carried over from the source chapters:

- Every claim carries an evidence tag: `[PEER-REVIEWED]`, `[PREPRINT/TRIAL]`, `[CITIZEN-SCIENCE]`, `[COMMUNITY-REPORT]`, `[HISTORICAL/CULTURAL]` (Part V also uses `[OFFICIAL/POLICY]` for government and regulatory documents). Community reports are never discarded for being anecdotal — they are labelled honestly and included because patterns in anecdote are data.
- Where sources conflict, the conflict is presented explicitly rather than smoothed over. "Unknown" and "contested" are treated as valid, final answers where that is what the evidence supports.
- Section numbers restart within each part and are retained unchanged from the source chapters. Internal cross-references of the form "§x.y" refer to sections within the same part unless another part is named. Pointers added during assembly are always marked *(Editor's note: …)*.
- All diagrams and tables are retained as found. No two diagrams from different chapters merged cleanly, so none were combined.
- Parts IV, V and VI keep their own reference lists (retitled "References (Part …)"); Parts I–III and VII cite sources inline.

Table of Contents

Executive Summary

Drawn entirely from the chapters that follow; every figure below is sourced and tagged in the body text.

Cluster headache (CH) is defined by ICHD-3 as attacks of severe, strictly unilateral orbital, supraorbital and/or temporal pain lasting 15–180 minutes untreated, occurring between once every other day and eight times a day, accompanied by ipsilateral autonomic signs (tearing, nasal congestion, drooping eyelid) and/or restlessness. It comes in two forms: episodic (bouts separated by remissions of three months or more) and chronic (a year or more without such remission). Chronic CH is roughly 10–15% of Western cases but markedly rarer (about 2–7.5%) in East Asian cohorts, a difference nobody has explained. The best quantitative pain study available (n=1,604) puts mean attack pain at 9.7 ± 0.6 out of 10 — 72.1% of respondents rated it a full 10 — significantly above childbirth, pancreatitis and kidney stones. The nickname “suicide headache” is old and its etymology unverified, but the burden behind it is documented: suicidality is strongly state-dependent (passive suicidal ideation 64.2% *during* attacks, near zero in remission), while whether CH carries a true population-level excess suicide risk is genuinely contested between a 2025 CH-specific meta-analysis and a large Danish registry study.

Historically, the condition was described piecemeal for three centuries — priority is contested among Tulp (1641), Willis (1672), van Swieten (1745) and others — recognised as its own entity by Wilfred Harris in 1926, named “cluster headache” by Kunkle in 1952, and made an independent diagnosis only in 1988. Mechanistically, the 1998 Lancet PET finding of posterior hypothalamic activation during attacks moved the field from vascular theories to a central, brain-origin model; the current view treats the hypothalamus as a “crossroads” in a wider network rather than a sole generator. The trigeminal-autonomic reflex explains why pain and same-side tearing arrive together. Much of the rest is contested: CGRP was classically elevated in CH but a well-powered 2024 Danish study found it *lower* than controls; orexin findings are contradictory; hypothalamic volume findings do not replicate. Genetics is firmer ground — the 2023 GWAS found eight loci, SNP heritability of 14.5%, and Mendelian-randomisation evidence that smoking is *causal* for developing CH — which sits paradoxically alongside consistent clinical evidence that quitting smoking essentially never improves established disease. The disease’s clockwork is its most distinctive feature: about 70% of patients show circadian attack timing with a 2 a.m. peak, and bouts cluster around the equinoxes, tracking the *speed* of daylight change rather than the solstices.

Epidemiologically CH affects roughly 1 in 1,000 people (pooled lifetime prevalence 124/100,000), with a pooled male:female ratio of 4.3:1 — whether that ratio has genuinely narrowed over recent decades is contested, with the most population-representative source unable to confirm the narrowing that clinic cohorts report. Onset peaks around age 30. Diagnostic delay pooled across studies is 10.43 years, but it is shrinking fast (Danish data: 39 years for 1950s onset, 0.9 years for 2010s onset); migraine, trigeminal neuralgia, sinusitis and dental disease are the standard misdiagnoses, and a meaningful minority of patients undergo unnecessary sinus or dental surgery first. No population-based prevalence study exists anywhere in the Southern Hemisphere, including Australia.

In treatment, one pattern dominates everything: **almost every therapy performs worse in chronic than episodic CH, and the headline figure quoted is almost always the episodic one.** The acute mainstays are high-flow oxygen (78% relief at 15 minutes vs 20% on air in the pivotal RCT; no daily ceiling, which makes it the structural workhorse for frequent attacks) and subcutaneous sumatriptan 6 mg (75% relief at 15 minutes, NNT 2.4, but capped at two injections per day — formally under-treating anyone with more than two attacks daily). Citizen-science data find the two comparably effective at adequate oxygen flow. For bridging, suboccipital/GON steroid injection has two positive RCTs and was the *only* Level A preventive in the AHS 2016 guideline. Verapamil remains first-line prevention on a strikingly thin, 26-year-old randomised base, with real arrhythmia risk and documented monitoring failure (41% of one 217-patient series had never had an ECG). CGRP monoclonal antibodies produced one marginal win (galcanezumab, episodic only) and failed every chronic-CH trial across three drugs. In neuromodulation, the best-evidenced device (SPG stimulation) is commercially unavailable after its manufacturer collapsed, stranding 700+ implanted patients; ONS is obtainable but two controlled designs failed to show the electricity itself is the active ingredient; DBS carries a documented death. Access, not efficacy, is often the binding constraint: Germany and Japan formally license and reimburse CH oxygen, while Australia — on the verified comparison in Part V — has the worst access position of the four jurisdictions reviewed: no PBS pathway for oxygen, no PBS listing for the injectable sumatriptan that is TGA-labelled *specifically for CH*, and no nasal triptan on the market at all.

The patient community has repeatedly outrun formal medicine. The clearest case is psychedelics: from a 1998 message-board report through Clusterbusters (founded 2002) to a 2006 Harvard survey and controlled Yale trials from 2022, with the community's claim that sub-hallucinogenic doses work now substantially validated. The high-dose vitamin D3 "Batch protocol" is widely used but its one formal RCT was terminated in 2024 on recruitment failure; energy-drink aborts, reported constantly, have never been formally tested. In citizen-science surveys, serotonergic psychedelics rank as the *most* effective self-reported prophylactic (~75%), above verapamil and corticosteroids — the largest community-vs-trial gap identified anywhere in these chapters.

At the frontier, PACAP is arguably the best-evidenced untried drug target in headache medicine (plasma PACAP-38 elevated 49.8% in chronic CH) with precisely zero CH trials anywhere; orexin has never been tested in CH at all. The live pipeline includes LSD minidosing (recruiting), Ceruvia's non-hallucinogenic BOL-148 (Phase 1/2 planned), candesartan Phase 3s, sodium oxybate for nocturnal attacks, and the first circadian light-therapy trial. Chronic CH increasingly looks biologically distinct — pro-inflammatory where episodic-in-bout looks anti-inflammatory — and has been argued for rare-disease designation. Structurally, the field is starved: the UK's three major funders have given CH £0 against roughly £227 million for comparably prevalent multiple sclerosis, the NIH runs two CH-specific grants, and patient organisations — on budgets as small as OUCH(UK)'s £29,444 a year — are doing the registry, survey and advocacy work that public funders are not. The Watchlist at the end of this document is the live monitoring table for what happens next.

Part I — The History and Nature of Cluster Headaches

Source: Chapter 1 (history and nature), sections 1–2. Section numbering retained from the source chapter.

The story begins with three centuries of physicians describing the same condition under different names — and with what the condition actually is, and what it feels like from the inside.

Compiled as a personal reference document. Every claim below carries an evidence tag: `[PEER-REVIEWED]`, `[PREPRINT/TRIAL]`, `[CITIZEN-SCIENCE]`, `[COMMUNITY-REPORT]`, *or* `[HISTORICAL/CULTURAL]`. *Community reports are never discarded for being anecdotal — they are labelled honestly and included because patterns in anecdote are data. Where sources conflict, the conflict is presented explicitly rather than smoothed over. "Unknown" and "contested" are treated as valid, final answers where that is what the evidence supports.*

---

1. History

1.1 The priority question: who described it first?

Historians of headache medicine do not agree on who first documented cluster headache (CH), and several credible claims compete for priority. This disagreement is itself part of the story: Pearce (2007) calls one commonly repeated "first description" claim (Isler's 1993 attribution to Gerard van Swieten) "gratuitous," pointing out that Nicolaes Tulp (1641) and Thomas Willis (1672) "have attracted claims for priority" of their own `[HISTORICAL/CULTURAL]` (Pearce, PMC2117620).

The candidate earliest accounts, roughly in chronological order:

- **Nicolaes Tulp**, 1641 — the case of Isaak van Halmaal, often cited as the earliest plausible description `[HISTORICAL/CULTURAL]` (PMID 8242723).
- **Thomas Willis**, *De Anima Brutorum*, 1672 `[HISTORICAL/CULTURAL]`.
- **Abraham de la Pryme**, c. 1702 — an English diarist's account, analysed retrospectively in *Cephalalgia* 2010 `[PEER-REVIEWED analysis of a HISTORICAL/CULTURAL source]` (doi: 10.1177/0333102410370871).
- **Francisco Suárez de Ribera**, 1726, Spain `[HISTORICAL/CULTURAL]` (PMID 21768182).
- **Gerard van Swieten**, 1745 — the account most often popularised as "the first," per Isler 1993 `[HISTORICAL/CULTURAL]` (PMID 8358775).
- Other 18th-century German cases: Oppermann (1747, Regensburg, described as "hemicrania horologica" — "clockwork hemicrania," a strikingly apt name for the circadian pattern discussed in Section 3), Morgagni (1761, Padua), and Whytt (1764, Edinburgh) — documented via the German historical wiki ck-wissen.de and cross-checked against Pohl (2022) `[HISTORICAL/CULTURAL]` (Pohl, *Cephalalgia Reports* 2022, snippet access only — full text blocked by publisher).

Non-Western and folk accounts (labelled `[HISTORICAL/CULTURAL]` throughout): The most substantive pre-modern non-Western parallel is the Ayurvedic concept of *Suryavarta*, attributed to the surgeon Sushruta — a circadian, periorbital headache described as tracking the sun's movement. This is plausible as an early CH-like description but not confirmed as CH specifically. The Persian/Arabic term *shaqiqa* ("shaqhiqheh") is generally understood as a migraine analogue rather than a CH-specific term. No confirmed pre-modern Traditional Chinese Medicine description of CH exists; TCM engagement with the condition appears to be a modern clinical adaptation rather than an ancient one.

1.2 The 19th century: fragments before synthesis

Through the 1800s, CH was described piecemeal, under many different names, without being recognised as a single distinct entity:

- **Müller**, 1813, Frankfurt — regarded as the first German-language report `[HISTORICAL/CULTURAL]`.

- **Marshall Hall**, 1836 — “hemicrania intermittens” / “brow ague” `[HISTORICAL/CULTURAL]`.
- **Romberg**, 1840 — “ciliary neuralgia”; a 1992 commentary by Pearce suggests this description “may merit priority” for capturing the syndrome accurately `[HISTORICAL/CULTURAL, with a PEER-REVIEWED retrospective assessment]`.
- **Möllendorff**, 1867 — “Red migraine”; historians note this description does not fully meet modern CH criteria `[HISTORICAL/CULTURAL]`.
- **Eulenburg**, 1871–1883 — “Hemicrania angioparalytica” and related terms; scholars disagree on whether this represents true CH or migraine `[HISTORICAL/CULTURAL, contested]`.
- **Francis Kilvert’s diary**, 1870s — a speculative retrospective diagnosis based on a English clergyman’s diary entries, analysed by Larner `[HISTORICAL/CULTURAL, speculative]`.
- **Sluder**, 1908, and **Vail**, 1932 — “sphenopalatine ganglion neuralgia” / “Vidian neuralgia,” an anatomically-focused theory that would echo (and be refuted, see §3.6) almost a century later `[HISTORICAL/CULTURAL]`.
- **Bing**, 1913 — “erythroprosopalgia.” Pohl (2022) notes the original description lacked strict unilaterality (only added in a 1945 revision) and lacked lacrimation, miosis, and nocturnal predominance — i.e., it was not yet a full match to the modern syndrome `[HISTORICAL/CULTURAL, with a PEER-REVIEWED critical re-reading]`.

1.3 Wilfred Harris and the 1926 turning point

Wilfred Harris’s 1926 monograph, *Neuritis and Neuralgia*, is regarded by several headache historians (Rooke, Rushton, Peters, as summarised by Pearce 2023) as the **first genuine recognition of CH as an entity separate from both migraine and trigeminal neuralgia** `[HISTORICAL/CULTURAL, PEER-REVIEWED historiography]`. This matters because it complicates the popular story that follows: historians argue that **Bacchus Traver Horton’s** 1939 “new syndrome” substantially duplicated Harris’s earlier, more complete account, even though Horton’s name became far more strongly attached to the condition in the decades that followed.

1.4 Horton, histamine, and the “suicide headache”

- **Horton BT, MacLean AR, Craig WM.** “A new syndrome of vascular headache: results of treatment with histamine.” *Proc Staff Meet Mayo Clin*. 1939;14:257–260. `[PEER-REVIEWED]` — the primary source located for the description that made Horton’s name synonymous with CH for much of the mid-20th century.
- Horton later termed it **“histaminic cephalgia”** (*J Lancet* 1952;72:92–98) `[PEER-REVIEWED]`, reflecting his belief — later abandoned as a general explanation — that histamine release was central to the attack (see §3.6 for the fate of vascular/histamine theories).
- The nickname **“suicide headache”** has a genuinely contested origin. One line of sourcing (JAMA) ties it to Horton’s 1939 description; a separate Italian source (leadershipmedica.it) claims it was coined by unnamed French authors. Neither claim is confirmed by primary-source verification in this research pass — **this is flagged as a genuinely unresolved point of etymology**, not a settled fact `[HISTORICAL/CULTURAL, contested]`.

Ekbom’s dissent. Kaare Ekbom (1947, *Acta Psychiatr Neurol Suppl* 46:105–113) `[PEER-REVIEWED]` proposed the term “Harris-Horton Disease,” but importantly **disputed the histamine-causation theory** even at this early stage, treating patients with oral ergotamine instead. Ekbom would go on to suggest the episodic/chronic distinction as early as 1971 — a distinction not formally adopted into classification until 2004 (see §1.6).

1.5 Naming evolution: a syndrome hunting for its name

The official IHS historical table (reproduced here from the sources) traces an unusually long chain of names for the same underlying condition, reflecting decades of competing anatomical and physiological theories about *where* the problem lived before consensus was reached:

Year	Name	Proposed by
1867	Red migraine	Möllendorff
1883	Angioparalytic hemicrania	Eulenburg
1910	Sphenopalatine ganglion neuralgia	Sluder
1913	Erythroprosopalgia	Bing
1925	Syndrome de vasodilatation…	Vallery-Radot / Blamoutier
1926	Ciliary neuralgia	Harris
1931	Syndrome du nerf nasal	Charlin
1932	Vidian neuralgia	Vail
1935	Autonomic faciocephalalgia	Brickner / Riley
1936	Migrainous neuralgia	Harris
1939	Erythromelalgia of the head	Horton et al.
1947	Greater superficial petrosal neuralgia	Gardner et al.
1952	Histaminic cephalgia	Horton
1952	**Cluster headache**	Kunkle et al.

`[HISTORICAL/CULTURAL, tabulated from PEER-REVIEWED primary sources]`. A parallel German tradition used **"Bing-Horton headache syndrome"** (Kaemmerer, 1961), a term still preserved today in ICD-10 code G44.0 `[HISTORICAL/CULTURAL]`.

Kunkle EC, Pfeiffer JB Jr, Wilhoit WM, Hamrick LW Jr. "Recurrent brief headache in cluster pattern." *Trans Am Neurol Assoc*. 1952;56(77th Meeting):240–243. `[PEER-REVIEWED]` — this is the paper that coined the name that stuck. It is a small irony of history that Kunkle himself regarded the condition as a migraine *variant* at the time, not an independent disease entity — the name outlived its author's own nosological view.

1.6 From migraine subtype to independent diagnosis: the classification story

- Before 1988, CH was classified as a subtype of migraine (per the 1962 Ad Hoc Committee classification) `[HISTORICAL/CULTURAL]`.
- **ICHD-1 (1988)** made CH an independent diagnostic entity for the first time, introducing the episodic/chronic subtype split within a shared chapter titled "Cluster headache and chronic paroxysmal hemicrania" `[PEER-REVIEWED, official classification]`.
- **ICHD-2 (2004)** introduced the umbrella category **Trigeminal Autonomic Cephalalgias (TACs)**, grouping CH with paroxysmal hemicrania (PH) and SUNCT, and added restlessness/agitation as a diagnostic criterion for the first time `[PEER-REVIEWED]`.
- **ICHD-3** (2013 beta, finalised 2018) tested whether facial flushing and ear fullness should be added as new criterion features. Field testing (Moon et al. 2019) found these features "did not add to diagnostic discrimination," so they were relegated to an appendix rather than the main criteria — a useful reminder that even very recent, formal diagnostic criteria are actively tested and revised, not handed down complete `[PEER-REVIEWED]`. ICHD-3 also finalised the chronic-CH definition around a remission threshold of less than 3 months (see §2.1 for the full current criteria).

1.7 Sjaastad, the "Cluster Club," and the birth of oxygen therapy

Ottar Sjaastad (Norway) described chronic paroxysmal hemicrania (CPH) in 1974/1976 — a crucial development because CPH's defining feature, an absolute response to indomethacin, became (and remains, with caveats — see §2.4) the main tool for telling CPH apart from CH `[PEER-REVIEWED]`. Sjaastad founded the **"Cluster Club"** (formally the International CH Research Group), which held its first meeting in Uppsala in 1979. Sjaastad was president and **Lee Kudrow** secretary; members included Ekbom, Horton, and Kunkle among others — effectively the founding generation of CH research meeting as one small, informal body `[HISTORICAL/CULTURAL]`.

Lee Kudrow went on to run the landmark controlled trial establishing oxygen as an effective abortive treatment:

> **Kudrow L.** "Response of cluster headache attacks to oxygen inhalation." *Headache*. 1981;21:1–4. `[PEER-REVIEWED]` — 52 patients; 75% got relief with a 7 L/min oxygen mask; 62% aborted their attack within 7 minutes.

The trial's origin is itself a small, human story worth preserving: an ophthalmologist and CH patient, **Jerold Janks**, wrote a 1978 letter to *JAMA* describing his own use of oxygen, which prompted Kudrow's formal trial `[HISTORICAL/CULTURAL]`. Non-CH-specific oxygen use for headache had actually been noted decades earlier (Rhein & Alvarez, Mayo Clinic, 1939–40), but it took until 1981 for CH-specific evidence to exist, and German-language medicine did not widely adopt oxygen therapy until 1986 (Heckl) — a reminder that even well-evidenced treatments diffuse unevenly and slowly across countries `[PEER-REVIEWED / HISTORICAL]`.

A 2024 bibliometric study (PMC11079126) identifies **Peter Goadsby** as the most prolific individual CH researcher in the literature (38 articles, 1.99% of total field output) `[PEER-REVIEWED]` — Goadsby's hypothalamic-imaging work is central to Section 3 below.

1.8 History in languages other than English

This chapter deliberately draws on non-Anglophone sources, since the historical record — like the patient experience discussed in Section 2 — is not confined to English-language medicine:

- **German** (richest single non-English historical source): ck-wissen.de's historical wiki documents the Oppermann/Morgagni/Whytt 18th-century cases above.
- **Italian**: SISC guidelines; Italian Wikipedia's own framing of the contested-priority debate; leadershipmedica.it's (unconfirmed) claim about French coinage of "suicide headache"; a 2001 *NEJM* report of hypothalamic deep-brain-stimulation as a treatment, an Italian-led clinical first.
- **Japanese**: Hirayama Keizō's clinical-neurology essay specifically on the difficulty of translating "cluster headache" into Japanese; a 2013 *Rinsho Shinkeigaku* phenotype study.
- **Norwegian**: Tidsskriftet (Norwegian Medical Journal), generally available only via English translation.
- **Russian**: a *Med-Alphabet* review that opens with a Russian translation of the original 1641 Tulp case.

No dedicated Swedish-language or Chinese-language primary *historical* source (as distinct from clinical/epidemiological sources, which are extensive — see Sections 3–4) was located in this research pass — **flagged as a gap**, not a confirmed absence.

---

2. What a Cluster Headache Is

2.1 The current formal definition (ICHD-3)

The International Classification of Headache Disorders, 3rd edition (ICHD-3) `[PEER-REVIEWED, official classification]` (ichd-3.org) defines cluster headache (3.1) as:

> **A.** At least 5 attacks fulfilling criteria B–D. **B.** Severe or very severe unilateral orbital, supraorbital and/or temporal pain lasting 15–180 minutes (when untreated). **C.** Either or both of the following: 1. At least one of the following symptoms or signs, ipsilateral to the headache: conjunctival injection and/or lacrimation; nasal congestion and/or rhinorrhoea; eyelid oedema; forehead and facial sweating; miosis and/or ptosis. 2. A sense of restlessness or agitation. **D.** Occurring with a frequency between one every other day and eight per day. **E.** Not better accounted for by another ICHD-3 diagnosis.

Episodic CH (3.1.1): attacks occur in bouts ("cluster periods") lasting 7 days to 1 year, separated by pain-free remission periods of ≥3 months. **Chronic CH (3.1.2)**: attacks occur for more than 1 year without remission, or with remission periods lasting less than 3 months.

Chronic CH accounts for roughly **10–15% of all CH** in Western cohorts (though — see Section 4 — this proportion is markedly lower, around 2–7.5%, in East Asian cohorts, a cross-cultural pattern that is not yet explained). Notably, about **25% of episodic-CH patients experience only one cluster period in their entire life** — a fact easily lost when CH is discussed as a lifelong recurring condition.

2.2 How much does it hurt? The best available quantitative answer

> **Burish MJ, Pearson SM, Shapiro RE, Zhang W, Schor LI.** "Cluster headache is one of the most intensely painful human conditions: results from the International Cluster Headache Questionnaire." *Headache*. 2021;61(1):117–124. doi: 10.1111/head.14021. PMID 33337540. `[PEER-REVIEWED + CITIZEN-SCIENCE]` (co-developed with Dr. Larry Schor of the University of West Georgia, funded/publicised by Clusterbusters; n=1,604 respondents to the International Cluster Headache Questionnaire).

This is the single best-designed quantitative pain-comparison study available. On a 0–10 scale:

Condition	Mean pain rating
Cluster headache	**9.7 ± 0.6** (72.1% of respondents rated a full 10/10)
Childbirth (labour)	7.2 ± 2.0
Pancreatitis	7.0 ± 1.5
Kidney stones	6.9 ± 1.9

All differences vs. CH were statistically significant ($p<0.001$). An older study using the McGill Pain Questionnaire — Jerome et al., *Pain* 1988;34(1):35–42, PMID 3405618 `[PEER-REVIEWED]` — independently found CH sufferers report not just more intense pain but different pain *qualities* and more affective distress than migraine sufferers, corroborating the newer survey with an entirely different methodology 33 years earlier.

A caveat worth flagging explicitly: at least one press report (Jerusalem Post) mis-described the Burish study's scale as running "1 to 100" — directly contradicting the paper's own stated 0–10 scale. This is a clear instance of secondary press coverage introducing a factual error; the primary paper should always be treated as the source of record for exact figures `[PEER-REVIEWED primary source vs. COMMUNITY/PRESS error]`.

2.3 Attack anatomy: onset, peak, duration, and the restlessness that defines the disease

Torelli & Manzoni (2003, *Funct Neurol*, PMID 15055745) `[PEER-REVIEWED]` found 85.7% of attacks are rated 8–10 on a visual analogue scale, reaching peak pain at roughly **8.9 minutes** on average.

Restlessness/agitation is not incidental to CH — it is one of the two alternative "C" criteria in the formal ICHD-3 definition (alongside autonomic signs), because it so reliably distinguishes CH from migraine (where patients typically want to lie still in the dark). The founding clinical paper is:

> **Blau JN.** *Lancet*. 1993. PMID 8103827. `[PEER-REVIEWED]` — 50 patients observed demonstrating characteristic agitated behaviour in clinic.

Prevalence estimates for restlessness cluster in the **80–93% range** across independent studies (AAFP review: 93%; Luerding et al., German multicentre study: 90%, doi 10.1177/0333102412443336) — high but not a single universally agreed figure, so this chapter presents it as a range rather than a false-precision point estimate `[PEER-REVIEWED]`. Luerding et al. also found rates of self-inflicted head injury higher in CH than in migraine.

A widely shared community heuristic captures the differential diagnosis vividly:

> "If you want to sit still in a dark quiet room — possibly a migraine. If you want to pace around while hitting yourself in the head with a hammer — possibly a cluster." — r/clusterheads `[COMMUNITY-REPORT]`

Interesting cross-cultural exception: Japanese and Taiwanese clinical cohorts (Ogawa et al. 2011, *Cephalalgia*, PMID 21278239) `[PEER-REVIEWED]` found an "uncoupling" between the subjective *feeling* of restlessness (68.9% of patients) and actually *displaying* restless behaviour (only 42.9%) — many patients reported forcing themselves to keep still despite the urge to move. This is a genuinely interesting minority finding, not replicated (or contradicted) in Western cohorts as far as this research located, and it is worth flagging as either a true behavioural/cultural difference or a measurement artefact of how the question was asked.

2.4 Differential diagnosis: cluster headache vs. its look-alikes

Feature	Cluster headache	Migraine	Tension-type headache	SUNCT/SUNA	Paroxysmal hemicrania	Trigeminal neuralgia
Typical duration	15–180 min	4–72 hrs	30 min–7 days	1 sec–10 min	2–30 min	Seconds
Attack frequency	1/other day – 8/day	Variable, less frequent	Variable	Up to 200/day	Up to 40/day	Up to 100s/day
Laterality	Strictly unilateral, usually side-locked	Often unilateral, can switch	Usually bilateral	Unilateral	Strictly unilateral	Unilateral, trigeminal distribution
Autonomic features	Prominent (lacrimation, ptosis, miosis, rhinorrhoea)	Rare/mild	Absent	Prominent	Prominent	Absent
Behaviour during attack	Restless/agitated	Wants to lie still	Variable	Variable	Variable	Wants to avoid triggering movement
Indomethacin response	Not absolute (see caveat below)	No	No	No	**Absolute (classic teaching)**	No
Sex ratio (M:F)	Historically male-predominant, contested trend (see §4.2)	Female-predominant	Roughly equal	Slight male predominance	Female-predominant	Slight female predominance

`[PEER-REVIEWED, synthesised from ICHD-3 and differential-diagnosis literature]`

Important caveat on indomethacin: the "absolute indomethacin response = PH, no response = CH" rule taught as a bright line in mainstream medical education is **not perfectly absolute**. A peer-reviewed critical review documents four genuine case reports of CH patients responding to indomethacin, complicating this classic differentiator and raising the possibility of occasional misdiagnosis between CH and PH in either direction `[PEER-REVIEWED, contested point]` (ihs-headache.org).

Photophobia/phonophobia laterality is another differentiator: Irimia et al. (2008, PMID 18422722) `[PEER-REVIEWED]` found unilateral photophobia/phonophobia is rare in episodic migraine (4%) but notably more common in TACs generally, though the exact TAC-specific rate was not fully recoverable from the sources reviewed.

2.5 What patients actually say it feels like

Formal clinical description only goes so far. The following are direct patient testimony, drawn from qualitative academic studies, patient organisations, and forums, in multiple languages — all `[COMMUNITY-REPORT]` unless otherwise noted, and included deliberately because, as the master brief for this chapter states, patterns in anecdote are data.

English-language:

> "The Sumatriptan shots do work but because you can only take a maximum of two a day, you have to be very selective about when you use them… usually what happens is I try and save the shots for when I wake up and one is full blown." — P10, male, 25–39, episodic CH, Andre & Cavers, "A cry in the dark," PMC8611293 `[qualitative study — PEER-REVIEWED, direct patient quote — COMMUNITY-REPORT]`

> "I do definitely live in fear… I've basically stopped drinking because of it… No candles, no bleach, no anything cleaning related." — P9, female, 25–39, episodic CH, same source.

> "They are the worst headaches known to medical science and one of the worst pains of any kind known to medical science… Those who suffer from cluster headaches wish they were called something else besides 'headache[s]'…" — Clusterbusters, "About CH"

> "[T]he most painful experience — like have knives slice into her brain whilst feeling like her eyeballs will explode and nose pain too." — Ollie, describing his wife Leah's attacks, OUCH(UK) forum

> "Yes, diagnosed about 10 years ago, kiddo about 8 years ago… Hands down I'd rather give birth once a day, every day, than get cluster headaches. They hurt more. They are depressing. They are relentless…" — r/clusterheads, on CH vs. childbirth pain

German (Schmerzklinik Kiel patient interview, Wolfgang Q., electrician, 20 years with CH, translated):

> "He became very aggressive, like an animal in a cage pacing restlessly back and forth." — his wife Kathrin, describing his attacks from an outside-observer perspective (independently corroborating the restlessness literature in §2.3). "Yes, that really was hell." — Wolfgang himself.

A German patient forum post also documents a striking, concrete self-harm-mitigation strategy: *"While I'm having an attack I hit a padded board (I used to injure myself during attacks before and found this way to avoid it… works great)."* — forum.clusterkopf.de

Italian (Corriere della Sera health forum, patient Alessandro Vita, 35, episodic CH for 13 years, translated):

> "Cluster headache, more commonly called the 'beast' by people belonging to the national OUCH association…, is a primary headache, with extremely intense attacks on one side of the head, recurring over a twenty-four-hour period." — forumcorriere.corriere.it

Japanese (patient blog, translated):

> "Subjectively, it reaches maximum pain in less than a minute, then continues for nearly an hour in time with my pulse, without subsiding." — note.com

Chinese (MSD Manuals Chinese professional edition, translated):

> "Unlike migraine, cluster headache patients often cannot lie down. They pace back and forth restlessly, and sometimes even bang their heads against the wall." — msdmanuals.cn

A striking cross-cultural convergence: patients independently personify the condition as a hostile entity in at least two unrelated language communities — English-speaking patients call it "the beast" or "an invader" (Clusterbusters), and Italian-speaking patients independently use the identical metaphor, "la bestia" (Grappolaiuto.it) — without any apparent direct borrowing between the two communities `[COMMUNITY-REPORT, cross-cultural pattern]`.

A genuine cross-cultural divergence, also worth flagging: when comparing CH to other severe pains, Western sources (including the Burish study itself) typically pair it with childbirth and pancreatitis. East Asian popular and clinical sources instead describe CH as one of the "world's three great pains" (/), paired instead with **myocardial infarction and kidney stones** — a meaningfully different comparison triad, appearing independently in both Japanese (TV Asahi news coverage) and Chinese (Baidu Baike, haodf.com clinical education) sources `[COMMUNITY/clinical-education hybrid, cross-cultural divergence]`.

A Chinese colloquial nickname is also worth preserving as a minority naming tradition distinct from "suicide headache": **" " ("alarm-clock headache")**, reflecting the condition's circadian regularity `[COMMUNITY-REPORT, Chinese-language]`.

2.6 The psychological weight of the disease

Qualitative research consistently finds CH's impact extends well beyond the physical attack itself:

> "It's always there in the background… It's not just when it's happening, it's the rest of the time as well." — P3, male, 60+, episodic CH, Andre & Cavers, PMC8611293 `[PEER-REVIEWED qualitative study]`

> **Palacios-Ceña D, et al.** "Living With Cluster Headache: A Qualitative Study of Patients' Perspectives." *Headache*. 2016;56(7):1171–1182. PMID 27432624. `[PEER-REVIEWED]` — the first qualitative phenomenological study of CH, 20 Spanish male patients: "Patients with CH often live in fear and uncertainty because of their condition," driven by attack intensity/frequency, ineffective treatments, perceived social/workplace scepticism, and physician unawareness.

Clinicians corroborate this from the outside: a UK qualitative study of GPs and neurologists (Buture et al. 2020, *Br J Gen Pract*, PMID 32482627) `[PEER-REVIEWED]` recorded a neurologist describing a patient who was "almost at the point of losing his job because… he was irritable, he was shouting at his colleagues and his boss," and a GP noting patients "may become depressed in the course of illness or even suicidal."

Suicidality figures vary enormously across studies and must not be quoted interchangeably — this is one of the clearest contested points in the whole literature, discussed fully with exact figures in Section 4.5. In brief: population-level meta-analysis puts lifetime suicidal ideation at 8.0%, while a Swedish Karolinska Institutet survey of 500 patients found more than 50% reporting

suicidal ideation, and a separate 175-patient study found 64.2% reporting *passive* suicidal ideation specifically *during* attacks. The most likely explanation is that these numbers measure different things (lifetime/general population vs. specialised clinical samples vs. active-bout-specific states), not that any one of them is simply wrong.

Part II — Mechanism and Pathophysiology

Source: Chapter 1, section 3. Section numbering retained from the source chapter.

From what the disease is to why it happens: the mechanistic picture, from the refuted vascular theories to the current network models, the contested signalling molecules, the genetics, and the clockwork.

---

3. Mechanism and Pathophysiology

3.1 The hypothalamus enters the picture

The single most influential modern paper in CH pathophysiology is:

> **May A, Bahra A, Büchel C, Frackowiak RSJ, Goadsby PJ.** "Hypothalamic activation in cluster headache attacks." *Lancet*. 1998 Jul 25;352(9124):275–278. doi: 10.1016/S0140-6736(98)02470-2. PMID 9690407. `[PEER-REVIEWED]`

A correction worth flagging explicitly: this landmark PET study is frequently misattributed to *Nature Medicine* in popular and even some semi-technical accounts. It was published in **The Lancet**. A separate, genuinely distinct paper — **May A, et al.** *Nature Medicine* 1999, doi: 10.1038/10561, a structural voxel-based morphometry (VBM) follow-up — is often conflated with the 1998 Lancet paper but should be cited separately, since it asks a different question (structural volume, not functional activation).

The 1998 finding — that the posterior/inferior hypothalamic grey matter activates specifically during CH attacks, a finding not seen in other headache types — is what shifted the field from believing CH originated in blood vessels (the older vascular theories, §3.6) to believing it originated in the brain itself, and specifically in a structure that governs circadian rhythm, among other things.

3.2 An important update: the "pure generator" model is now outdated

Even the hypothalamic model itself has moved on since 1998. Goadsby's own more recent position, and a 2024 review, describe a more distributed picture:

> **Coppola G, et al.** *Cephalalgia*. 2024. doi: 10.1177/03331024231209317. `[PEER-REVIEWED]` — proposes a "central permissive" multi-network model, in which the hypothalamus functions as a "crossroads" or coordinating hub rather than the sole attack generator.

A striking piece of supporting evidence: CH attacks have been documented to continue even after surgical sectioning of the trigeminal nerve — a finding that is hard to reconcile with any model where a single anatomical structure alone is both necessary and sufficient to generate the attack `[PEER-REVIEWED]`. VBM findings on hypothalamic *volume* are also contested rather than settled: an early study found increased hypothalamic grey-matter volume in CH patients, but this was not confirmed by Arkink et al. (2017) or by Coppola et al. (2024). Newer network-topology approaches (Lee et al. 2022, Korean cohort) find altered brain-network *organisation* rather than a simple volume difference `[PEER-REVIEWED, contested]`.

3.3 The trigeminal-autonomic reflex: why pain and tears happen together

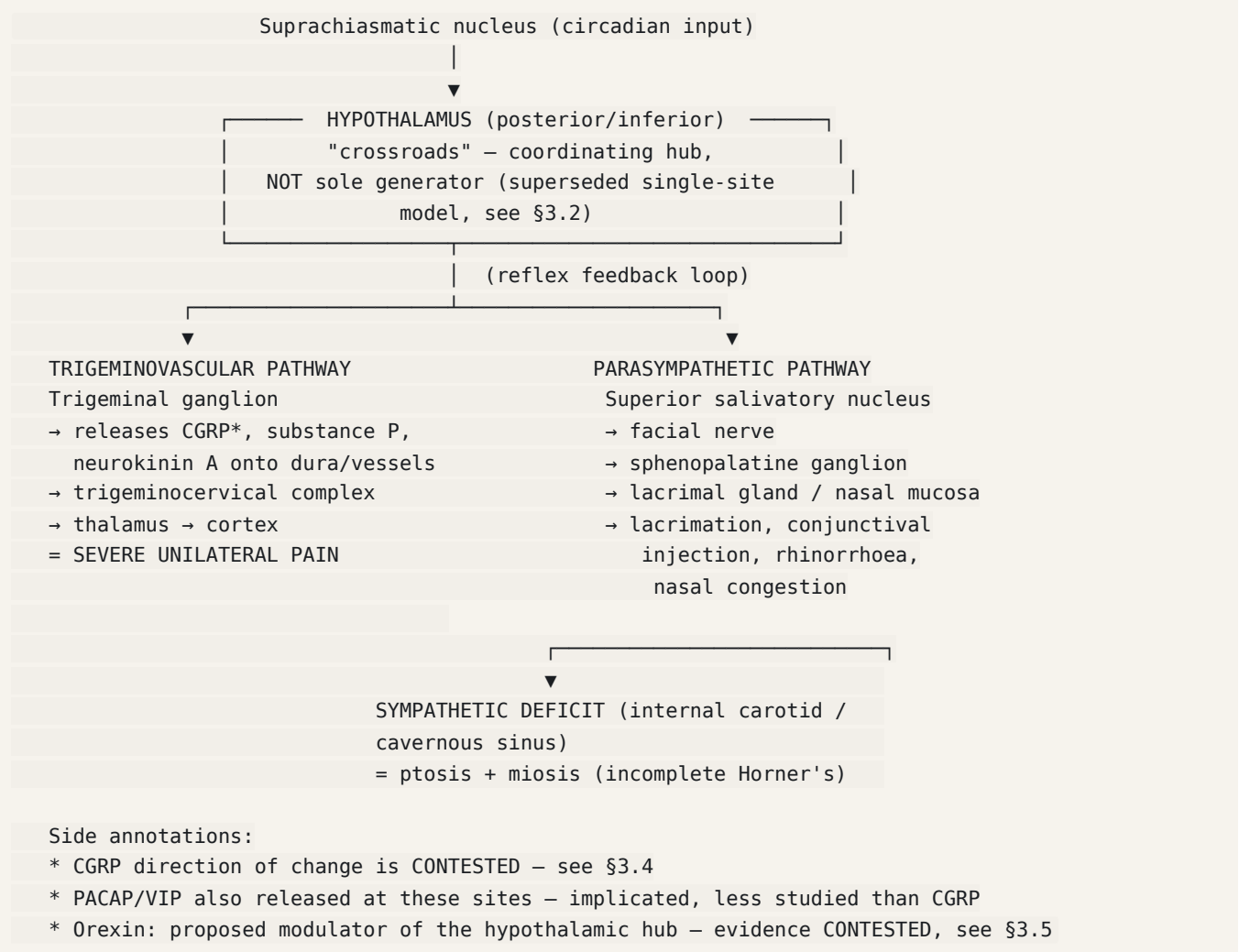
The defining clinical puzzle of CH — why does severe unilateral pain co-occur, tightly time-locked, with tearing, a runny nose, and a drooping eyelid on the same side? — has a well-documented anatomical answer, independently confirmed by Western, Japanese, and German sources:

- **Pain pathway**: trigeminal ganglion → releases CGRP, substance P, and neurokinin A onto cerebral vessels and the dura → signal passes to the trigeminocervical complex → thalamus → cortex, producing the severe unilateral pain.

- **Parasympathetic pathway**: superior salivatory nucleus → facial nerve → sphenopalatine ganglion → lacrimal gland and nasal mucosa, producing lacrimation, conjunctival injection, rhinorrhoea, and nasal congestion.
- **Sympathetic deficit**: a concurrent sympathetic deficiency via the internal carotid artery/cavernous sinus region produces an incomplete Horner's syndrome — ptosis and miosis, but typically without the anhidrosis seen in full Horner's syndrome.
- A **feedback loop** runs from the trigeminocervical complex/thalamus back to the hypothalamus, forming a reflex arc that explains why the pain and the autonomic symptoms are so precisely time-locked to each other.

Primary source: **Wei DY, Ong JJY, Goadsby PJ**, PMC5909131 `[PEER-REVIEWED]`, independently corroborated by Japanese Headache Society guideline material and a German (LMU Munich) dissertation.

Diagram description (attack mechanism pathway — described here in place of a rendered figure, per the master brief's instruction that a described figure is acceptable):



(Structure mirrors the figure in Wei, Ong & Goadsby 2018, PMC5909131, using their anatomical abbreviations IML, SCG, ICA, SSN, SPG, TCC, HT, SN.)

3.4 CGRP: a genuinely contested signalling molecule

The "classic" view, going back three decades, is that CGRP is *elevated* during CH attacks:

> **Goadsby PJ, Edvinsson L.** *Brain*. 1994;117:427–434. `[PEER-REVIEWED]`

But a recent, well-powered Danish study directly contradicts the direction of this finding:

> **Petersen AS, et al.** (Danish Headache Center). *Cephalalgia*. 2024;44(3). doi: 10.1177/03331024231223970. `[PEER-REVIEWED]` — n=301, found CH patients (across subtypes) had **significantly lower** plasma CGRP than controls — the opposite direction to the classic literature.

This is presented here as a genuine, unresolved contradiction rather than smoothed over. It has real clinical consequences: CGRP-targeting drugs have had mixed results in CH trials. Galcanezumab is FDA-approved for **episodic** CH (NEJM, 2019) but **failed its primary endpoint in chronic CH** (per EMA documentation) — an important negative result that is easy to miss if one only remembers the positive episodic-CH approval. Eptinezumab (the ALLEVIATE trial) also missed its primary endpoint in episodic CH. The clean, simple "CGRP is the culprit, block it and CH improves" story that holds reasonably well for migraine does **not** transfer cleanly to CH `[PEER-REVIEWED]`.

3.5 Orexin/hypocretin: an interesting but unreplicated hypothesis

Orexin (also called hypocretin), a hypothalamic neuropeptide involved in wakefulness regulation, has been proposed as a modulator relevant to CH's circadian pattern — but the supporting evidence is low-to-moderate confidence and directly contradictory between the two key CSF studies:

- Cevoli et al. (2011) found normal orexin/hypocretin CSF levels in CH patients.
- Barloese et al. (2015, Danish Headache Center) found significantly *reduced* levels.

`[PEER-REVIEWED, contested, unreplicated]` — this hypothesis should be described as speculative rather than established, pending further replication.

3.6 Genetics: heritable, but not simply so

- **Family history**: Waung, Taylor, Qualmann, Burish (2020, *JAMA Neurol*, PMID 32310255) `[PEER-REVIEWED]` systematic review of 22 cohorts found a median family-history rate of 8.2% (range 0–22%); 69% of pedigrees were consistent with autosomal dominant inheritance; sex ratio among familial cases was 1.39 M:F (notably less male-skewed than sporadic CH — see also the Italian familial data in §4.6).
- **Twin studies**: Ekbom K, et al. *Neurology*. 2006;67(5):798–803. doi: 10.1212/01.wnl.0000233786.72356.3e. `[PEER-REVIEWED]` — Swedish national twin registry, 37 pairs, concordance only **5.4%** (2/37, both monozygotic). This low concordance rate argues *against* a simple, deterministic single-gene model of inheritance, even though family clustering is real.
- **Russell MB, et al.** *Headache*. 1996;36(10):608–612. PMID 8990601. `[PEER-REVIEWED]` — first-degree relatives of CH patients have a **14-fold** increased risk of CH themselves; segregation analysis is consistent with an autosomal dominant gene of variable penetrance (0.30–0.34 in males, 0.17–0.21 in females), estimated to be present in 3–4% of affected males and 7–10% of affected females.

The HCRTR2 candidate-gene saga — a clear case study in non-replication: Early positive associations between CH and the HCRTR2 (orexin receptor 2) gene were reported by Rainero (2004), Baumber (2006), Schürks (2006, German cohort), and Rainero again (2008). A key negative replication came from:

> **Weller CM, et al.** *Cephalalgia*. 2015;35(9):741–747. PMID 25398231. `[PEER-REVIEWED]` — Leiden LUCA cohort, n=575/874, found no significant association alone (OR=0.91, p=0.319). A pooled meta-analysis across 6 populations *did* show a significant association (OR=0.69, p=0.006), but this weakened substantially (to OR=0.80) once one outlier study was excluded.

The most authoritative and recent statement on this comes from the largest genome-wide association study to date (below): none of the earlier HCRTR2 candidate-gene associations were replicated at genome-wide significance. This is a useful, concrete illustration of how a plausible, widely-cited early finding can fail to hold up under larger and more rigorous later testing.

The definitive current genetic picture:

> **Winsvold BS, et al.** "Cluster Headache Genomewide Association Study and Meta-Analysis Identifies Eight Loci and Implicates Smoking as Causal Risk Factor." *Ann Neurol*. 2023;94:713–726. doi: 10.1002/ana.26743. PMID 37486023. `[PEER-REVIEWED]`

This is the largest GWAS conducted to date: 10 European cohorts plus 1 East Asian cohort; European meta-analysis of 4,043 cases vs. 21,729 controls; trans-ancestry meta-analysis of 4,777 cases vs. 31,575 controls.

- SNP-based heritability: **14.5%** (SE 1.74%).
- **Eight loci identified**: seven in the European analysis (DUSP10, MERTK, FTCDNL1/SATB2, FHL5, WNT2, PLCE1, and the novel LRP1), plus one East-Asian-specific locus (CAPN2, also independently found by a Taiwanese Han Chinese GWAS — Chen SP, et al., 2022, *J Headache Pain* 23:147).
- **Genetic correlation with smoking, other pain disorders, and neuropsychiatric diagnoses.** Critically, Mendelian randomisation analysis found evidence for a **causal** (not merely correlational) effect of smoking on CH risk — discussed further, along with the clinical paradox this creates, in Section 4.4.
- Three of the eight loci are shared with migraine, offering a partial genetic-overlap explanation for the two conditions' occasional clinical overlap. *(Editor's note: per-locus lead SNPs, odds ratios and p-values for these eight loci — and corrections to earlier locus lists in circulation — are tabulated in Part VII, §5.2.1.)*

Other candidate genes examined over the years but **not consistently verified** include ADH4, GNB3, CACNA1A (formally excluded), NOS, MTHFR, PER3, CLOCK, and CRY1, plus a single-patient Japanese mitochondrial finding (MT-TL1, 1994) that was never replicated.

3.7 Circadian and circannual rhythmicity

CH's clockwork timing is one of its most distinctive — and mechanistically informative — features:

- A meta-analysis of 16 studies / 4,953 participants (Benkli et al., summarised in *Neurology* 2023, PMC10259280) `[PEER-REVIEWED]` found **70.5%** of patients show a circadian attack pattern, peaking between **21:00 and 03:00**, with 2 a.m. the single most common hour (6.5% of 8,856 recorded attack times).
- An older analysis (Manzoni, cited in a Canadian Journal of Neurological Sciences review) found a **trimodal** pattern (peaks around 01:00–02:00, 13:00–15:00, and ~21:00). The midday peak is explicitly flagged by the reviewing source's own caveat as potentially confounded by the Italian custom of a midday lunch/rest break — a good concrete example of a real, specific data point that should not be over-generalised as pure neurobiology divorced from cultural or occupational schedule `[PEER-REVIEWED, with an explicit cultural-confound caveat]`.
- Nocturnal attacks are linked to REM sleep: in one recorded series, roughly 60% of nocturnal attacks followed REM sleep, despite REM comprising only about 20% of total sleep time — a striking overrepresentation. *(Editor's note: the REM association is contested in more recent work — see the fuller sleep-architecture discussion in Part IV, §4.)*
- **Melatonin**: a meta-analysis (Liampas et al. 2020, *Acta Neurol Scand*, PMID 32677039) `[PEER-REVIEWED]` found significantly reduced nocturnal melatonin *during* active bouts (mean difference −29.89 pg/mL), but *not* significantly reduced serum melatonin during remission — though the urinary metabolite aMT6s *is* reduced even during remission. This is a nuanced, partially-state-dependent finding, not a simple "CH patients always have low melatonin."
- **Circannual pattern — and a genuine correction to common assumptions**: bouts cluster in spring and autumn, not, as commonly assumed, around the solstices. **Riederer F & Schankin C** (2024, *Headache*, doi: 10.1111/head.14830) `[PEER-REVIEWED]` found circannual clustering correlates specifically with the **square of the velocity of daylight change** (Spearman R=0.762, p=0.006) — meaning attacks cluster around the **equinoxes**, when day length is changing fastest, not around the solstices, when day length is nearly static. This is worth flagging explicitly since "solstices" is the more intuitive (and incorrect) assumption.

3.8 Neuroimaging and historical/competing theories

The refuted vascular theories: Horton's original histamine/vascular theory (§1.4) was historically influential but is now understood as, at best, a partial or secondary phenomenon rather than the primary driver. A separate vascular-adjacent theory — the **cavernous sinus hypothesis** — went through a full cycle of proposal and refutation that is instructive about how the field progressed toward the current central/hypothalamic model:

- Gawel et al. (1990) — SPECT gallium-67 imaging showed increased cavernous sinus uptake, initially seeming to support a cavernous-sinus origin.
- Sianard-Gainko (1994) — showed the same imaging finding is non-specific, occurring in migraine too.
- Schuh-Hofer (2006) — SPECT findings did not support the hypothesis.
- High-resolution MRI found no cavernous sinus dimension differences between CH patients and controls.

`[PEER-REVIEWED, historical refutation documented in Silvestro et al. 2022, PMC9314615]` — this refutation was a key transition point that helped redirect the field toward the central/hypothalamic model that dominates today (§3.1–3.2).

Non-English contributions to mechanism research (tallied explicitly per the task brief): Japanese sources (Japanese Headache Society guideline material on reflex anatomy and melatonin/cortisol chronobiology); German sources (an LMU Munich dissertation confirming the parasympathetic/sympathetic pathway anatomy, and Schürks 2006 on HCRTR2); Danish sources (the Danish Headache Center's substantial body of work on CGRP, PACAP/VIP, and hypocretin — Snoer, Petersen, Pellesi, Barloese); Italian sources (Leone 1998, *Cephalalgia*, on melatonin excretion); Chinese sources (Qiu 2013, *PLoS One*, fMRI hypothalamic connectivity; Fan 2018; Chen 2022 Taiwan GWAS); Korean sources (Lee 2022, *J Neurol*; Kim 2025, *Sci Rep*, on structural covariance and white-matter markers). No dedicated Italian-language pathophysiology-specific primary research beyond the single Leone 1998 melatonin study was located — flagged as a gap.

Part III — Epidemiology and Demographics

Source: Chapter 1, section 4. Section numbering retained from the source chapter.

Who gets it, where, and how the disease is distributed — and misdiagnosed — across populations.

---

4. Epidemiology and Demographics

4.1 How common is it, worldwide?

The foundational meta-analysis remains:

> **Fischera M, Marziniak M, Gralow I, Evers S.** *Cephalalgia*. 2008;28(6):614–618. PMID 18422717. `[PEER-REVIEWED]` — pooled 16 population-based studies.

- Pooled **lifetime prevalence: 124 per 100,000** (95% CI 101–151) — commonly rounded to "about 1 in 1,000."
- Pooled 1-year prevalence: 53 per 100,000 (range 3–150 across the individual included studies — a very wide spread).
- Overall sex ratio 4.3:1 (M:F), with chronic CH more male-skewed (15.0:1) than episodic CH (3.8:1).
- A trend toward higher prevalence in northern vs. equatorial countries was noted but explicitly called inconclusive by the authors.
- **A gap that remains unaddressed as of this research pass (2026): no population-based CH prevalence study exists anywhere in the Southern Hemisphere.**

Country-level figures illustrate just how wide the spread across individual studies is:

Country / study	Prevalence (per 100,000)
Vågå, Norway (door-to-door survey, Sjaastad)	381 (highest single study)
Parma, Italy (Torelli 2005)	279
Sweden (twin registry)	151
Georgia (country)	87
Norway (national registry, Crespi 2022)	48.6
USA (AAFP estimate)	~100 ("about 1 in 1,000")

`[PEER-REVIEWED, tabulated]`. Later, more comprehensive reviews (Kim SA, et al., *Cephalalgia* 2023; Membrilla JA, et al., *Front Pain Res* 2024, PMC10957682) largely confirm this picture without resolving the north/south or latitude question — see §4.7.

4.2 The sex ratio: a historical shift that is itself contested

The classic teaching is that CH is strongly male-predominant, historically cited at 5:1 to 6.7:1 before the 1960s. Two major studies document what looks like a steady narrowing of this ratio over subsequent decades:

> **Manzoni GC.** *Cephalalgia*. 1998;18(3):138–142. PMID 9595206. `[PEER-REVIEWED]` — 482 patients, Parma. M:F ratio by decade of onset: 6.2:1 (pre-1960) → 5.6:1 → 4.3:1 → 3.0:1 → 2.1:1 (1990s). Manzoni's own interpretation ties this directly to lifestyle change: the female:male ratio of smoking rates in the same population fell from 8.6:1 to 1.9:1 over the same period, and the female:male employment-rate ratio moved from 2.6:1 to 1.7:1 — his argument is that changing female smoking and workforce participation, not biology, drove the apparent narrowing.

> **Ekbom K, et al.** *Cephalalgia*. 2002;22(2):94–100. `[PEER-REVIEWED]` — Swedish cohort, 554 patients. Ratio by onset decade: 5.9:1 → 5.9:1 → 3.9:1 → 3.6:1 → 3.1:1. Important nuance: the *proportion* of female patients did **not** change significantly across this period (p=0.30) — meaning some of the apparent "narrowing" may be a denominator artefact rather than a true increase in female incidence.

Explicit dissent, and arguably the single most important contested point in this entire section: the foundational Fischera et al. 2008 **population-based** meta-analysis (the most methodologically rigorous, least clinic-selection-biased source available) explicitly states it could **not confirm** the sex-ratio-narrowing trend — directly contradicting the near-universal clinic-cohort narrative found in Manzoni, Ekbom, and most 2020s review articles. This chapter treats the sex-ratio narrowing as **genuinely contested**, with the most population-representative source occupying the minority position, rather than presenting it as settled fact `[PEER-REVIEWED, explicitly contested]`.

Present-day country-by-country spread also remains wide, and shows a striking geographic/cultural pattern:

Registry/study	Country	M:F ratio
Norway national registry (2022)	Norway	1.47:1
Swedish CH biobank (Fourier 2023)	Sweden	1.9:1
Danish Cluster Headache Survey	Denmark	~2:1
UK (Bahra, May, Goadsby 2002)	UK	2.5:1
Japan (Kikui 2023)	Japan	4.5:1
China (CHRIS registry 2024)	China	4.33:1
China (Dong 2013, clinic-based)	China	7:1
Taiwan (2004)	Taiwan	6.4:1
India (2014)	India	10:1

`[PEER-REVIEWED, tabulated]`. **Asian clinic-based cohorts consistently show much higher male predominance (4.3:1–10:1) than recent Northern European national registries (1.47:1–2:1)** — a pattern that is not resolved in the literature reviewed: it could reflect a genuine biological/cultural difference (e.g., different female smoking prevalence or care-seeking behaviour by country), or simply different diagnostic ascertainment. Flagged as an under-discussed pattern deserving more dedicated research.

Sex ratio also varies dramatically **by age of onset**: from 3.3:1 in the 10–19 age bracket, up to a peak of 8.4:1 at ages 40–49, down to essential **parity (1:1) by ages 60–69** — male predominance largely disappears after age 50. Proposed explanations across the sources include changing smoking/lifestyle patterns in women (Manzoni's argument), historical underdiagnosis of women due to a "male disease" stereotype among physicians (a distinct, complementary hypothesis), general increased disease recognition over time, and speculative age-dependent hormonal factors — the last explicitly labelled "postulated" rather than established in the reviewing literature.

4.3 Age of onset

> **Manzoni GC, Taga A, Russo M, Torelli P.** *J Headache Pain*. 2016;17:44. PMID 27102121. `[PEER-REVIEWED]` — Parma Headache Centre, 808 patients.

- Mean age of onset: **30.2 ± 13.8 years** (men 30.1 ± 13.0; women 30.4 ± 15.7) — essentially identical between sexes on average, with a peak in the third decade of life for both.
- Women with **primary chronic** CH had markedly later onset (mean 42.8 ± 21.7 years) than women with episodic CH.
- A **bimodal onset pattern specific to women with chronic CH** was found: peaks in the 2nd and 6th decades of life; men with chronic CH showed a milder bimodality (3rd and 5th decades).

- At the onset-age extremes (≤15 years or ≥50 years), the usual male preponderance was actually **inverted** — more women than men.

Ekbom's Swedish cohort similarly found a possible second onset peak in women with episodic CH in their 50s, "with a number of sufferers having their first attacks after the menopause" `[PEER-REVIEWED]`. A distinctly different pattern was found in one Japanese study cited by Kim et al. (2023, *Cephalalgia*): men peaking in their 20s–30s, but women peaking in their **10s and 60s** — a different bimodal shape from the Western (Manzoni) pattern `[PEER-REVIEWED]`.

National variation in mean onset age:

Country	Mean age of onset
France	33.9 ± 14.7
Norway	32.5 ± 13.4
Sweden	31.9 ± 13.6
Germany	31.6 ± 12.0
Denmark	31.6 ± 13.7
Netherlands	31.1 ± 13.0
Japan	31.0 ± 13.8
Italy	30.3 ± 14.0
Taiwan	27.2 ± 12.1
China (Dong 2013)	26.7 ± 10.9
China (CHRIS 2024)	24.9 ± 9.8 (women significantly younger: 23.1 vs. men 25.3, p=0.011)

`[PEER-REVIEWED, tabulated from Kim et al. 2023 review and national cohorts]`. East Asian cohorts trend toward a slightly younger mean onset (~25–27 years) than European cohorts (~31–34 years) — flagged as a pattern, not a settled causal finding, since it could reflect differing registry-entry ages rather than a true biological difference.

4.4 Smoking: a strong correlation with a genuinely paradoxical causality story

Prevalence: smoking rates among CH patients are strikingly high and consistent across independent countries:

- USA (Rozen & Fishman, 2012, n=1,134): 77% smokers.
- Italy (Rossi et al., n=200): 81% ever-smokers ("up to 90% of males, ~70% of females").
- Denmark (Lund et al. 2019, case-control, n=400 vs. 200 controls): 48.3% current smokers vs. 9.0% of controls ($p<0.001$); 74.5% ever-smokers vs. 30.0% of controls.
- South Korea (Chung et al., KCHR, n=250): 60.8% ever-smokers; strikingly sex-differentiated — 70.3% of male patients vs. only 12.2% of female patients.
- Kuwait (Al-Hashel et al., n=172): 83.7% smokers.
- Pooled meta-analytic estimate (2025 systematic review, PMC12139338): **65% (95% CI 55–76)** weighted current-smoking prevalence in CH, vs. 19% in tension-type headache.

All `[PEER-REVIEWED]`.

The causality paradox — presented here explicitly, not smoothed over:

Evidence for causality: the Winsvold 2023 GWAS (§3.6) found Mendelian randomisation evidence that smoking intensity has a **causal** effect on CH risk (genetic-causality proportion >0.6, $p=8.57\times10^{-10}$).

Evidence against simple causality: multiple independent clinical studies find that **quitting smoking essentially never improves established CH**: - Rossi et al. (Italy): only 23.8% of former smokers reported any reduction in active-phase length after quitting; 66.7% reported no change; average time since quitting was ~8 years (ample washout time). - Rozen & Fishman (US): of smokers who quit specifically to try to improve their CH, only **3%** experienced relief. - Danish Cluster Headache Survey (Lund et al. 2019): explicitly states "smoking cessation has not been found to improve CH… and not all smokers develop [CH]" — arguing smoking is neither necessary nor sufficient. - Korean cohort: the latency between starting smoking and CH onset (mean 15.6–15.9 years across Korean and Danish cohorts) was judged "too long to suspect a direct causal relationship" in the classic sense.

How the sources attempt to reconcile this: the leading hypothesis is that smoking (including secondhand/parental exposure in childhood — one analysis found a 2.5-times increased risk of earlier-onset CH with childhood secondhand exposure) may act as an early-life triggering exposure that permanently alters CH liability, such that once the disease is "switched on," removing the trigger does not reverse it. An alternative explanation is that smoking and CH share common underlying genetic/behavioural vulnerability (impulsivity, risk-taking, ADHD-linked traits — all genetically correlated with CH in the Winsvold GWAS) rather than one directly causing the other. **Neither explanation is proven; this is presented as an open question**, and a 2025 meta-analysis (PMC12139338) adds a further wrinkle by finding **no significant association between current smoking and CH** in its own pooled odds-ratio analysis — despite the ~65% raw prevalence — directly in tension with the Danish case-control data's highly significant finding. This discrepancy is flagged as genuinely unresolved, possibly due to different control-group definitions across the pooled studies `[PEER-REVIEWED, explicitly contested]`.

4.5 Geography, latitude, and seasonality

- Fischera et al. (2008) noted a trend toward higher prevalence in northern countries but called it inconclusive, given the near-total absence of Southern Hemisphere data.
- A dedicated 2024 review (*Curr Pain Headache Rep*, PMID 38441794) `[PEER-REVIEWED]` — the first systematic literature review specifically testing the latitude hypothesis — found **positive associations between latitude and**: 1-year prevalence, proportion of chronic (vs. episodic) CH, and proportion of cranial autonomic signs (miosis/ptosis). It concluded latitude "may affect the phenotypic presentations of cluster headache, probably partially mediated via temperature and sunlight variations" — directly in tension with Fischera's earlier "independent of region" conclusion. **Presented here as unresolved.**
- **Seasonality**: circannual peaks cluster in spring and autumn (accounting for 53.8% of reported onset timing across studies), most pronounced at higher latitudes (Denmark, Sweden, Norway, Italy, northeastern USA, northern China) where seasonal daylight variation is more pronounced. Lower-latitude regions show genuinely different seasonal phenotypes: India reported peaks in summer (30%) and winter (16%); the southwestern USA (California, Kudrow 1984 cohort) reported peaks in January and July rather than the spring/autumn pattern. This latitude-dependent seasonal shift is a real, specific, and likely under-appreciated finding.

4.6 East Asia as a distinct epidemiological cluster

A consistent, independently cross-replicated pattern across Japanese, Chinese, and Taiwanese cohorts sets East Asian CH populations apart from Western ones in at least four ways:

1. **Much lower proportion of chronic (vs. episodic) CH**: Japan (Kikui 2023) 4.5%; Japan (Ogawa 2011) 3.5%; China (Dong 2013) 7.5%; China (CHRIS 2024) 2.33% — versus 10–37% typically reported in Western cohorts.
2. **Higher male predominance** (4.3:1–7:1) than recent Northern European registries (1.5:1–2:1) — see §4.2 table.
3. A distinctive **"uncoupling" of subjective restlessness from overt restless behaviour** during attacks, specifically documented in Japanese and Taiwanese patients (§2.3).
4. **Broadly similar, if not longer, diagnostic delays** to Western countries despite very different healthcare systems (§4.7) — e.g., China's CHRIS registry found 39.22% of patients experienced a 10-year-plus diagnostic delay.

There is also a genuinely notable finding within the Chinese CHRIS registry (Zhang S, et al., *Cephalalgia* 2024, PMID 38501875, n=816, the first large multicentre national CH registry in China) `[PEER-REVIEWED]`: women had significantly *earlier* onset than men (23.1 vs. 25.3 years, p=0.011) — the opposite direction to some Western later-onset-in-women findings, and worth flagging as

its own distinct, possibly under-highlighted result. The same registry found only 35.67% of patients received guideline-recommended acute treatment and 24.26% preventive treatment, indicating substantial undertreatment alongside diagnostic delay.

Explicit gap: no true general-population epidemiological prevalence study exists for CH in Japan as of the most recent review located — only small clinic- or claims-based samples. No equivalent of the Danish/Dutch/Italian national registries exists for South America, Africa (beyond a single small Ethiopian clinic sample), or Oceania.

4.7 Diagnostic delay: a real, shrinking, but still substantial problem

The most authoritative pooled figure:

> "Cluster headache diagnostic delay and its predictors." PMC11980061 (2025 meta-analysis). `[PEER-REVIEWED]` — **overall pooled diagnostic delay: 10.43 years (95% CI 9.09–11.77)**.

Country-level mean delays vary considerably: UK 2.6 years; Flanders (Belgium) 3.6 years; Spain 4.9 years; Italy/Eastern Europe 5.3±6.4 years; Denmark 6.2–9 years (two studies); USA 6.6–8.5 years; Japan 7.3±6.9 years; Serbia 7.8±8 years. In one US study, 42% of patients waited more than 5 years for a correct diagnosis. **Migraine, trigeminal neuralgia, sinusitis, and dental/jaw disease are the most consistently cited misdiagnoses** — a meaningful minority of patients undergo unnecessary sinus surgery, dental extractions, or septum surgery before correct diagnosis (one Italian hospital-based study found 93% underwent instrumental/laboratory investigations before correct diagnosis, and 4% of a US survey sample had unnecessary sinus or deviated-septum surgery). *(Editor's note: a fuller country-by-country table of diagnostic delay, including within-country discrepancies, is in Part IV, §3.)*

The good news, clearly documented across multiple independent national datasets: diagnostic delay has been **shrinking substantially decade over decade**, especially since 2000. The Danish Cluster Headache Survey shows this most clearly:

Decade of onset	Mean diagnostic delay (years)
1950s	39.0
1960s	25.1
1970s	20.8
1980s	12.1
1990s	6.6
2000s	3.9
2010s	0.9

`[PEER-REVIEWED, Frederiksen et al. 2020, *Cephalalgia*]`. A Greek study found an even starker version of the same trend: patients with onset before 2000 waited a median of 13 years, versus a median of 1 year for onset after 2010.

Predictors of longer delay appearing consistently across independent studies: younger age at onset (age <20 at onset → 13.8 years delay in the Danish cohort, vs. 2.1 years for onset after age 40); attack duration >180 minutes; migraine-like features; nocturnal attacks.

A subtle but important point that should not be collapsed into a simpler claim: despite a strong general narrative that women are underdiagnosed relative to men, the most rigorous primary studies that directly tested this (Danish 2020 cohort study; Dutch 2003 nationwide survey; the 2025 meta-analysis of predictors) consistently found **no significant independent association between female sex and diagnostic delay duration**. However, some of the same cohorts *did* find women were more frequently misdiagnosed at some point in their diagnostic journey (Danish data: 61% of women vs. 46% of men were misdiagnosed at some

stage, even though the average delay length did not differ significantly by sex). These are two different claims — "takes longer to diagnose" vs. "more often misdiagnosed along the way" — and the evidence supports the second more clearly than the first `[PEER-REVIEWED, contested/nuanced]`.

4.8 Comorbidities and suicidality: another genuinely contested area

- **Rozen & Fishman (2012, US survey, n=1,134)**: 55% reported suicidal ideation. `[PEER-REVIEWED]`
- **Karolinska Institutet Swedish survey (n=500)**: more than 50% reported suicidal ideation (vs. ~9% in the Swedish general population); more than 50% reported self-harm behaviour during attacks (vs. ~5–17% in the general population). `[PEER-REVIEWED]`
- **Lee MJ, et al.** *Cephalalgia*. 2019;39(10):1249–1256. `[PEER-REVIEWED]` — Korean registry, 175 patients in-bout: during attacks, passive suicidal ideation 64.2%, active ideation 35.8%, suicidal planning 5.8%, suicide attempt 2.3%; interictally (still in-bout but between attacks) these figures dropped sharply (4.0%, 3.5%, 2.9%, 1.2%); during remission, near zero. This strongly suggests suicidality in CH is largely **state-dependent**, tightly tied to active attacks rather than a constant background trait.
- **The most recent and largest formal meta-analysis** (PMC12676835, late 2025) `[PEER-REVIEWED]` found a much lower **overall pooled** rate: suicidal ideation 8.0% (95% CI 7.7–8.3), suicide attempts 1.2% (95% CI 1.1–1.3) — but in **specialised clinical/patient-organisation settings** specifically (the kind of sample most other studies here draw from), ideation rose to 44.6% and attempts to 5.1%. The authors' own conclusion: "the overall suicidal risk in CH does not appear to be higher than that of the general population, but there is a suicidal risk increase among CH patients followed up in specialized field[s]" — i.e., much of the widely-quoted ~50%+ figures likely reflect **sample selection bias** toward more severely affected, treatment-seeking patients, not the average person with CH.
- **In apparent tension with this more reassuring population-level conclusion**: a large Danish national registry study (*JAMA Neurology*, 2025, n=119,486 headache-diagnosed individuals including 6,872 with trigeminal autonomic cephalalgias) found headache diagnoses broadly **are** associated with meaningfully elevated suicide risk at a true population level (TAC diagnosis: adjusted hazard ratio 1.97 for suicide attempt, 2.40 for completion, versus matched controls). This study's TAC category is not CH-specific, so it is suggestive context rather than a CH-specific figure — but it sits in real tension with the CH-specific meta-analysis's more cautious conclusion, and this chapter presents both rather than picking a winner `[PEER-REVIEWED, genuinely unresolved]`.

Broader comorbidity profile (Norway national registry, Crespi et al. 2022, the most methodologically rigorous true-population-level comorbidity study available, n=1,891 CH patients among 3,892,260 adults) `[PEER-REVIEWED]`: significantly elevated, age/sex-adjusted odds ratios for medication-overuse headache (OR 50.7), migraine (OR 25.2), chronic post-traumatic headache (OR 22.2), somatoform disorders (OR 4.2), suicide attempt (OR 3.9), personality disorder (OR 3.6), bipolar disorder (OR 3.6), depression (OR 2.8), substance abuse (OR 2.6), and cerebrovascular disease (OR 2.4).

Familial CH and demographics (Russo, Manzoni, Taga, et al., Parma, PMID 26017530, n=785 probands) `[PEER-REVIEWED]`: positive family history in 5.1% of probands; M:F ratio *lower* among familial cases (2.3:1) than non-familial cases (2.7:1); women with familial CH had significantly younger onset (28.5 years) than women with non-familial CH (46.7 years, $p<0.01$) — no such difference in men, suggesting a possible sex-specific genetic effect on both onset age and sex ratio within familial CH specifically.

Compiled from PubMed/PMC, ICHD-3 official classification text, the journals Cephalalgia, Headache, The Lancet, Pain, Annals of Neurology, and JAMA Neurology, the Danish Headache Center (Rigshospitalet), Clusterbusters.org, OUCH(UK), Reddit r/clusterheads and r/ClusterHeadaches, and German, Danish, Italian, Japanese, and Chinese-language clinical literature and patient communities. Four detailed research memos (history, clinical picture, mechanism/pathophysiology, epidemiology) underpin this chapter; full source lists with URLs are preserved in the underlying research files for follow-up verification.

Part IV — Types, Diagnosis and What Else It Might Be

Source: Chapter 2 in full. Section numbering and the part's own reference list retained from the source chapter.

With the nature, mechanism and distribution established, this part places CH inside the trigeminal autonomic cephalalgia family, works through the differentials and the diagnostic journey, and lays out what triggers and comorbidities the evidence actually supports.

This chapter maps cluster headache (CH) inside the trigeminal autonomic cephalalgia (TAC) family, sets out the differential diagnoses most often confused with it, works through what a proper diagnostic workup looks like, and lays out what triggers and comorbidities the evidence base — formal and informal, English and non-English — actually supports.

---

1. Classification

Episodic vs chronic cluster headache

CH is defined by ICHD-3 (International Classification of Headache Disorders, 3rd edition) as attacks of severe, strictly unilateral orbital, supraorbital and/or temporal pain lasting 15–180 minutes untreated, occurring between once every other day and eight times a day, accompanied by ipsilateral cranial autonomic signs (conjunctival injection/lacrimation, nasal congestion/rhinorrhoea, eyelid oedema, forehead/facial sweating, miosis/ptosis) and/or restlessness or agitation [PEER-REVIEWED][^1][^2]. *(Editor's note: the verbatim ICHD-3 criteria are reproduced in Part I, §2.1.)*

- **Episodic cluster headache (ECH)**: attacks occur in bouts of 7 days to 1 year (untreated), separated by pain-free remission periods of 3 months or more; requires at least two such bouts [PEER-REVIEWED][^3].
- **Chronic cluster headache (CCH)**: attacks persist for a year or longer with no remission, or with remissions lasting less than 3 months [PEER-REVIEWED][^4]. CCH can arise *de novo* ("primary chronic") or evolve from ECH ("secondary chronic") [PEER-REVIEWED][^4].
- **The 1-month → 3-month criterion change matters and is a real source of confusion in circulating literature.** ICHD-2 and the ICHD-3-beta draft used a ≥1-month remission cutoff for episodic CH; the final ICHD-3 (2018) text raised this to ≥3 months, on the reasoning that shorter "remissions" often represented under-treated chronic disease rather than a true separate episodic bout [PEER-REVIEWED][^7][^73]. Many older papers, some patient-facing summaries, and even some newer secondary sources still quote the 1-month figure — this chapter uses the current ≥3-month ICHD-3 standard throughout, and any 1-month figures cited below are flagged as pre-2018 sourcing.
- **Proportions** vary more across studies and countries than pop-science summaries usually admit. ICHD-3 commentary and most reviews put episodic CH at roughly 80–90% and chronic at 10–15% [PEER-REVIEWED][^1][^5]. But cohort-level numbers scatter: a German dissertation cohort found 82.8% episodic / 9.7% primary-chronic / 7.5% secondary-chronic [PEER-REVIEWED][^58]; a German bibliographic dissertation found 72.9% episodic / 27.1% chronic [PEER-REVIEWED][^59]; a large German-population epidemiological summary (Ärzteblatt) states 85% episodic / 15% chronic [PEER-REVIEWED][^60]; and a Japanese clinic cohort found chronic CH prevalence as low as 2.8%, one of several markers of a possible East-Asian phenotype difference discussed further below [PEER-REVIEWED][^57].

Conversion between forms — the numbers, precisely

This is an area where the older, frequently-repeated round numbers ("about 10–15% convert") turn out to understate how genuinely fluid CH phenotype is. The best current data come from the Danish Headache Center (Rigshospitalet), using structured interview-based follow-up of a large, well-characterised cohort:

- An interview-based follow-up study of 430 CH patients from the Danish Headache Center found a **total transition-incidence of 20.7%** — one-fifth of the whole cohort experienced at least one phenotype change during the disease course. Of the whole cohort, 14.4% transitioned from episodic to chronic, and 6.3% transitioned from chronic to episodic. Side-shifting attacks (pain moving to the other side over time) predicted transition (p = 0.007) [PEER-REVIEWED][^61].
- A follow-up study of the same/related cohort (430 patients, re-interviewed) found: **1-year transition rate 6.5%, 5-year transition rate 19.8%** for the whole cohort. Specifically, the risk of episodic → chronic conversion was 4.0% at 1 year and 12.3% at 5 years; the risk of chronic → episodic conversion was markedly higher — 11.1% at 1 year and 25.0% at 5 years. Side-shifting attacks were reported in 32% of chronic patients and carried an odds ratio of 2.24 for being chronic rather than episodic [PEER-REVIEWED][^62][^63].
- An older but influential ten-to-twenty-five-year natural-history follow-up (Manzoni et al.) of 123 episodic and 9 chronic patients found: of initially episodic patients, 80.7% remained episodic, 12.9% shifted to chronic ("secondary chronic"), and 6.4% shifted to a "combined" pattern. Of initially chronic patients, 52.4% remained chronic, **32.6% reverted to episodic**, and 14.3% shifted to combined [PEER-REVIEWED][^64][^65]. This 32.6%/33% chronic-to-episodic reversion figure recurs across several reviews as "about a third," sometimes rounded up to "as many as 50%" in older secondary literature [PEER-REVIEWED][^66] — treat the 50% figure as an upper-bound outlier rather than a central estimate.
- A large multicentre South Korean study specifically tracking *frequent relapse* (not just chronic conversion) found a relapse rate of 0.29 per person-year (95% CI 0.27–0.32) among episodic patients followed for a mean of 4.2 years, and separately found that only 3.8% of first-onset CH newly became chronic, and 1.4% of those with an episodic history newly became chronic, during prospective observation — notably lower than the Danish/Italian retrospective figures, possibly reflecting shorter follow-up windows or a different at-risk population [PEER-REVIEWED][^67].
- The European Academy of Neurology's 2023 guideline states plainly: up to 12% of episodic patients progress to chronic; primary chronic presentations make up ~15% of all CH; and reversion from chronic to episodic "can also be seen, although rarely" [PEER-REVIEWED][^68] — this "rarely" framing sits in direct tension with the Danish Headache Center's 25% five-year reversion figure and Manzoni's 32.6%, and is presented here as an open discrepancy rather than resolved.
- **Total, spontaneous remission** (permanent cessation of all cluster activity) is documented but not well quantified: one source states remission after a single cluster period occurred in only 17% of a small cohort after 3+ years of follow-up, while most patients experience recurrence [PEER-REVIEWED][^69]; a separate source notes "total remission of the disease has been described" without giving a rate [PEER-REVIEWED][^70].

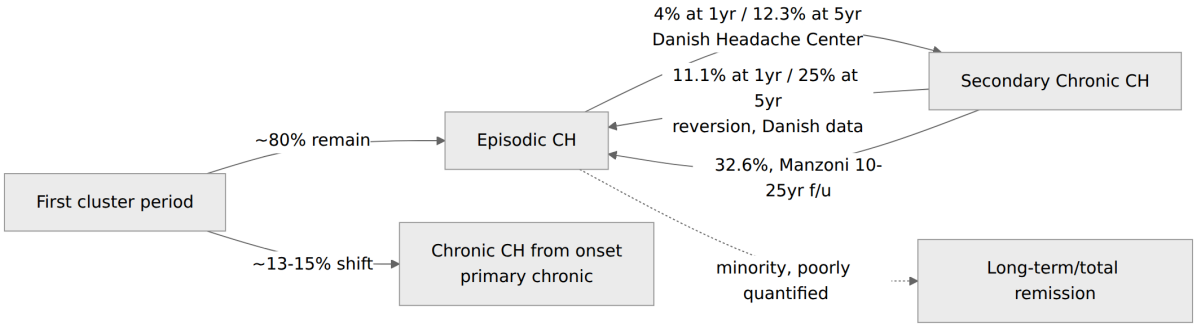


Diagram 1

Refractory chronic cluster headache (rCCH) is not a formally separate ICHD-3 entity but has working criteria from the European Headache Federation: at least three severe CCH attacks per week impacting quality of life despite treatment, and failure of at least three evidence-based prophylactic agents at maximum tolerated dose, with symptomatic chronic CH ruled out via MRI/MRA [PEER-REVIEWED][^6].

Where CH sits within the TACs

The term "trigeminal autonomic cephalalgia" was coined by Goadsby and Lipton in their landmark 1997 *Brain* paper, grouping short-lived, unilateral, trigeminally-distributed headaches with prominent cranial parasympathetic autonomic features, and separating them from headaches with sparse/no autonomic activation (trigeminal neuralgia, hypnic headache, cough headache, etc.)

[PEER-REVIEWED][^8][^9]. ICHD-2 (2004) formally established the TAC category with three members (CH, paroxysmal hemicrania, SUNCT); ICHD-3 (2013/2018) expanded the group by adding SUNA as a sibling to SUNCT (both now under the umbrella “short-lasting unilateral neuralgiform headache attacks”, SUNHA) and reclassifying hemicrania continua from “other primary headaches” into the TACs, on the basis of shared hypothalamic activation and cranial autonomic features [PEER-REVIEWED][^8][^10]. The unifying pathophysiological thread across the TAC family is thought to be excessive reflex activation of the trigeminal-autonomic reflex arc, permitted by dysfunction in the posterior hypothalamic grey matter [PEER-REVIEWED][^9].

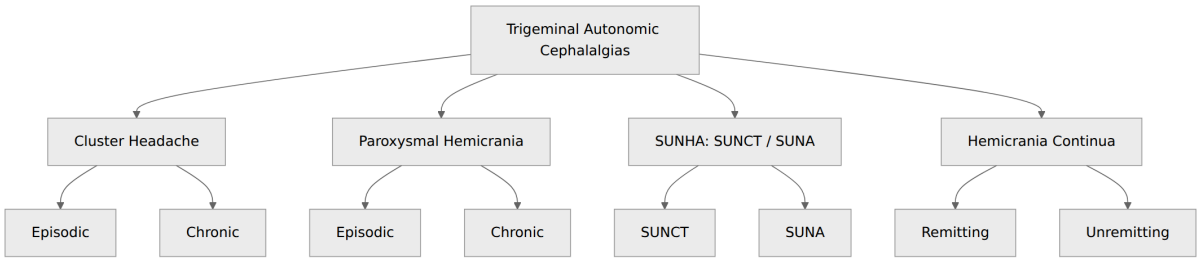


Diagram 2

2. The TAC Family & Differentials

Treatment response — particularly to indomethacin — functions as a diagnostic tool within the TAC family, not merely as therapy. This is a critical, non-obvious point: if a “cluster-like” daily headache resolves absolutely with indomethacin, the correct diagnosis is very likely paroxysmal hemicrania or hemicrania continua, not CH — and CH itself does *not* reliably respond to indomethacin [PEER-REVIEWED][^11].

Condition	Attack duration	Frequency	Autonomic features	Indomethacin response	Other diagnostic notes
Cluster headache	15–180 min	Every other day to 8/day	Prominent, ipsilateral	Generally poor/absent — triptans/oxygen work instead [PEER-REVIEWED][^11]	Circadian/circannual rhythmicity; alcohol/nitroglycerin/histamine can provoke attacks during a bout [PEER-REVIEWED][^1]
Paroxysmal hemicrania	2–30 min	>5/day for at least half the time (≥20 lifetime attacks)	Present	**Absolute** — sine qua non for diagnosis; effective dose range 25–300 mg/day [PEER-REVIEWED][^12][^13]	Chronic form more common than episodic in most series; some cases take up to a week to show response [PEER-REVIEWED][^12]
Hemicrania continua	Continuous, >3 months, with exacerbations	Daily, continuous (remitting or unremitting subtype)	Present during exacerbations	**Absolute** — required for diagnosis; oral dose often 25 mg tid titrated to 100–225 mg/day	Critical differential for any *daily* unilateral head pain; easily mistaken for chronic migraine or CCH [PEER-REVIEWED][^14][^15]
SUNCT	1–600 seconds, single/grouped/saw-tooth stabs	≥1/day (often far more; up to 200/day)	Must have BOTH conjunctival injection AND lacrimation	Not indomethacin-responsive; lamotrigine most effective preventive; IV lidocaine for severe bouts	Triggerable without refractory period, unlike trigeminal neuralgia [PEER-REVIEWED][^16][^17]
SUNA	1–600 seconds	≥1/day	Only one, or neither, of conjunctival injection/lacrimation, but ≥1 other autonomic sign	Not indomethacin-responsive; same treatment profile as SUNCT	Considered by many experts to be the same underlying entity as SUNCT (a spectrum) [PEER-REVIEWED][^18][^19]
Migraine with autonomic features	4–72 hours	Variable	Can occur but usually milder, bilateral-leaning	Not indomethacin-responsive	Photophobia/phonophobia/nausea more typical of migraine; overlap with CH is a major misdiagnosis driver [PEER-REVIEWED][^20]
Trigeminal neuralgia	Seconds	Variable, often clustered stabs	Absent or minimal	Not indomethacin-responsive; carbamazepine first-line	Has a post-attack refractory period, unlike SUNCT/SUNA; occasional diagnostic overlap reported with SUNCT [PEER-REVIEWED][^21]
Secondary causes (e.g. pituitary lesions, vascular lesions, sinusitis mimics)	Variable	Variable	Can mimic CH exactly	N/A	Pituitary/suprasellar masses account for a disproportionate share (~28.6% of secondary CH cases; 77.3% of mass lesions) of structural mimics — this is why baseline MRI (with dedicated pituitary/sella views) is recommended for every CH

Condition	Attack duration	Frequency	Autonomic features	Indomethacin response	Other diagnostic notes
					diagnosis, and pituitary hormone testing considered in refractory cases even with negative imaging [PEER-REVIEWED][^22][^23]

Two structural points worth internalising: first, SUNCT is now widely regarded as possibly a subform of SUNA rather than a fully distinct entity, though ICHD-3 still classifies them separately pending further study [PEER-REVIEWED][^17][^19]. Second, "cluster headache" itself carries a strong positive likelihood ratio (~11) for detecting significant intracranial abnormality on imaging, and red flags such as late age of onset, abnormal neurological exam (especially cranial nerve findings, likelihood ratio 5.3), a changing headache pattern, or pain worsened by Valsalva substantially raise suspicion for a secondary cause [PEER-REVIEWED][^22].

A further, less-discussed complication: a large German cohort study (825 patients, Kiel Pain Clinic) found considerable clinical variability within CH itself — some patients report persistent, lower-grade pain *between* attacks, a feature technically outside strict ICHD-3 criteria but clinically real and potentially confused with hemicrania continua. The authors argue that overly strict application of ICHD-3 criteria can itself delay diagnosis in atypical presentations [PEER-REVIEWED][^71].

---

3. Diagnosis in Practice

How diagnosis is made

CH diagnosis is clinical: a detailed patient history and neurological examination against ICHD-3 criteria, with no laboratory or electrophysiological test able to confirm it [PEER-REVIEWED][^5]. A brain MRI including the craniocervical junction (and ideally dedicated pituitary/sella views) is recommended at initial diagnosis, particularly given the risk of secondary mimics, especially in patients with increasing age at onset [PEER-REVIEWED][^5][^22].

Why misdiagnosis is so common, and how long it takes — a global picture

Diagnostic delay is one of the best-documented failures in CH care worldwide, and it is *not* an Anglophone-specific problem — every country and language group studied shows the same pattern, though the magnitude differs. *(Editor's note: decade-by-decade data showing the delay shrinking, and predictors of longer delay, are detailed in Part III, §4.7.)*

Country / population	Mean or median delay	Notable detail	Evidence
Global meta-analysis (7,177 subjects across studies)	10.43 years (95% CI 9.09–11.77)	Delay decreasing every decade since the 1960s, continuing since 2000; younger onset age, alternating attack side, and nocturnal headaches predict longer delay	[PEER-REVIEWED][^24b]
USA (nonclinic population survey)	6.6 years	Average 4.3 physicians seen, 3.9 incorrect diagnoses per patient; only 21% correctly diagnosed at first presentation	[PEER-REVIEWED][^25]
Italy / Eastern Europe (hospital-based)	5.3 ± 6.4 years (range 0–30)	34% waited 12.4 ± 6.3 years; country range 4.0 yrs (E. Europe) to 5.6 yrs (Italy)	[PEER-REVIEWED][^24]
Italy (Cefalea a Grappolo clinic series, 100 patients)	7.3 ± 8 years	Only 10% diagnosed at first attack; only 35% diagnosed within 3 years	[COMMUNITY/CLINICAL][^72]
UK (tertiary centre, historical trend)	Dropped from 22 years (1960s) to 2.6 years (1990s)	Mean GPs seen before diagnosis stayed at ~3 despite the improvement	[PEER-REVIEWED][^25b]
Netherlands (nonclinical population)	3.0 years	Fastest of the Western cohorts found in this search; 16% self-diagnosed from books/magazines before seeing a doctor	[PEER-REVIEWED][^20]
Germany (LMU Munich cohort, 93 patients)	9.6 years mean; 28.6% waited ≥10 years	Only 23.7% diagnosed promptly	[PEER-REVIEWED][^58]
Germany (population-level, Ärzteblatt clinical review)	44 months (3.7 years)	Cites 15% chronic / 85% episodic split	[PEER-REVIEWED][^60]
Germany (2015 press estimate, Kiel Pain Clinic director)	~8 years	Only ~30% of an estimated 400,000 German CH patients ever receive correct diagnosis; ~60% never receive adequate contemporary treatment	[COMMUNITY-REPORT/PEER-REVIEWED-ADJACENT — press-reported clinical estimate, not a published dataset][^74]
Denmark (Danish Cluster Headache Survey, 400 patients)	Decreasing by decade since 1950; 13.8 yrs if onset <20, 5.4 yrs if onset 20–40, 2.1 yrs if onset >40	Attack duration >180 min, migraine-like features, and nocturnal attacks independently predicted longer delay	[PEER-REVIEWED][^75]
Spain (SEN, national report)	4.9 years (one report); 7.8 ± 8.3 years (Valladolid registry, separate study)	Only 21% diagnosed correctly at first visit; 42% waited ≥5 years, 22% waited ≥10 years; 57% received a wrong diagnosis first, ~2 wrong diagnoses per patient on average	[PEER-REVIEWED][^76][^77][^78]
China (clinic-based, 120 patients, Journal of Headache and Pain)	8.2 ± 7.1 years	40% waited ≥10 years; only 10.8% diagnosed within 1 year	[PEER-REVIEWED][^79]

Country / population	Mean or median delay	Notable detail	Evidence
China (CHRIS registry, 816 patients)	Not given as a mean; 39.22% waited ≥10 years	Only 11.89% correctly diagnosed at first presentation	[PEER-REVIEWED][^80]
China (184-patient case series)	Median 8.0 years (IQR 4.0–13.0)	65.2% waited >5 years; 35.4% waited ≥10 years; only 12.4% diagnosed within 1 year	[PEER-REVIEWED, Chinese-language][^81]
Japan (Imai et al., 110 patients)	8.1 years mean	Only 19% received a correct diagnosis from a prior institution despite 85% having sought care elsewhere first; low chronic-CH prevalence (2.8%) and low reported “restlessness” noted as possible East Asian phenotype features	[PEER-REVIEWED][^57]
Japan (Japanese Headache Society data, cited in a 2021 proceedings paper)	3.6–9 years to final diagnosis	Only 21% correctly diagnosed at first visit; 25% diagnosed within 1 year; 22% took ≥10 years; ~49% of patients received at least one wrong diagnosis, averaging 1.7 misdiagnoses each	[PEER-REVIEWED][^82]

The dominant misdiagnoses at first consultation, across essentially every country studied, are trigeminal neuralgia, migraine without aura, and sinusitis [PEER-REVIEWED][^24]. In the German LMU cohort, dental and sinus causes were also common; in the Dutch cohort, 34% first saw a dentist and 33% first saw an ENT specialist [PEER-REVIEWED][^20]. The mechanism is partly that CH’s autonomic and nasal symptoms mimic sinus disease, and partly that CH patients can present with migraine-like features (photophobia, phonophobia, nausea) that push clinicians toward a migraine diagnosis instead [PEER-REVIEWED][^20].

A genuinely interesting cross-cultural finding: Japanese clinic cohorts consistently report a markedly *lower* prevalence of chronic CH (as low as 2.8%, versus the 10–20% typical of Western cohorts) and a lower reported prevalence of restlessness/agitation during attacks, alongside an “uncoupling” between subjectively reported restlessness and observed restless behaviour. The authors explicitly frame this as suggesting genuine ethnic/phenotypic variation in CH presentation between East Asia and the West, not merely a reporting artefact — though this remains a minority, under-replicated observation [PEER-REVIEWED][^57].

Patient experiences of the diagnostic journey [COMMUNITY-REPORT]

Patient community accounts (forums, r/clusterheads, Clusterbusters, and national patient associations such as Germany’s CSG and Spain’s AEPAC) consistently describe: repeated ER visits during attacks being dismissed as migraine or drug-seeking behaviour; dental extractions or root canals performed unnecessarily due to pain localisation near the jaw/teeth; sinus surgery pursued without benefit; and the eventual correct diagnosis frequently credited to either a neurologist, a headache specialist, or — commonly reported anecdotally — the patient self-diagnosing from internet research and presenting the ICHD criteria to their doctor. This self-diagnosis pathway is not purely anecdotal: the Dutch cohort study found 16% of patients had self-diagnosed from books or magazines before a doctor confirmed it [PEER-REVIEWED][^20], giving at least partial quantitative support to what is otherwise a widely repeated community narrative.

4. Triggers & Patterns

Established triggers

Alcohol — the in-bout vs out-of-bout distinction matters enormously. During an active cluster bout, alcohol reliably triggers attacks in the majority of drinkers — one Japanese cohort found alcohol triggered a new attack in 95% of habitual drinkers who were in-bout [PEER-REVIEWED][^26]. Outside of a bout (in remission), the same patients typically tolerate alcohol without triggering attacks — this in-bout-only sensitivity is a hallmark feature distinguishing CH from most other headache-alcohol relationships [PEER-REVIEWED][^26][^27]. More than 50% of CH patients report alcohol as a trigger during active bouts, though this proportion is notably lower in some Asian cohorts and older Italian data, suggesting either a reporting effect or a genuine population difference tied to drinking habits [PEER-REVIEWED][^27]. Curiously, some patients report the opposite effect — large amounts of alcohol producing transient remission or delaying the next attack — an unexplained and minority finding [PEER-REVIEWED][^27]. Overall population-level epidemiological data on alcohol and CH risk is genuinely contested: one large cohort found lower CH risk in non-drinkers (RR 0.65), while another found higher risk in non-drinkers (RR 1.54) — directly contradictory results that a meta-analysis could not resolve [PEER-REVIEWED][^28].

Histamine and nitroglycerin are both established provocation-test triggers used experimentally and clinically to confirm CH activity during a bout, per ICHD-3 commentary, though they are not typically encountered as "natural" everyday triggers [PEER-REVIEWED][^1].

Altitude. Unlike the previous pass through this material, a specific CH case report was located: a 40-year-old woman with episodic CH had an attack specifically triggered by high-altitude exposure; her attack was refractory to sumatriptan (which normally worked for her at sea level) but responded to oxygen [PEER-REVIEWED][^83][^84]. This confirms altitude *can* trigger CH in at least some patients, and that the acute-treatment response profile may shift at altitude — but this is case-report-level evidence (n=1), not a cohort or population study, so the frequency of altitude as a CH trigger across the general CH population remains unquantified. Separately, "high-altitude headache" (HAH) is itself a distinct ICHD-3 secondary headache diagnosis, generally bilateral and exertion-aggravated, and should not be confused with altitude-triggered CH [PEER-REVIEWED][^85][^86]. Population-level data quantifying how common altitude-triggering is *specifically* among CH patients was not found in this pass and remains a gap.

Barometric pressure and weather — a genuine, unresolved conflict between two different kinds of study. A large, nationwide, peer-reviewed Taiwanese population study (758 episodic CH patients, 2,452 recorded cluster-period episodes, National Health Insurance Research Database, case-crossover design) found that **higher mean temperature was significantly associated with the onset of a new cluster period** (OR 1.014, 95% CI 1.005–1.023, p = 0.003 on the event day, with similar associations at 7–56 days prior), and that temperature *changes* following either warm or cold baseline periods could precipitate bout onset, with no such association in tropical climates [PEER-REVIEWED][^87][^88]. By contrast, a 2026 Spanish 14-year primary-care time-series study (99 CH consultations across three centres, ETSX modelling against 14 meteorological variables including barometric pressure, temperature, wind, rainfall, and sunshine) found **no statistically significant association between any climatic variable and CH consultation frequency** — the authors explicitly note their result diverges from the Taiwanese finding and suggest individual-level triggers (sleep irregularity, stress, behavioural change) may swamp population-level weather signals in a small consultation dataset [PEER-REVIEWED][^89]. These two studies are not strictly contradictory — one measures *new bout onset* against temperature specifically, the other measures *consultation frequency* against a wider basket of weather variables in a much smaller sample — but the tension between "temperature/weather affects CH periodicity" and "no weather variable predicts CH" should be treated as a live, unresolved question rather than settled science. No peer-reviewed source specifically confirmed barometric pressure (as opposed to temperature) as a validated trigger for CH bout onset or individual attacks; the widely repeated patient and clinical claim that dropping barometric pressure triggers CH attacks remains supported mainly by migraine-literature extrapolation and community report, not CH-specific primary data.

Sleep timing and naps: CH shows strong chronobiological and circadian patterning, with nocturnal attacks common and a documented tendency for attacks to cluster around specific hours and around REM sleep onset (see below) [PEER-REVIEWED][^29][^30]. A South Korean multicentre study found circadian rhythmicity in 55.0% and seasonal rhythmicity in 39.7% of patients,

with spring the most commonly cited season for bout onset in a separate Korean cohort (37.5% of those with seasonal propensity) [PEER-REVIEWED][^90][^91].

Sleep architecture: REM association and obstructive sleep apnoea

Cluster headache has one of the most sleep-entangled profiles of any primary headache disorder:

- Early polysomnography studies found a strong association between nocturnal CH attacks and REM sleep — in one series, almost 60% of recorded CH attacks followed REM sleep despite REM comprising only ~20% of total sleep time [PEER-REVIEWED][^30]. Patients with CH also report vivid dream recall when woken by an attack, consistent with REM waking [PEER-REVIEWED][^30].
- However, more recent studies have complicated this picture: several have found CH attacks are *not* significantly associated with REM sleep after all, and a 2012 review concluded the REM association appears present in episodic CH but not in chronic CH — a genuine, unresolved split in the literature [PEER-REVIEWED][^31][^30].
- **Obstructive sleep apnoea (OSA)** is markedly overrepresented in CH populations. A Brazilian study found 58.3% of CH patients had OSA vs 14.3% of controls and 2–4% of the general population, translating to an 8.4-fold increased odds of OSA in CH (rising to 24.4-fold in patients with BMI >25, and 13.5-fold in patients over 40) [PEER-REVIEWED][^32]. A separate US study found an even higher rate: 80.6% of episodic CH patients had sleep apnoea on polysomnography [PEER-REVIEWED][^33].
- A 2024 polysomnography study found that greater OSA severity was associated with later CH onset age and longer maximum cluster bout duration, and that even patients with only *mild* OSA showed elevated susceptibility to hypoxia specifically during REM sleep [PEER-REVIEWED][^31].
- Case reports describe CPAP/BiPAP treatment of comorbid OSA abolishing or greatly reducing nocturnal cluster attacks in some patients, though this remains anecdotal/case-level evidence rather than a controlled trial finding, and the causal direction is explicitly unresolved — current thinking treats CH and OSA as possibly parallel outputs of hypothalamic dysfunction rather than one causing the other [PEER-REVIEWED][^31][^34][^35][^36].

Community-reported triggers and protective factors

Smoking: the overwhelming majority (up to ~80%, and 48.3% current/past smoking specifically per the Danish national cohort vs 9.0% in controls) of CH patients are smokers or ex-smokers, one of the strongest lifestyle associations in the condition [PEER-REVIEWED][^37][^38]. However, this looks like association rather than causation: in a pilot survey of 200 patients, active smokers had a more severe CH phenotype (longer active periods, more attacks/day) than never-smokers, but the majority of former smokers reported no change in their CH after quitting — and only around 3% of an internet-surveyed CH population reported improvement after smoking cessation [PEER-REVIEWED][^39][^38]. During an active bout, most patients report either decreasing (45.7%) or keeping stable (45.7%) their smoking, with most of those who cut back reporting a genuinely reduced desire to smoke during the bout [PEER-REVIEWED][^39] [CITIZEN-SCIENCE/COMMUNITY-REPORT for the cessation-outcome framing, PEER-REVIEWED for underlying survey data]. *(Editor's note: the fullest treatment of smoking prevalence and the causality paradox is in Part III, §4.4.)*

Psychedelics — citizen science and clinical convergence. This is one of the most striking and well-triangulated findings in the CH literature, originating almost entirely from patient-organised research before formal science caught up. *(Editor's note: the full account — the Clusterbusters origin story, the 2006 Harvard-affiliated survey of 53 patients, the 2015 Clusterbusters Medication Use Survey (496 respondents), the Yale randomised trials and the 2025 case series — is given in Part VI, §§1 and 3, with the current trial pipeline in Part VII, §5.1.3. The duplicate detail that originally sat here was consolidated into Part VI during assembly; this part's original citations for it remain in the reference list below as [^40]–[^46].)*

Other citizen-science-flagged patterns: the same Clusterbusters-driven International Cluster Headache Questionnaire (>3,000 respondents, published in *Headache*, November 2021) also generated formal peer-reviewed papers on oxygen vs sumatriptan effectiveness and patient-reported tolerability [CITIZEN-SCIENCE][^44]. Germany's CSG (Bundesverband der

Clusterkopfschmerz-Selbsthilfe-Gruppen) has run its own patient surveys on sex differences in CH presentation and psychological burden, though results from these specific surveys were not retrieved in publicly accessible peer-reviewed form in this pass — flagged as a community data source worth following up directly [CITIZEN-SCIENCE][^92][^93].

---

5. Comorbidities & Impact

Psychiatric comorbidities

- **Depression**: a nationwide Taiwanese cohort found CH patients had a 5.6-fold increased hazard of developing depression compared to controls (aHR 5.6, 95% CI 3.0–10.6), with the annual number of cluster bouts itself predicting depression risk (aHR 3.8 per bout) [PEER-REVIEWED][^47]. Another French cohort found depression in 43% of chronic CH patients [PEER-REVIEWED][^48].
- **Anxiety**: a multicentre registry found moderate-to-severe anxiety in 38.2% and moderate-to-severe depression in 34.6% of CH patients during active bouts, both dropping sharply during remission (e.g. PHQ-9 depression score falling from 6.1±5.0 in-bout to 1.8±2.4 in remission) — showing these symptoms are substantially state-dependent on bout activity, not fixed traits [PEER-REVIEWED][^49]. Co-existing migraine massively amplifies this risk (aOR for depression up to 16.88 vs controls) [PEER-REVIEWED][^49].
- **Suicidality — "the suicide headache":** CH has carried this nickname since B.T. Horton's early descriptions [PEER-REVIEWED][^50]. Findings are more nuanced than the nickname suggests. A large 2025 systematic review/meta-analysis found the *overall* suicidal risk in CH is not clearly elevated above general-population rates (suicidal ideation ~8.0% overall vs 5.2% in non-specialised comparison groups), but risk is markedly elevated specifically during attacks (ictal) and among patients seen in specialised headache clinics, where severity is higher [PEER-REVIEWED][^51]. A study of 175 patients in-bout found passive suicidal ideation in 64.2% during attacks, versus only 4.0% interictally and 0% between bouts — suicidality in CH is overwhelmingly attack-linked, not a constant background state [PEER-REVIEWED][^52]. Separately, a case-control study found CH patients had double the odds of lifetime suicidal ideation versus matched controls, and that this was best predicted by **demoralization** rather than depression itself [PEER-REVIEWED][^50]. Some surveys report far higher lifetime figures — one large US CH survey found 55% had experienced suicidal thoughts and 2% had attempted suicide [PEER-REVIEWED][^48] — a notable divergence from the 2025 meta-analysis's more moderate estimate, likely reflecting differences between clinic-referred/self-selected survey samples and population-representative cohorts. This divergence is presented as an open, unresolved tension rather than resolved. *(Editor's note: the full set of suicidality figures, including the population-level registry tension, is in Part III, §4.8; psychological-burden context is in Part I, §2.6.)*
- A large multi-headache-type study found TAC patients overall (CH included) had more than double the risk of completed suicide (aHR 2.40) compared with headache-free controls [PEER-REVIEWED][^53].

Sleep and physical comorbidities

OSA (detailed in Section 4) and lifestyle-related disease are both elevated: the Danish Cluster Headache Survey found current or past smoking prevalence of 48.3% in CH patients vs 9.0% in controls, alongside excess prevalence of other lifestyle-related comorbid diseases [PEER-REVIEWED][^37].

Quality of life and employment impact

- A large European Migraine and Headache Alliance (EMHA) survey of 1,500 CH patients across the EU (2019) found 29% of chronic CH patients had prematurely exited the workforce (14% of the full sample); 22.5% reported being unfit for paid work due to CH; 12.7% had lost one job and 8% had lost more than one; and patients missed an average of 14 work days in the prior 3 months (19.8 days for chronic CH vs 4 days for episodic) [CITIZEN-SCIENCE/PEER-REVIEWED survey][^54]. 75% overall (90% of chronic CH patients) reported career interference [PEER-REVIEWED][^54].
- A validated CH-specific quality-of-life scale (the CHQ) has been developed from 406 patients in England, reflecting growing recognition that generic headache QoL tools understate CH's distinct burden [PEER-REVIEWED][^55].

- A Korean prospective study specifically examined employment status, job type, sick leave and productivity loss in CH patients, reinforcing the EU findings with a separate national dataset [PEER-REVIEWED][^55].
- Spain's national health system data show a similarly steep access-to-care problem underlying the employment burden: Spanish Society of Neurology reporting states diagnostic and treatment delays translate directly into avoidable years of unmanaged disability before patients reach appropriate care [PEER-REVIEWED][^76].

References (Part IV)

1. 3.1 Cluster headache
2. The International Classification of Headache Disorders (ICHD-3 pocket version)
3. 3.1.1 Episodic cluster headache
4. 3.1.2 Chronic cluster headache
5. CLINICAL SYNDROME, European Journal of Neurology
6. Hallmarks of primary headache: part 3 – cluster headache
7. Trigeminal Autonomic Cephalalgias: Diagnosis and Management
8. Classification of Trigeminal Autonomic Cephalalgia: What has Changed
9. Trigeminal autonomic cephalalgias. Pathophysiology
10. Overview of Trigeminal Autonomic Cephalalgias
11. Indomethacin responsive headache syndromes
12. 2.4.2 Paroxysmal hemicrania - BASH
13. Paroxysmal hemicrania: a prospective clinical study of 31 cases
14. 3.4 Hemicrania continua
15. Hemicrania continua: clinical review, diagnosis and management
16. Short-lasting unilateral neuralgiform headache attacks
17. 3.3 Short-lasting unilateral neuralgiform headache attacks
18. SUNCT, SUNA and Trigeminal Neuralgia
19. SUNCT and SUNA: An Update - Neurology India
20. Features involved in the diagnostic delay of cluster headache
21. 3.3.1 SUNCT
22. Preferred Imaging for Ruling Out Secondary Causes of Cluster-like Headache
23. A triad of cluster-like headaches with delayed development of a macroscopic prolactinoma
24. Diagnostic and therapeutic errors in cluster headache: a hospital-based study 24b. Cluster headache diagnostic delay and its predictors (meta-analysis)
25. The misdiagnosis of cluster headache: a nonclinic-based study 25b. Cluster Headache: Epidemiology, Pathophysiology, Clinical Features
26. Differences in clinical features of cluster headache between Japan and other countries
27. Alcohol-induced headaches: Evidence for a central mechanism
28. Relationship between alcohol and primary headaches
29. Sleep-related headache and its management
30. Cluster headache and sleep, is there a connection? A review
31. Cluster Headache Characteristics and the Severity of Obstructive Sleep Apnea
32. Investigation into sleep disturbance of patients suffering from cluster headache
33. Obstructive sleep apnea and cluster headache
34. Cluster headache and obstructive sleep apnea
35. Cluster headache associated with sleep apnoea
36. Nocturnal Cluster Headache Associated with Sleep Apnea. A Case Report
37. Cluster headache is associated with unhealthy lifestyle and lifestyle-related comorbid diseases: Danish Cluster Headache Survey

38. Trigeminal autonomic cephalalgias — addictions and drugs
39. Impact of continuing or quitting smoking on episodic cluster headache
40. Research and History - Clusterbusters
41. Sewell et al. 2006, Neurology
42. Response of cluster headache to psilocybin and LSD
43. Indoleamine Hallucinogens in Cluster Headache: Clusterbusters Medication Use Survey
44. Past Research - Clusterbusters
45. Psilocybin pulse regimen reduces cluster headache attack frequency (NCT02981173)
46. Clinical treatment of cluster headache with psilocybin, LSD and ketamine: A case series
47. Cluster headache is associated with an increased risk of depression
48. Personality traits in patients with cluster headache
49. The impact of remission and coexisting migraine on anxiety and depression in cluster headache
50. Demoralization predicts suicidality in patients with cluster headache
51. Cluster headache suicidality: a systematic review with a meta-analysis
52. Increased suicidality in patients with cluster headache
53. Headache Strongly Linked to Attempted, Completed Suicide
54. Cluster Headache (CH) and work life in the European Union
55. Patient-identified burden and unmet needs in patients with cluster headache
56. Clinical profile of cluster headaches in Japan: Low prevalence of chronic cluster headache, and uncoupling of sense and behaviour of restlessness
57. Clusterkopfschmerz - Klinische Symptomatik, Therapie (LMU Munich dissertation)
58. Epidemiologie und Verlauf von Patienten mit Clusterkopfschmerzen
59. Clusterkopfschmerz - Ärzteblatt
60. Transition of cluster headache phenotype: An interview-based study
61. Transition of cluster headache: Depicting side-changing attacks as a chronic trait
62. Transition of cluster headache follow-up study - PubMed
63. Cluster headache–course over ten years in 189 patients
64. Cluster Headache: A review of clinical presentation - JAAPA
65. Is Sudden and Permanent Relief from Cluster Headaches Common?
66. Subtype shift, relapse rate and risk factors of frequent relapse in cluster headache
67. European Academy of Neurology guidelines on cluster headache
68. A Follow-Up Study of 60 Patients After an Assumed First Period of Cluster Headache
69. Cluster headache - PMC
70. Phenotype of Cluster Headache: Clinical Variability, Persisting Pain Between Attacks, and Comorbidities (825 patients)
71. Cefalea a grappolo: un problema di inadeguatezza diagnostica
72. Zusammenhang von Krankheitsaktivität, Depression und Tagesschläfrigkeit bei Patient:innen mit Clusterkopfschmerz
73. Auf bessere Versorgung und Vernetzung pochen - Ärztezeitung
74. Diagnostic delay of cluster headache: A cohort study from the Danish Cluster Headache Survey
75. Sólo un 21% de los pacientes con cefaleas en racimos recibió un diagnóstico adecuado - SEN
76. Características clínico-demográficas de un registro de pacientes con cefalea en racimos (Valladolid)
77. Los afectados por cefalea en racimos en España tardan casi cinco años - Famma
78. Clinical profile of cluster headaches in China – a clinic-based study
79. Profile of Chinese Cluster Headache Register Individual Study (CHRIS): 816 patients
80. 184
81. Oft verkannt – obwohl die Symptome eigentlich eindeutig sind
82. Efficacy of oxygen inhalation in sumatriptan refractory “high altitude” cluster headache attacks
83. Efficacy of oxygen inhalation in sumatriptan refractory “high altitude” cluster headache attacks - PMC
84. Craniofacial sensations induced by transient changes of barometric pressure in healthy subjects
85. High-altitude headache: Insights into pathophysiology and potential treatment implications

86. Temperature variation and the incidence of cluster headache periods: A nationwide population study
87. Temperature variation and the incidence of cluster headache periods - PubMed
88. 14-year time series analysis of cluster and tension-type headache and climatic factors
89. Treatment pattern and response for cluster headache in Korea: A prospective multicenter observation study
90. Clinical Features of Cluster Headache Patients in Korea
91. Bundesverband der Clusterkopfschmerz-Selbsthilfe-Gruppen (CSG) — survey on CH in women and men
92. Bundesverband der Clusterkopfschmerz-Selbsthilfe-Gruppen (CSG) — survey on psychological burden

---

Part V — Treatment

Source: Chapter 3 in full. Section numbering and the part's own reference list retained from the source chapter.

The clinical response: acute, bridge and preventive treatment, neuromodulation and surgery — and the country-by-country access realities that often decide more than the evidence does.

Compiled as a personal reference document. Every claim below carries an evidence tag: `[PEER-REVIEWED]`, `[PREPRINT/TRIAL]`, `[CITIZEN-SCIENCE]`, `[COMMUNITY-REPORT]`, *or* `[HISTORICAL/CULTURAL]`. *Community reports are never discarded for being anecdotal — they are labelled honestly and included because patterns in anecdote are data. Where sources conflict, the conflict is presented explicitly rather than smoothed over. "Unknown" and "contested" are treated as valid, final answers where that is what the evidence supports.*

This chapter covers acute/abortive treatment, transitional/bridge therapy, preventive treatment, neuromodulation and surgical procedures, and country-by-country access realities — with particular attention to Australia, and South Australia specifically. It draws on peer-reviewed trials and meta-analyses, registered trials and preprints, structured citizen-science surveys, community reports from r/clusterheads and r/ClusterHeadaches, and non-English clinical literature and guidelines from Germany, Denmark, Japan, Italy, and elsewhere, sourced and cross-checked over four dedicated research passes covering roughly 280 unique sources between them.

The single most important pattern threading through everything below: chronic cluster headache is worse-served by the evidence base than episodic cluster headache, on almost every treatment, at almost every level of evidence. Where trials report a chronic subgroup at all, it almost always does worse than the episodic group — sometimes dramatically so. Readers with chronic daily CH should discount headline efficacy figures accordingly unless a section explicitly says otherwise.

---

1. Acute / Abortive Treatment

Acute treatment aims to shorten or stop an individual attack. Because chronic sufferers face attacks daily, sometimes several times a day, the ceiling on how often each acute option can be used safely is as important as its per-attack efficacy — and is where community practice and formal guidance diverge most sharply.

1.1 High-Flow Oxygen

1.1.1 Evidence base

The landmark RCT

`[PEER-REVIEWED]` **Cohen AS, Burns B, Goadsby PJ. "High-flow oxygen for treatment of cluster headache: a randomized trial." JAMA. 2009;302(22):2451–7.** Double-blind randomised placebo-controlled crossover trial at the National Hospital for Neurology and Neurosurgery, London, 2002–2007. 109 enrolled, 76 analysed (57 episodic, 19 chronic). Each participant treated four attacks — two with 100% oxygen at **12 L/min via face mask for 15 minutes**, two with high-flow air (JAMA 2009; PMID 19996400, DOI 10.1001/jama.2009.1855, ISRCTN94092997).

Outcome at 15 min	Oxygen	Air
Pain-free or adequate relief	**78%** (95% CI 71–85; 150 attacks)	**20%** (95% CI 14–26; 148 attacks)

Wald $\chi^2(5) = 66.7$, $P < .001$. **No important adverse events.** This single trial is the backbone of every "Level A / strong recommendation" for oxygen worldwide, and its 78% number is the one you will see repeated in German, Japanese and Australian sources alike.

Earlier trials

[PEER-REVIEWED] **Kudrow L, Headache 1981;21(1):1–4** — the first systematic study. 7 L/min for 15 minutes aborted more than 7 of 10 attacks in **82%** of patients, compared with **70%** for sublingual ergotamine. Kudrow also noted a rebound effect in some oxygen users (Guo et al., Med Gas Res 2019, PMC7802413). The Japanese Headache Society records Kudrow's timing detail: improvement within 7 minutes in **62%**, with a further **31%** improving at 8–10 minutes (JHS CQ1) — *non-English source, Japanese*.

[PEER-REVIEWED] **Fogan L, Arch Neurol 1985;42(5):362–3** — double-blind oxygen vs room air, **6 L/min for 15 min**, N=19 men aged 20–50. Relief score (0=none to 3=complete relief) **1.93 ± 0.22 for oxygen vs 0.77 ± 0.23 for air, F test P<.01** (JHS CQ1, *Japanese source*). Described elsewhere as **56% of oxygen users getting relief in more than 80% of attacks vs 7% on air** (Guo et al. 2019).

[PEER-REVIEWED] **Igarashi et al. 1988** (, *Nihon Naika Gakkai Zasshi* 77(2):267) — open-label, N=23, oxygen 7 L/min via face mask side port. 17 patients improved, mean onset of improvement **3.1 ± 3.1 min**, pain resolution at **13.5 ± 6.2 min** (JHS CQ1). *Non-English source, Japanese — this trial is essentially invisible in the Anglophone literature and is part of why Japan's guideline settled on 7 L/min.*

Cochrane

[PEER-REVIEWED] **Bennett MH, French C, Schnabel A, Wasiak J, Kranke P, Weibel S. "Normobaric and hyperbaric oxygen therapy for the treatment and prevention of migraine and cluster headache." Cochrane Database Syst Rev. 2015; (12):CD005219** (PMC8720466, DOI 10.1002/14651858.CD005219.pub3, PMID 26709672). 11 trials, 209 participants in the abstract analysis. For cluster headache: **normobaric oxygen — 3 trials, 145 participants; hyperbaric oxygen — 2 trials, 29 participants.**

For hyperbaric oxygen in CH the pooled result was **RR 11.38 (95% CI 0.77–167.85, P=0.08), single trial, no evidence of effectiveness** — the enormous confidence interval reflects that Di Sabato 1993 had **n=13** and produced complete resolution within 20 minutes in **6/7 (86%) HBOT vs 0/6 sham**, sustained at ≥48 h in 86% vs 0%. Trial quality across the review was rated **"poor to moderate."** The review was declared stable in 2016 and has not been updated.

Read this honestly: Cochrane's verdict is that *normobaric* oxygen has real supporting evidence (driven by Cohen 2009), while *hyperbaric* oxygen is unproven — the studies are tiny, the point estimate is dramatic, and the confidence interval spans "no effect" to "miraculous." Do not let the 86% figure travel without its n=13.

The flow-rate trial that complicated things

[PEER-REVIEWED] **Dirkx THT, Haane DYP, Koehler PJ. "Oxygen treatment for cluster headache attacks at different flow rates: a double-blind, randomized, crossover study." J Headache Pain. 2018;19(1):94** (PMC6755552, DOI 10.1186/s10194-018-0917-4, PMID 30306284). 98 enrolled at 28 Dutch centres (target 110), 70 valid, 56 used both flow rates, 604 attacks analysed. Salter Labs E-8140 non-rebreather mask. **7 L/min vs 12 L/min.**

Outcome	7 L/min	12 L/min	p
Pain-free, first 2 days (median %)	0% (IQR 0–37.5)	0% (IQR 0–83.5)	0.180
VAS drop (median)	4.09	4.33	0.243
Successfully treated attacks (median %)	92.86%	—	—

Exploratory analysis gave **OR 0.73 (95% CI 0.52–1.02, p=0.061) for pain-freedom at 12 vs 7 L/min** — i.e. numerically *favouring the lower flow rate*, and on one measure **more patients were pain-free at 7 L/min (p=0.039)**. Yet **patients preferred 12 L/min**. Critically, the primary endpoint rested on only **5 patients and 27 attacks**, so this trial is badly underpowered for its own

primary question.

This is a genuine, unresolved conflict. The EAN guideline cites a flow-comparison odds ratio of **3.75 (95% CI 0.58–24.28) favouring 12 L/min** (EAN 2023) — a point estimate in the opposite direction from Dirkx, with a confidence interval so wide it means almost nothing. **Honest summary: nobody has convincingly established the optimal flow rate.** The community consensus (≥15 L/min) is not evidence-based in the trial sense; neither is Japan's 7 L/min. What *is* established is that 12 L/min via a proper mask beats air.

Demand-valve and mask-comparison studies

`[PEER-REVIEWED]` **Petersen AS, Barloese MCJ, Lund NLT, Jensen RH. "Oxygen therapy for cluster headache. A mask comparison trial. A single-blinded, placebo-controlled, crossover study." Cephalalgia** — Danish Headache Center, Rigshospitalet. 57 CH patients, 102 attacks, inpatient single-blinded semi-randomised placebo-controlled crossover, comparing **demand-valve oxygen (DVO) vs O2ptimask vs simple mask at 15 L/min** (Cephalalgia PDF). O2ptimask and DVO **decreased the need for rescue medication** compared with the simple mask. However, the EAN guideline's reading is that **no statistically significant effect was demonstrated between groups** (EAN 2023) — flagging this as a contested interpretation. *Danish source — the Danish Headache Center is the main non-Anglophone group doing oxygen delivery research.*

`[PEER-REVIEWED]` A demand-valve pilot published in **Pain Medicine 2013;14(4):455–9** (DOI 10.1111/pme.12055, PMID 23369112, NCT01298921) had only **4 participants** — worth knowing so that community claims of "trial-proven demand valves" can be sized correctly. Review: Oude Nijhuis, Haane, Koehler, *Cephalalgia* 2016, DOI 10.1177/0333102415616878.

1.1.2 Mechanism of action

Genuinely unsettled. Candidate mechanisms:

`[PEER-REVIEWED]` **Cerebral vasoconstriction; attenuation of neurogenic inflammation; attenuation of parasympathetic overactivity** — the three mechanisms listed by the Japanese Headache Society, which states plainly that the mechanism "is still not clear in many respects" ( ) (JHS CQ1). *Japanese source.*

`[PEER-REVIEWED]` **Akerman/Goadsby preclinical work**: oxygen inhibits neuronal activation in the trigeminocervical complex *after* stimulation of the trigeminal-autonomic reflex, but **not** during direct dural activation — implying oxygen acts on the parasympathetic/facial nerve limb rather than on trigeminal nociception directly (King's College London research portal). This is the most mechanistically satisfying explanation currently on offer, and it predicts that oxygen should work *better* the earlier in the attack it is given — which matches patient experience.

`[PEER-REVIEWED]` The Australian Prescriber review lists: "vasoconstriction; blocks the trigeminal autonomic reflex; inhibits protein release and activity in the superior salivatory nucleus" (Ray, Stark, Hutton, Aust Prescr 2022;45:15–20, DOI 10.18773/austprescr.2022.004).

`[COMMUNITY-REPORT]` OUCH-UK's patient-facing leaflet offers a different and **almost certainly wrong** mechanism: "the hypothalamus… sends out a false message that the brain is short of oxygen [evidenced by yawning] and the blood vessels immediately start expanding in the search for O2; this puts enormous pressure on the nerves inside the skull" (OUCH-UK, Oxygen for CH 2023). **Flagged as a folk mechanism.** The vascular-pressure model of headache pain was abandoned by researchers decades ago. It does no harm to patients — the practical advice attached to it is sound — but it should not be cited as science.

1.1.3 Delivery technique — what the numbers actually mean

`[PEER-REVIEWED]` **Mo H, Chung SJ, Rozen TD, Cho S-J. "Oxygen Therapy in Cluster Headache, Migraine, and Other Headache Disorders." J Clin Neurol. 2022;18(3):271–279** (PMC9163947, DOI 10.3988/jcn.2022.18.3.271) gives the delivery-device table that explains most of the confusion in this field:

Device	Flow rate	Delivered FiO_2
Nasal cannula	1–6 L/min	0.24–0.44
Simple face mask	5–12 L/min	0.20–0.50
Non-rebreather / reservoir mask	**10–15 L/min**	**0.55–0.95**
Demand-valve oxygen (DVO)	**40–160 L/min**	**0.40–1.00**
Venturi mask	40–50 L/min	variable
High-flow nasal cannula	40–60 L/min	variable

The key insight buried in that table: a non-rebreather at 12–15 L/min does not deliver 100% oxygen. Mo et al. explicitly classify 6–15 L/min via NRM as *intermediate* flow, not true high flow. The reason is peak inspiratory flow: an adult breathing hard during a cluster attack can inhale at 30–60 L/min. A 15 L/min supply cannot keep up, the reservoir bag collapses, and room air is entrained around the mask seal. **A demand valve solves this by delivering gas as fast as you can pull it**, shutting off on exhalation and delivering undiluted 100% oxygen.

This single physiological fact reconciles most of the guideline-vs-community disagreement below. The community is not being irrational when it pushes for higher flow rates; it is trying to defeat dilution.

Guideline-recommended technique

Source	Flow	Duration	Mask	Position
EAN 2023 (Europe) `[PEER-REVIEWED]`	**100% O_2 at ≥12 L/min**, "in some cases up to 15 L/min"	15 min (detailed section says 20 min)	Non-rebreather required; **"nasal cannulae are not sufficient"**	not specified
Japanese Headache Society 2018 `[PEER-REVIEWED]`	**>90% O_2 at 7 L/min via face mask side port**	15 min	face mask	not specified
DMKG (Germany) `[PEER-REVIEWED]` / `[COMMUNITY-REPORT]`	**7–15 L/min**	**15–20 min**	High-concentration (non-rebreather) mask; nasal cannula "usually not sufficient"	**sitting, leaning forward**; **do not hyperventilate**
Australian Prescriber 2022 `[PEER-REVIEWED]`	**7–12 L/min**	15 min	non-rebreather, from a cylinder	not specified
Exeter Headache Clinic (UK NHS) `[COMMUNITY-REPORT]`	**Start 15 L/min, then reduce to 6–8 L/min** — enough to keep the reservoir bag inflated	until pain gone **+5 min to "mop up"**	reservoir-bag mask	not specified

Sources: EAN 2023; JHS CQ1; DMKG "Sauerstoffbehandlung bei Cluster-Kopfschmerz"; Australian Prescriber; Exeter Headache Clinic 2021/2023.

The German guidance is the most complete patient-facing protocol in any language, and it is the only official document that specifies both body position and a warning against hyperventilating. Verbatim, from the DMKG:

> „Sauerstoffflasche, kein Sauerstoffkonzentrator." (Oxygen cylinder, **not** an oxygen concentrator.) „Sofort bei Beginn der Attacke mit der Sauerstofftherapie beginnen." (Start immediately at attack onset.) „Inhalation in sitzender, vornüber gebeugter Position." (Inhale sitting, leaning forward.) „Nicht hyperventilieren (übermäßiges Atmen)." (Do not hyperventilate.) „Verwendung einer Hochkonzentrationsmaske (Non-Rebreather Maske)… eine sogenannte Nasensonde oder Nasenbrille ist meist nicht ausreichend."

German source. Note the direct conflict with clusterinfo.org's community protocol below, which instructs demand-valve users to hyperventilate deliberately.

Timing

`[PEER-REVIEWED]` / `[COMMUNITY-REPORT]` Every source agrees on this and it is probably the highest-yield practical point in the whole chapter: **start at the first hint of the attack, before pain is established.** OUCH Belgium's patient leaflet is explicit that treatment should begin at the first symptom, before pain (OUCH Belgium oxygen leaflet) — *Belgian/French source*. Exeter: "As soon as you know an attack is starting" (Exeter). DMKG: „Sofort bei Beginn der Attacke."

For someone with chronic daily CH this has an operational consequence: **the cylinder needs to be within arm's reach of where you sleep and where you work**, not in a cupboard. Access latency is part of efficacy.

The "mop up" question

`[COMMUNITY-REPORT]` Both Exeter Headache Clinic and OUCH-UK's forum advise staying on oxygen **after the pain has stopped** — Exeter says 5 minutes, "to 'mop up' the attack and prevent possible rebound, which some patients find is a problem"; the OUCH-UK forum consensus is **5–10 minutes** at 15 L/min (Exeter; OUCH-UK forum, oxygen use).

No trial has tested this. It rests entirely on the rebound phenomenon Kudrow described in 1981 `[HISTORICAL/CULTURAL]` and on accumulated patient experience. It costs nothing and is plausible; label it as practice wisdom, not evidence.

1.1.4 Community-optimised technique — where the community diverges from the guidelines

This is the most interesting divergence in the acute-treatment literature, because the community is arguably ahead of the guidelines on delivery and behind them on mechanism.

Flow rate

`[COMMUNITY-REPORT]` **Clusterbusters (US)** recommends prescriptions be written for a **minimum of 12–15 LPM**, and its advocacy page states patients need "a non-rebreather mask (no holes near the nose), a flow rate of **at least 15 lpm**, and to use one of two breathing techniques for **15–20 minutes**" (Clusterbusters CMS coverage page; Clusterbusters oxygen knowledgebase).

`[COMMUNITY-REPORT]` **clusterinfo.org goes considerably further**: "**25 LPM or more is recommended**"; "**At least 25 LPM is strongly recommended**"; and "Regulators delivering **40 LPM** are often available and inexpensive — at that flow the setup can abort attacks about as quickly as a demand valve," at the cost of using more oxygen per attack (clusterinfo.org oxygen guide).

Divergence, stated plainly: guidelines say 7–15 L/min. Clusterbusters says ≥15. clusterinfo says ≥25, ideally 40. **There is no trial evidence at 25 or 40 L/min via non-rebreather.** The physiological rationale (matching peak inspiratory flow, preventing reservoir-bag collapse and room-air entrainment) is sound and is supported by the Mo et al. FiO_2 table above `[PEER-REVIEWED]`, but the specific numbers are extrapolation, not data. The one trial that directly compared flow rates found **no benefit** of 12 over 7 L/min, and hinted at the reverse `[PEER-REVIEWED]` (Dirkx 2018).

My honest read: the community position is more likely right than wrong on physiological grounds, but it is currently a hypothesis wearing the clothes of a consensus. If you are going to try higher flow, the reservoir bag is your instrument — turn it up until the bag no longer collapses on your deepest inhale, and no further.

Breathing technique

`[COMMUNITY-REPORT]` clusterinfo.org describes two distinct techniques (clusterinfo.org):

- **Demand valve:** "Hyperventilate on pure oxygen: full inhale, full exhale, repeat as fast as possible." Described as "widely considered the fastest and easiest way to abort a cluster attack with oxygen."

- **Non-rebreather / reservoir bag:** “Forceful deep breathing: empty your lungs, then take a deep breath of pure oxygen. Repeat as fast as your reservoir bag can keep up. Only pause between breaths if the bag hasn’t refilled.”

`[COMMUNITY-REPORT]` **Clusterbusters** describes “one of two breathing techniques” but does not name them on the CMS page (Clusterbusters). Its provider-facing prescription wording, authored with **Dr Stewart Tepper (2017)**, specifies: “**Sit up and lean forward and breathe deeply** 10–15 L/minute for up to 20 minutes per attack” (Clusterbusters provider guide).

`[COMMUNITY-REPORT]` A minority technique from r/clusterheads uses **reverse diaphragmatic / Ujjayi-style breathing** as an abortive (r/clusterheads thread). **Single-patient anecdote. Included for completeness, not endorsed.**

Direct conflict to be aware of: the German DMKG explicitly warns **against** hyperventilation `[PEER-REVIEWED]`; clusterinfo.org explicitly instructs hyperventilation with a demand valve `[COMMUNITY-REPORT]`. These are not fully reconcilable. The plausible resolution is that hyperventilating on *room-air-diluted* gas causes hypocapnia and cerebral vasoconstriction with little benefit and some risk of dizziness/tetany, whereas hyperventilating on *genuinely 100%* oxygen from a demand valve may accelerate the therapeutic effect. **This is my inference, not a documented finding.** Treat as unresolved.

Non-rebreather vs demand valve

`[COMMUNITY-REPORT]` clusterinfo.org’s comparison (source):

	Demand valve	Non-rebreather + high-flow regulator
Speed	“the quickest way to abort an attack with oxygen”	slower unless flow is very high
Prescribing	“can be harder to get prescribed”	“often easier to get prescribed”
Cost	“Demand valves themselves are expensive”	40 LPM regulators “often available and inexpensive”

Explicitly ruled out by the same guide: **nasal cannulas; masks with open side vents; simple face masks without a reservoir bag; oxygen concentrators** (“They produce oxygen at lower purity and at a flow rate too low for cluster aborts”). Practical hack given: “If your prescribed non-rebreather mask has side vents, **you can block them**.”

`[COMMUNITY-REPORT]` **OUCH-UK** distinguishes “standard high flow oxygen [Short Burst Oxygen Therapy]” from “**ultra high flow oxygen, delivered via a device known as a demand valve**… similar to the device used for entonox in childbirth” (OUCH-UK 2023).

`[PEER-REVIEWED]` The trial evidence behind the demand-valve preference is thin: one 4-participant pilot (Pain Med 2013) and the Danish mask-comparison trial where DVO reduced rescue medication use but did not reach significance between groups on the EAN’s reading (Petersen et al.; EAN 2023). clusterinfo.org’s summary — “demand valves roughly halved the need for rescue medication compared with a standard mask, and most patients preferred them” — is a fair reading of the Danish data but omits the significance caveat `[COMMUNITY-REPORT]`.

The welding-oxygen route

`[COMMUNITY-REPORT]` Both Clusterbusters and clusterinfo.org document patients **bypassing the medical system entirely and buying oxygen and regulators from welding suppliers** — clusterinfo.org calls it “**Welding oxygen: a cheaper, prescription-free route**”; Clusterbusters says that because Medicare/Medicaid patients must pay out of pocket, “**many people resort to using welding oxygen**” (clusterinfo.org; Clusterbusters provider guide).

Stated without endorsement. Welding-grade oxygen is chemically the same gas but is not manufactured, handled or documented to pharmaceutical standards, and the practice sits outside any regulatory framework. Its prevalence is itself the strongest available indictment of oxygen access policy — people in this much pain do not improvise with compressed-gas cylinders for fun.

1.1.5 Citizen-science efficacy data

`[CITIZEN-SCIENCE]` **Schindler EAD, Wright DA, Weil MJ, Gottschalk CH, Pittman BP, Sico JJ. "Survey Analysis of the Use, Effectiveness, and Patient-Reported Tolerability of Inhaled Oxygen Compared With Injectable Sumatriptan for the Acute Treatment of Cluster Headache." Headache. 2018;58(10):1568–1578** (PMID 30221765, DOI 10.1111/head.13405). Secondary analysis of the **Clusterbusters® Medication Use survey**, funded by Clusterbusters, analysed at Yale/VA Connecticut. **N=493 adults** with validated CH diagnosis. This is the single best example of citizen science and academic medicine collaborating in this disease.

Finding	Result
Oxygen efficacy at flow rates **>10 L/min**	**81.5%**
Injectable sumatriptan efficacy in the same group	**80.5%**
Difference	Did not differ significantly in any group examined
Flow rate >10 L/min as predictor of oxygen response	**OR 2.36, P=.016**
Male gender as predictor of oxygen response	**OR 2.07, P=.031**
Current or historical cigarette smoking as predictor	**OR 2.25, P=.017**
Predictors of sumatriptan response	**None identified**

Most commonly used delivery system: **non-rebreather-type mask.** The authors conclude that oxygen at sufficiently high flow has efficacy comparable to injectable sumatriptan, and note that "**most comments about side effects and concerns were directed at triptans**."

Two odd findings worth flagging. First, **smoking history predicts better oxygen response** — the authors say the reason "requires further exploration." Second, **male gender predicts better response.** Neither has a satisfying explanation. The smoking association recurs independently below.

`[PEER-REVIEWED]` **Backx et al. 2010**, summarised in Guo et al. 2019: shorter attacks and absence of interictal pain were *positively* associated with oxygen response; photophobia/phonophobia, nausea/vomiting and restlessness were *negatively* associated. Three predictors of **poor** response: **no past history of smoking; interictal headache; longest attack period >180 min.**

Unexplained correlation, flagged: two independent datasets — one clinical, one community-survey — both find that *never having smoked* predicts a **worse** oxygen response. This is counterintuitive (oxygen is contraindicated in active smokers for fire-safety and respiratory reasons) and has no accepted mechanistic explanation. It may be a marker for a distinct CH phenotype rather than a causal effect of smoking. **Unknown.**

`[CITIZEN-SCIENCE]` **Pearson et al. 2019, Cluster Headache Questionnaire, n≈3251** (subjective oxygen efficacy): complete remission **13%**, very effective **41%**, moderately effective **27%**, minimally effective **12%**, completely ineffective **7%** (reported in Guo et al. 2019). *The full PubMed record (PMID 30632614) returned an NCBI access block during research and could not be independently verified — treat the exact percentages as second-hand.*

`[PEER-REVIEWED]` Aggregated survey data: subjective efficacy rated complete or very effective in **29–54%** of patients; time to complete pain relief **≤20 min in 51%**, but **>40 min in 27%** (Mo et al. 2022).

`[PEER-REVIEWED]` **Rusanen SS, De S, Schindler EAD, Artto VA, Storvik M. "Self-Reported Efficacy of Treatments in Cluster Headache: a Systematic Review of Survey Studies." Curr Pain Headache Rep. 2022;26(8):623–637** (PMC9436841, DOI 10.1007/s11916-022-01063-5, PMID 35759175). University of Eastern Finland / Yale / Helsinki. 994 articles screened, **9 surveys, 5419 respondents**, 2000–2020. *Finnish-led — note the search used English-language terms only, so non-Anglophone surveys were structurally excluded.*

Findings directly relevant here: - **Oxygen and subcutaneous triptan injections were the two most-reported-effective abortive treatments.** - **Injectable sumatriptan was consistently reported as more effective than oral or nasal triptans.** - Oxygen was "the clinically most effective conventional abortive treatment and… most reported as efficacious in all reviewed studies." - **Statistically significant episodic-vs-chronic differences were found only for oxygen and triptans — both considered more effective in episodic than in chronic CH.** *This matters enormously for a chronic daily sufferer and is repeated in the triptan section below.* - Overall: "There were no results disagreeing with the current knowledge" — i.e. for the acute treatments, **community self-report and trial data broadly agree.**

Respondent characteristics across the nine surveys: male:female **2.03–3.82**; mean/median ages 40–50 in seven of nine studies; **53.8–77% current or former smokers**; CCH/ECH ratios ~0.18–1.16.

1.1.6 Access barriers by country

This is where oxygen stops being a medical question and becomes an administrative one. `[PEER-REVIEWED]` Mo et al. note that a 2017 survey found oxygen and its delivery devices are **not uniformly covered** anywhere in the world (Mo et al. 2022).

Australia

`[PEER-REVIEWED]` Oxygen "may be ordered from **medical gas supply companies with a prescription**" (Ray, Stark & Hutton, Australian Prescriber 2022;45:15–20). The same review states that drugs used for acute and preventive CH treatment in Australia are **off label** though evidence-supported, that **choice of acute therapy depends on patient factors and cost**, and that **intranasal zolmitriptan is not available in Australia**. Contraindications listed for oxygen: **active smokers; type 2 respiratory failure.**

Assessment: Australia has no PBS pathway for cluster-headache oxygen; supply is a private arrangement with a medical gas company (BOC, Air Liquide, Supagas and similar) on a doctor's prescription, and the cost falls on the patient. There is no national home-oxygen scheme for CH equivalent to the UK's HOOF. State-based domiciliary oxygen programmes exist but are written around chronic hypoxaemic respiratory disease, which CH patients by definition do not have. **I could not locate an Australian government document that explicitly addresses cluster-headache oxygen funding — treat the absence of a scheme as likely but not formally verified.**

Practical implication for a chronic Australian patient: you are looking at private cylinder rental plus refills, indefinitely, with no rebate. Ask specifically for a **large static cylinder plus a small portable one**, a **regulator that goes to at least 15 L/min** (higher if you can get it), and **non-rebreather masks** — and expect to specify all of it yourself, because the supplier's default assumption will be a 2–4 L/min respiratory patient.

United Kingdom

`[COMMUNITY-REPORT]` OUCH-UK gives the most operationally detailed access guidance of any patient organisation in any country (OUCH-UK, Oxygen for CH 2023):

England and Wales: - Patient downloads the **Home Oxygen Order Form (HOOF)** from OUCH's website — "part completed ready for a cluster headache sufferer." - GP must also complete the **Home Oxygen Consent Form (HOC)** and the **Individual Home Oxygen Risk Management Form (IHORM)**, both available at the surgery. - GP submits the HOOF **online via the oxygen company's portal**, entering flow rate, cylinder type and mask. - "If the GP has not signed the HOOF form to say he has completed the risk management form, **the oxygen supply company will reject the HOOF form**." - "**If you smoke, or anyone in your house smokes, then oxygen will not be supplied.**" - The supplier contacts the patient directly; the delivery engineer demonstrates use and supplies masks "as well as a spare cylinder upon request." - **Demand-valve oxygen** has its own HOOF form, also pre-completed by OUCH, and "at present demand valve oxygen therapy is **only available in England and Wales**."

The single most useful piece of advocacy intelligence in this entire chapter `[COMMUNITY-REPORT]`:

> "Some GPs may say they can't prescribe the oxygen and that it has to be prescribed by a secondary clinician [i.e., a consultant]. **This is not so, as it is specifically laid down in the Home Oxygen Assessment Service (HOAS) specification that GPs can prescribe oxygen for CH sufferers for pain relief.** There is a copy of the HOAS specification in every doctor's surgery."

Scotland and Northern Ireland: "oxygen can only be prescribed by a secondary clinician, i.e. a consultant, so it is more important than ever that you seek a referral to a headache specialist."

`[COMMUNITY-REPORT]` OUCH-UK's clinician-facing sheet states 100% oxygen at **12 L/min for up to 15 min** and describes CH as "the only evidence-based use for short-burst oxygen therapy in patients who do not have hypoxaemia" (OUCH-UK GP/neurologist information). NHS England London published borough-level cluster headache oxygen guidance in September 2021 (NHS England London).

`[COMMUNITY-REPORT]` Fire-safety framing from Exeter Headache Clinic: "**Two out of every three fires where there is home oxygen are the result of the user smoking**" and "**one in four people where the fire is a result of smoking while using oxygen die from their injuries.** Vaping is also a significant risk" (Exeter). Given that CH populations are 54–77% current or former smokers `[CITIZEN-SCIENCE]`, this exclusion criterion removes oxygen from a large fraction of the people who most need it — a structural cruelty in the system that is rarely discussed.

United States

`[PEER-REVIEWED]` Inhaled oxygen for CH is **not FDA-approved**; injectable sumatriptan is "the only FDA-approved pharmacologic intervention for cluster headache" (Schindler et al. 2018). The same paper: "**Current restrictions on access to inhaled oxygen, which exist at many levels, limit the therapeutic options available for patients with cluster headache**… [and] do a disservice to this patient population and the providers who deliver their care."

`[COMMUNITY-REPORT]` Concrete US cost figures, from Clusterbusters (provider guide): - "Centers for Medicaid and Medicare Services (CMS) continue to deny coverage for home oxygen for cluster headache." - Commercial insurance often does cover it (Cigna is named as listing it), though "your commercial insurance may try to deny coverage and request more information." - **"Cluster patients who have Medicaid or Medicare will have to pay out of pocket, which can be less than $1,000 per year for episodics, but could exceed $5,000 a year for chronics."** - Billing codes given: **HCPCS E0424, E0441, E0443**; ICD-10 **G44.009 / G44.019 / G44.029 / G44.011 / G44.021 / G44.001**.

`[COMMUNITY-REPORT]` The CMS advocacy arc: the original National Coverage Determination denied home oxygen for CH (CMS decision memo); a **Proposed Decision Memo issued 2 July 2021** signalled benefit for "selected individuals," with a comment deadline of **31 July 2021, 5pm ET** (Clusterbusters; CMS public comments).

Clusterbusters' objections to the proposed wording are worth recording because they are a case study in how coverage language becomes a clinical barrier: - The word "**selected**" would make neurologists hesitate, "because they might not know whether a patient qualifies to try it." Clusterbusters' position: "**every clusterhead needs to try high-flow oxygen, not a 'selected' few.**" - The proposal left determination to the **four Medicare Administrative Contractors** via **Local Coverage Determination policies**, meaning "a person with Medicare in one U.S. region could receive oxygen while Medicare might deny oxygen to someone in another region." Clusterbusters demanded a **National Determination**. - The proposal contemplated requiring patients to **demonstrate that oxygen aborts their attacks, in an ED or physician's office, during an attack.** Clusterbusters' objection: attacks come on fast and destroy concentration; driving anywhere during one is unreasonable; the venue "would likely not have the oxygen setup needed to try the treatment correctly," and incorrect administration could produce a false negative that then **disqualifies the patient from home oxygen.**

Related advocacy: Alliance for Patient Access; US Pain Foundation, "The Never-Ending Battle for Oxygen Coverage".

Status caveat: Clusterbusters' page headline states CMS "will soon cover" oxygen for select patients, but the page is undated and describes a *proposed* memo from 2021. **Whether a final national determination has been issued, and in what form, is not established by the sources gathered here — treat as unresolved.**

Germany / EU

`[PEER-REVIEWED]` / `[COMMUNITY-REPORT]` Germany has the cleanest reimbursement pathway found in any country (DMKG):

- „Die Kosten für die Sauerstoffbehandlung werden von den **gesetzlichen Krankenkassen** übernommen, dazu ist eine **ärztliche Verordnung** erforderlich." — *Costs are covered by the statutory health insurers; a medical prescription is required.*
- The **BfArM approved, on 14 December 2007**, "Sauerstoff, 100% Gas zur medizinischen Anwendung, druckverdichtet (Druckgasflaschen)" **specifically for the indication "Behandlung von Cluster-Kopfschmerz in Deutschland"** — approval number **69557.00.00**. *Germany formally licensed oxygen as a medicine for cluster headache. Almost nowhere else has.*
- The statutory insurers' aids catalogue (Hilfsmittelkatalog) lists **"Druckminderer für Druckgasflaschen"** for the indication cluster headache under position number **14.24.05.0**.

The DMKG even publishes a **model prescription** — a template a patient can hand to a GP:

Standard supply	Spec
1 × pressure regulator	range **0–15 L/min**, Hilfsmittel position **14.24.05.0**
2 × cylinder	**10 litre**, medical oxygen, **200 bar**, product type 14.99.99.1
2 × non-rebreather inhalation mask	—

Additional, for mobile use	Spec
1 × pressure regulator	range **0–15 L/min**
2 × cylinder	**2 litre**, medical oxygen, **200 bar**
1 × carry bag for cylinder	—
1 × non-rebreather inhalation mask	—

DMKG also advises contacting the insurer's aids department immediately on diagnosis and faxing the prescription through. *German source.* ***The 10 L / 2 L cylinder split is the most concrete portability guidance found anywhere*** *and is worth copying regardless of country: one large static cylinder, one 2-litre portable with a bag.* Further German guidance: DMKG 2016 cluster guideline; DGN guideline.

Japan

`[PEER-REVIEWED]` **Home oxygen therapy (HOT) for cluster headache became reimbursable under Japanese national health insurance in the April 2018 fee revision (** 2018 home oxygen therapy: HOT **).** Prior to that, HOT reimbursement was restricted to severe chronic respiratory failure (COPD, post-TB sequelae, interstitial pneumonia, lung cancer), pulmonary hypertension and chronic heart failure. The new criterion is narrow and precise: **patients diagnosed with cluster headache who are in a cluster period and have at least one headache attack per day on average (** **)** (JHS CQ1). See also MHLW documentation and the Japanese Neurology Society 2021 headache guideline. *Japanese sources.*

Two further Japanese details that do not appear in English-language reviews: - **Oxygen concentrators capable of ≥90% concentration at ≥7 L/min have been confirmed as equivalent in usefulness to cylinder oxygen (** 90 L/ **)**, citing Yamada 2017, *Kōchi-ken Ishikai Igaku Zasshi* 22(1):214–219. **This directly contradicts the German and community position that concentrators are useless.** The

reconciliation is that Japan's target flow is 7 L/min, which a high-capacity concentrator can meet, whereas 15–40 L/min it cannot. If you are running a low-flow protocol, a concentrator may be viable; if you are running the community high-flow protocol, it is not. - **"Spray-can oxygen is ineffective because the concentration is insufficient"** (
) — a useful explicit debunking of the canned-oxygen products sold in Japanese convenience stores.

Japan explicitly frames oxygen as the answer to the triptan dose-limit problem. The guideline states that oxygen is expected to help patients with sumatriptan contraindications or side effects, and those "with frequent attacks for whom the insurance-approved sumatriptan kit limit of **twice daily** made adequate treatment difficult," noting that oxygen inhalation "can be used many times a day" (1). *This is the clearest official articulation anywhere of the logic that matters most to a chronic daily sufferer.*

Denmark

`[PEER-REVIEWED]` / `[COMMUNITY-REPORT]` The Danish Headache Center at Rigshospitalet is the principal non-Anglophone research group on oxygen delivery hardware (see Petersen et al. mask-comparison trial above). Danish patient- and clinician-facing material: Sundhed.dk patient handbook, klyngehovedpine; Ugeskrift for Læger review; DHOS Referenceprogram 2010. *Danish sources.*

1.1.7 Oxygen — bottom line for a chronic daily sufferer

Advantages that matter specifically in chronic CH: `[PEER-REVIEWED]` EAN states oxygen "can be used several times per day," has "no contraindications" and "no interactions," and has a low adverse-event profile (EAN 2023). In a disease where the best drug has a hard ceiling of two doses per day, **the treatment with no ceiling is structurally the most important one you have**, even if its per-attack efficacy were slightly lower.

The honest caveat: `[PEER-REVIEWED]` the systematic review of survey studies found oxygen is **significantly less effective in chronic than in episodic CH** (Rusanen et al. 2022). Cohen 2009 included only 19 chronic patients out of 76 and did not report a chronic-specific response rate. **The 78% figure should not be assumed to apply to chronic CH.**

1.2 Triptans

1.2.1 Subcutaneous sumatriptan — the strongest acute drug

`[PEER-REVIEWED]` **The Sumatriptan Cluster Headache Study Group. "Treatment of acute cluster headache with sumatriptan." N Engl J Med. 1991;325(5):322–6** (PMID 1647496, DOI 10.1056/NEJM199108013250505). Double-blind placebo-controlled crossover, 49 enrolled, 39 evaluable, **6 mg subcutaneous**.

Outcome	Sumatriptan 6 mg SC	Placebo	p
Headache severity decreased at 15 min	**74%** of attacks	26%	<0.001
Pain-free at 10 min	**36%**	3%	<0.001
Pain-free at 15 min	**46%**	10%	<0.001
Required rescue oxygen	13%	49%	—

No serious adverse events. The Australian Prescriber review reports the equivalent figures as **mild or no pain at 15 min: 75% vs 32% placebo; pain-free at 15 min: 48% vs 17%** (Aust Prescr 2022).

`[PEER-REVIEWED]` **Law S, Derry S, Moore RA. "Triptans for acute cluster headache." Cochrane Database Syst Rev. 2010; (4):CD008042** (PMC4170909, DOI 10.1002/14651858.CD008042.pub2, PMID 20393964). Six crossover studies. Exposures: zolmitriptan 5 mg n=231, zolmitriptan 10 mg n=223, sumatriptan 6 mg SC n=131, sumatriptan 12 mg n=88, sumatriptan 20 mg intranasal n=77, placebo n=430. Three studies scored 5/5 and three 4/5 on the Oxford quality scale; none was at high risk of bias.

Headline: NNT 2.4 for 15-minute pain relief with sumatriptan 6 mg SC (75% response).

Four limitations Cochrane flagged that remain unaddressed sixteen years later, and which map exactly onto real-world chronic use: - **No study reported recurrence data.** - **No study used multiple dosing for a single attack.** - **No study examined treatment before the attack reached moderate intensity.** - Washout periods were only 18–24 hours.

In other words: the trial literature has never studied the way chronic daily patients actually use this drug.

`[PEER-REVIEWED]` Sumatriptan's half-life is approximately **120 minutes** (Leone & Proietti Cecchini 2016, PMC4731683).

1.2.2 Intranasal sumatriptan

`[PEER-REVIEWED]` **van Vliet JA, Bahra A, Martin V, Ramadan N, Aurora SK, Mathew NT, Ferrari MD, Goadsby PJ. "Intranasal sumatriptan in cluster headache: randomized placebo-controlled double-blind study." Neurology. 2003;60(4):630–3** (PMID 12601104, DOI 10.1212/01.WNL.0000046589.45855.30). 5 centres, 118 patients, 154 attacks (77 per arm), attacks lasting ≥45 min, **20 mg intranasal**.

Outcome at 30 min	Sumatriptan 20 mg IN	Placebo	p
Responder	**57%**	26%	0.002
Pain-free	**47%**	18%	0.003

No serious adverse events. **Note the endpoint is 30 minutes, not 15** — nasal sumatriptan is meaningfully slower than subcutaneous, which matters when the median attack is under two hours and the peak is early.

1.2.3 Zolmitriptan

`[PEER-REVIEWED]` **Cittadini E, May A, Straube A, Evers S, Bussone G, Goadsby PJ. "Effectiveness of intranasal zolmitriptan in acute cluster headache: a randomized, placebo-controlled, double-blind crossover study." Arch Neurol. 2006;63(11):1537–42** (PMID 16966497, DOI 10.1001/archneur.63.11.nct60002, ISRCTN27362692). 92 randomised (80 M / 12 F, mean age 40 ± 10), ITT 69.

Headache relief at 30 minutes:

Subgroup	Placebo	Zolmitriptan 5 mg	Zolmitriptan 10 mg
All patients	21%	40%	**62%**
Episodic CH	30%	47%	**80%**
Chronic CH	**14%**	**28%**	**36%**

Wald $\chi^2(1) = 29.4$, $P < .001$ overall.

This table is the single most important piece of information in this section for a chronic daily patient. Intranasal zolmitriptan 10 mg produces relief in 80% of episodic patients and **36% of chronic patients** — barely more than double the chronic placebo rate. The headline "62%" figure quoted in guidelines and reviews is driven almost entirely by the episodic subgroup. **If you have chronic CH and nasal zolmitriptan has underwhelmed you, you are not an outlier; you are the modal chronic patient in this trial.**

`[PEER-REVIEWED]` **Rapoport AM, Mathew NT, Silberstein SD, Dodick D, Tepper SJ, Sheftell FD, Bigal ME. "Zolmitriptan nasal spray in the acute treatment of cluster headache: a double-blind study." Neurology. 2007;69(9):821–6** (PMID 17724283, DOI 10.1212/01.wnl.0000267886.85210.37). 52 patients, 151 attacks, three-period crossover.

Outcome	Placebo	ZNS 5 mg	ZNS 10 mg
Headache response at 30 min	30%	50%	**63.3%**
Relief at 10 min	10%	—	**24.5%**
Pain-free at 15 min	6%	—	**22.0%**
Pain-free at 30 min	20%	38.5%	**46.9%**
Mild side effects	16%	25%	**32.7%**

`[PEER-REVIEWED]` **Bahra et al. 2000** studied **oral** zolmitriptan: 13 centres, 153 randomised, 123 in the efficacy analysis, mean age 44 ± 11, 86% men, 73% episodic (per Cochrane 2010). **Oral triptans are consistently the weakest option** and are the main reason self-reported triptan efficacy looks inconsistent in community surveys `[PEER-REVIEWED]` (Rusanen et al. 2022).

Australian availability note: `[PEER-REVIEWED]` **intranasal zolmitriptan is not available in Australia** (Aust Prescr 2022). For an Australian patient the practical acute drug menu is subcutaneous sumatriptan, intranasal sumatriptan, and oxygen.

1.2.4 Comparison table — acute drug efficacy

From the Australian Prescriber peer-reviewed summary table (Aust Prescr 2022;45:15–20) `[PEER-REVIEWED]`:

Therapy	Dose / max per 24 h	Efficacy
Sumatriptan SC	**6 mg; max 12 mg/24 h**	Mild/no pain at 15 min **75%** (placebo 32%); pain-free at 15 min **48%** (17%)
Sumatriptan intranasal	**20 mg; max 40 mg/24 h**	Mild/no pain at 30 min **57%** (26%); pain-free at 30 min **47%** (18%)
Zolmitriptan intranasal 5 mg	max 20 mg/24 h	Mild/no pain at 30 min **45%** (30%); pain-free at 30 min **32%** (18%)
Zolmitriptan intranasal 10 mg	max 20 mg/24 h	Mild/no pain at 30 min **62%** (30%); pain-free at 30 min **48%** (18%)
High-flow oxygen	**7–12 L/min, 15 min**	Pain reduction at 15 min **78%** (20%)
nVNS (episodic only)	3 stimulations × 2 min	Mild/no pain at 15 min **39%** (12%)

Triptans may be repeated after **two hours**.

1.2.5 Dose limits and cardiovascular contraindications

`[PEER-REVIEWED]` **Official ceiling: 12 mg subcutaneous sumatriptan per 24 hours (two 6 mg injections).** The NHS states no more than two injections, two nasal doses, or 300 mg of tablets per 24 hours (NHS, sumatriptan dosing). The WHO Essential Medicines List submission for CH (2025) specifies **sumatriptan 6 mg/0.5 mL prefilled syringe or autoinjector, maximum 12 mg/day** (WHO EML application).

Cross-cultural divergence worth knowing `[PEER-REVIEWED]`: the **Japanese Headache Society uses subcutaneous sumatriptan 3 mg, maximum 6 mg/day** — half the Western dose and half the Western ceiling (WHO EML application); the JHS guideline refers to the insurance-covered frequency as **twice daily** (JHS CQ1). *Japanese source.* No source found explains whether the halved dose reflects pharmacogenomic differences, body mass, or regulatory conservatism. **Unknown.**

Contraindications `[PEER-REVIEWED]`: - Australian Prescriber lists **ischaemic heart disease** (Aust Prescr 2022). - The Japanese guideline lists **ischaemic heart disease, cerebrovascular disease, peripheral vascular disease**; adverse effects **nausea, chest discomfort, palpitations**; and notes that “not a few patients cannot use it because self-injection is difficult” ( ) (JHS CQ1). *Japanese source — the needle-phobia point is rarely mentioned in Western guidelines but is a real limiter.* - The WHO submission specifies the same dose in elderly patients with added cardiovascular monitoring (WHO EML).

1.2.6 The chronic/daily problem — the central tension of this chapter

Set out the arithmetic. `[PEER-REVIEWED]` The ICHD-3 diagnostic criterion permits attack frequency **from one every other day up to eight per day** (ICHD-3 criteria as reproduced in JHS CQ1; Aust Prescr 2022). The maximum permitted sumatriptan dose is **two injections per day**. A patient with four attacks per day is therefore formally under-treated **by design** for half of them, and a patient with eight is under-treated for three-quarters.

Guidelines do not resolve this. They mostly do not mention it.

What the real-world data actually shows

`[PEER-REVIEWED]` **Leone M, Proietti Cecchini A. "Long-term use of daily sumatriptan injections in severe drug-resistant chronic cluster headache." Neurology. 2016;86(2):194–195** (PMC4731683, DOI 10.1212/WNL.0000000000002117, PMID 26475695). Istituto Neurologico Carlo Besta, Milan. *Italian source — and the only systematic dataset on this question that exists.*

- **53 consecutive chronic CH patients**, 2003–2014, all using **≥2 subcutaneous sumatriptan injections per day for ≥2 years**.
- **All required the full 6 mg dose**; none could manage on less.
- Patients "**overdosed sumatriptan despite recommendations of their physicians**."
- A cited multicentre observation records a maximum of **36 mg in 24 hours** — six times the labelled daily ceiling.
- **No serious adverse events. No ECG abnormalities. No discontinuations.**
- **But: 42% noticed a subjective reduction in efficacy** — longer latency to effect and less pain reduction over time.
- Sumatriptan nonetheless remained their first-choice treatment.
- Classified **Class IV evidence** (retrospective, uncontrolled).

`[PEER-REVIEWED]` A cited 3-month prospective study of **138 CH patients treating 6,353 attacks** with a maximum of two injections per day found **no clinically significant ECG or laboratory effects** (reported in Leone & Proietti Cecchini 2016).

`[PEER-REVIEWED]` **Case report, Headache (2011), PMID 22082424**: a 49-year-old woman used subcutaneous sumatriptan for **15 years** at daily doses of **12–222 mg**, averaging **150 mg/day in the final year**, with continued efficacy and "**without adverse events**." **This is a single case and should be read as such** — it establishes possibility, not safety.

`[PEER-REVIEWED]` **Centonze V et al. Funct Neurol. 2000;15(3):167–70** (PMID 11062845), University of Bari, Italy. 13 episodic CH patients, all with more than three attacks per day, all exceeding the recommended dose for one year. **No tolerance, no tachyphylaxis, no rebound, no dependence.** Only 4 patients had minor adverse events — and those 4 all also had migraine without aura and a family history of migraine. *Italian source. That last correlation is odd and unexplained; flagged as a minority observation, n=4.*

`[PEER-REVIEWED]` **Brandt RB, Doesborg PGG, Haan J, Ferrari MD, Fronczek R. "Pharmacotherapy for Cluster Headache." CNS Drugs. 2020;34(2):171–184** (PMC7018790, DOI 10.1007/s40263-019-00696-2, PMID 31997136) states the tension explicitly: "In daily practice, patients with cluster headache experiencing daily attacks use multiple sumatriptan injections per day for a long time. Official guidelines state that no more than two injections per day can be used." The same review notes **suicidal ideation in 55% of CH patients** — relevant context for why patients exceed limits.

Reading this honestly

What the evidence supports: several independent groups (Milan, Bari, plus case reports) have observed chronic CH patients exceeding the 12 mg/day ceiling — sometimes grossly — over periods of years, without detecting serious cardiovascular events, ECG changes, tachyphylaxis or dependence.

What the evidence does not support: a conclusion that this is safe. Every one of those studies is **retrospective, uncontrolled, small, and conducted in patients who had already self-selected by tolerating high doses**. A patient who had a cardiac event on injection three would not be in the Milan cohort of long-term daily users. **This is textbook survivorship bias**, and it is the single

most important caveat in this chapter.

What is genuinely established: `[PEER-REVIEWED]` **42% of long-term daily users report declining efficacy** (Leone & Proietti Cecchini 2016). Whatever the safety position, the drug appears to get less useful the more you rely on it.

Where community and guidelines diverge: `[CITIZEN-SCIENCE]` the Clusterbusters survey found that "most comments about side effects and concerns were directed at triptans," not oxygen (Schindler et al. 2018) — patients themselves are wary of triptans in a way the enthusiasm for high-dose use might not suggest. The community position is not "triptans are safe at any dose"; it is closer to "triptans are rationed too tightly and oxygen should carry the load."

The practical resolution every credible source converges on

Use oxygen as the workhorse; reserve triptans for the attacks oxygen cannot hold.

This is stated most explicitly by the Japanese Headache Society, which frames oxygen reimbursement as the solution for "patients with frequent attacks for whom the insurance-approved twice-daily sumatriptan limit made adequate treatment difficult," noting that oxygen "can be used many times a day" and "has no serious side effects" (JHS CQ1) `[PEER-REVIEWED]`, *Japanese source*. EAN makes the same point structurally: oxygen has "no contraindications," "no interactions," and "can be used several times per day" (EAN 2023) `[PEER-REVIEWED]`. Schindler's survey supplies the empirical backing — at >10 L/min, **oxygen 81.5% vs sumatriptan 80.5%, not significantly different** `[CITIZEN-SCIENCE]` (Schindler et al. 2018).

The second half of the resolution is **effective prevention**, because the triptan ceiling is only a crisis if attack frequency stays high. That is what the next section is about.

1.3 Other Acute Options

1.3.1 Intranasal lidocaine

`[PEER-REVIEWED]` **Robbins L. "Intranasal lidocaine for cluster headache." Headache. 1995;35(2):83–4** (PMID 7737866, DOI 10.1111/j.1526-4610.1995.hed3502083.x). 30 male patients. **4% lidocaine solution, four sprays ipsilateral to the pain, two more if needed.**

Response	Proportion
Moderate relief	**27%**
Mild relief	**27%**
No relief	**46%**

Side effects minimal. Robbins' own conclusion: "**only a marginally helpful therapy**," though it "may remain worthwhile as an adjunctive medication."

`[PEER-REVIEWED]` Earlier work: **Kittrelle et al. 1985, n=5** (reviewed at BestBETs). A systematic review (PMID 30098024) covering **6 studies** found that **benefit appeared only in the four poor-quality studies and not in the two fair-quality ones** — a classic signature of a treatment whose apparent effect is an artefact of weak methodology. A case report describes application into the sphenopalatine fossa (PMC3359256).

`[PEER-REVIEWED]` The EAN 2023 guideline gives lidocaine only a **weak/consensus recommendation** (EAN 2023).

Verdict: low cost, low risk, low ceiling. Reasonable as an add-on when oxygen is unavailable or partially effective; not a substitute for anything. The technique matters — the target is the sphenopalatine ganglion region high in the nasal cavity, which requires head extension and rotation toward the affected side, not a casual spray into the nostril.

1.3.2 Ergotamine and dihydroergotamine (DHE)

`[HISTORICAL/CULTURAL]` Ergotamine has been used for headache "since the middle ages, and as a pharmaceutical since 1926," but was "limited by poor tolerability (nausea, vomiting, and cardiovascular effects)" (DHE narrative review, PMC7003832). Kudrow's 1981 oxygen study used **sublingual ergotamine as the comparator, which aborted attacks in 70% of patients** — historically, ergotamine was the reference acute treatment before triptans existed `[PEER-REVIEWED]` (Guo et al. 2019). "For many years, until the advent of the triptans, the ergotamines were the only specific antimigraine drugs" (PMC7003832).

Oral ergotamine is essentially obsolete for CH and was largely withdrawn from many markets. No modern controlled trial in CH was located.

DHE pharmacology

`[PEER-REVIEWED]` From the DHE narrative review (PMC7003832): - Synthesised by **Stoll and Hofmann in 1943**; approved **1946**; "continues to be a choice today for acute migraine, status migrainosus, and cluster headaches." - Agonist at **5-HT1B, 5-HT1D, 5-HT1F**, but also binds **5-HT1A, 5-HT2A, adrenergic, cholinergic and dopaminergic** receptors — a far dirtier drug than a triptan. - **Receptor dissociation half-life 1.38 h (5-HT1B) and 1.28 h (5-HT1D)**, versus sumatriptan's **0.17 h and 0.09 h**. *This is the pharmacological basis for DHE's long duration and low recurrence rate — it stays on the receptor roughly eight to fourteen times longer.* - Systemic DHE has **rapid onset and sustained effects lasting up to 48 hours**. - **Oral bioavailability 0.07–0.14%** — effectively zero; gut absorption 10–60% and erratic. "This molecule is limited to non-oral routes of administration." - **Minimal risk of medication-overuse headache** — a genuinely important property for a chronic daily patient, and a point of real differentiation from triptans. - Often effective in patients who are "**triptan resistant**," who wake with headache, or who have prolonged/severe attacks.

Routes and evidence

Route	Detail	Evidence
IV (D.H.E. 45)	1 mg every 8 h for 1–3 days, inpatient	"very high response rate for refractory migraine patients: **97% pain reduction, 60–78% pain freedom**"
IV + metoclopramide ("Raskin protocol")	every 8 h up to 2 days	Series of **55 intractable migraine patients: 49/55 headache-free by 48 h**, 39 with sustained benefit up to **16 months**; comparator 54 matched diazepam patients, only **7/54** headache-free
SC / IM	1 mg	"limited efficacy due to needle phobia and poor tolerability, including local irritation"
Nasal (Migranal)	2 mg delivered	32% bioavailability; four US RCTs
Orally inhaled (MAP0004/Levadex)	1–2 mg	NDA filed, **never approved** — FDA complete response letter June 2014 citing manufacturing concerns; "**No issues related to clinical safety or efficacy were cited**"; development apparently terminated

Sources: PMC7003832; Raskin's original protocol **Neurology 1986;36(7):995–7** (PMID 3520384, DOI 10.1212/wnl.36.7.995); inpatient 5-day IV DHE protocol described by Nagy et al., Neurology; further review at PMC7200221.

Important honesty caveat: the impressive IV DHE numbers above (97% pain reduction, 49/55 headache-free) are from *migraine* and *status migrainosus* populations, not cluster headache. They are frequently quoted in cluster contexts without that qualification. **Cluster-specific controlled data for IV DHE could not be located.** The rationale for using it in refractory CH is

inpatient clinical experience plus mechanistic plausibility, not RCT evidence.

Migranal nasal spray efficacy (migraine data)

`[PEER-REVIEWED]` Four randomised double-blind placebo-controlled US studies (PMC7003832):

Study	n (Migranal/placebo)	2-h response	Therapeutic gain	4-h response	Gain
1	105 / 98	61%* vs 23%	38%	70%** vs 28%	42%
2	103 / 102	47% vs 33%	14%	56%* vs 35%	21%
3	50 / 50	32% vs 20%	12%	48%* vs 22%	26%
4	47 / 50	30% vs 20%	10%	47% vs 30%	17%

(*P<.01, **P<.001.) **The review's own verdict: therapeutic gain ranged from** 10% to 42%**, "suggesting a variability in response that might translate into a lack of clinical reliability — especially in the initial 2 hours after dosing." Adverse effects:** rhinitis 26%**, disturbed taste 8%.

Two-hour endpoints are close to useless for cluster headache, where untreated attacks last 15–180 minutes. This is a fundamental mismatch between the available DHE evidence and the disease.

`[PEER-REVIEWED]` **EAN 2023 gives DHE nasal spray only a weak/consensus recommendation for acute CH** (EAN 2023).

Current status, summarised honestly: DHE is a real option in **refractory, inpatient, or bridge settings**, delivered IV, and its long receptor occupancy and low MOH risk are genuinely attractive in chronic daily disease. But the cluster-specific evidence is essentially absent, the non-IV routes are weak or unreliable, and the inhaled formulation that might have solved the delivery problem was never approved. **Availability in Australia is limited and it is not a realistic outpatient option** — this route generally requires a headache specialist and hospital admission.

1.3.3 Octreotide

`[PEER-REVIEWED]` **Matharu MS, Levy MJ, Meeran K, Goadsby PJ. "Subcutaneous octreotide in cluster headache: randomized placebo-controlled double-blind crossover study." Ann Neurol. 2004;56(4):488–94** (PMID 15455406, DOI 10.1002/ana.20210). 57 recruited; efficacy data from 46 octreotide-treated and 45 placebo-treated attacks. **Octreotide 100 µg subcutaneous.**

Outcome at 30 min	Octreotide 100 µg SC	Placebo	p
Headache response	**52%**	36%	<0.01

The authors' framing is the key point: "**Nonvasoconstrictor treatment of acute cluster headache is possible.**"

`[PEER-REVIEWED]` **CNS Drugs rates octreotide 100 µg SC as evidence level 2B, "probably effective,"** with mild gastrointestinal disturbance and injection-site reactions as the main adverse effects (Brandt et al. 2020, PMC7018790).

Why this matters and why nobody uses it. Octreotide is a somatostatin analogue with **no vasoconstrictor action**, which in principle makes it the acute option for patients with ischaemic heart disease, cerebrovascular disease, or peripheral vascular disease — exactly the patients triptans are forbidden in. That is a meaningful unmet need. But: the response rate (52% vs 36% placebo, a 16-point therapeutic gain) is **substantially weaker than sumatriptan**; it is another subcutaneous injection; it is expensive; and it has essentially no follow-up literature in twenty-plus years. **It remains a niche option for triptan-contraindicated patients, and is rarely used in practice.** No community discussion of octreotide was located in the sources reviewed — **it appears to be effectively absent from patient-community practice**, which is itself informative.

2. Transitional / Bridge Therapy

2.1 Why bridging exists at all

`[PEER-REVIEWED]` Verapamil is the first-line preventive, and it works — in the randomised trial **80% of patients had a halving of attack frequency and 26% became attack-free** (Aust Prescr 2022). But it must be titrated slowly under ECG surveillance:

- Start **80 mg three times a day for at least 2 weeks**, then increase by **80 mg every 2 weeks**, range **240–960 mg/day** (Aust Prescr 2022). - EAN specifies **≥240 mg/day** as the effective threshold (EAN 2023). - ECG **before starting and at every dose change**, repeated at a stable dose after 10 days, then every 1–2 months, then every 6 months. - **One in five patients will develop an arrhythmia** — first- or second-degree heart block, junctional rhythms, right bundle branch block, bradycardia — and **delayed-onset arrhythmias have been reported** (Aust Prescr 2022).

Do the arithmetic. Starting at 240 mg/day and increasing by 80 mg every two weeks, reaching 480 mg takes **six weeks**; reaching 960 mg takes **three months**. During that entire period the patient is having attacks at full frequency, capped at two triptan injections a day.

That gap is what bridge therapy exists to fill. It is not an optional refinement. `[PEER-REVIEWED]` Australian Prescriber: “Bridging therapies are frequently used at the start of a cluster to control attacks while up-titrating preventive therapy” (Aust Prescr 2022).

A note on the chronic case. Bridge therapy is conceptualised around *episodic* CH — get the patient through the first weeks of a bout. In **chronic** CH there is no bout to get through; the same intervention is being used to buy relief while a preventive is optimised, or simply to buy relief. The evidence base reflects the episodic framing, and this shows up in the response rates below.

2.2 Corticosteroids

The only RCT

`[PEER-REVIEWED]` **Obermann M, Nägel S, Ose C, Sonuc N, Scherag A, Storch P, Gaul C, Böger A, Kraya**

T, Jansen J-P, Straube A, Freilinger T, Kaube H, Jürgens TP, Diener H-C, Katsarava Z, Kleinschnitz C, Holle D. “Safety and efficacy of prednisone versus placebo in short-term prevention of episodic cluster headache: a multicentre, double-blind, randomised controlled trial.” Lancet Neurol. 2021;20(1):29–37 (PMID 33245858, DOI 10.1016/S1474-4422(20)30363-X). EudraCT 2011-006204-13; DRKS00004716. *German multicentre trial — 10 German headache centres, April 2013 to January 2018.* **Stopped early** due to slow recruitment and expired funding.

Regimen: prednisone 100 mg orally for 5 days, then taper by 20 mg every 3 days — total 17 days. All patients simultaneously started **verapamil 40 mg three times daily, titrated to 120 mg three times daily by day 19** — i.e. the trial tested exactly the real-world bridging scenario.

118 enrolled, 116 randomised (57 prednisone / 59 placebo), mITT 109 (53/56).

| Outcome | Prednisone | Placebo | Difference | |—|—|—|—| | **Mean attacks, first week** | **7.1 (SD 6.5)** | **9.5 (SD 6.0)** | **−2.4 (95% CI −4.8 to −0.03), p=0.002** | | Patients with adverse events | 37/52 (71%) | 39/55 (71%) | — | | Total adverse events | 135 | 135 | — | | Serious adverse events | 0 | 2 (inguinal hernia; severe CH deterioration) | — |

Most common prednisone adverse effects: headache, palpitations, dizziness, nausea.

Read the effect size honestly. A reduction of **2.4 attacks in the first week** — from 9.5 to 7.1 — is statistically significant and clinically worth having, but it is not dramatic. The confidence interval nearly touches zero. **This is the entire randomised evidence base for oral steroids in cluster headache, and it is in episodic CH only.** Anyone describing oral prednisone as a reliably effective bridge is going beyond what this trial shows.

Regimens in use

| Source | Regimen | |—|—| | EAN 2023 `[PEER-REVIEWED]` | **250 or 500 mg**

IV prednisone in the morning, or **60–100 mg orally for 5 days then reduce 10 mg every 4 days** | | Obermann 2021 RCT `[PEER-REVIEWED]` | **100 mg × 5 days, then −20 mg every 3 days** (17 days total) | | Australian Prescriber `[PEER-REVIEWED]` | **Prednisolone 1 mg/kg, max 75 mg daily**, with gastric ulcer prophylaxis, **down-titrated over two weeks** | | Leroux & Ducros review `[PEER-REVIEWED]` | "at least **50 mg prednisone or equivalent daily for 1 week then a taper**," cumulative **~500 mg or more** |

Sources: EAN 2023; Obermann 2021; Aust Prescr 2022; Leroux & Ducros, Curr Pain Headache Rep 2013;17:325.

The recurrence problem

`[PEER-REVIEWED]` **"Recurrence of attacks upon weaning is a common problem"** (Leroux & Ducros 2013). Ambrosini et al. put it more bluntly: "Oral steroids can interrupt bouts of cluster headache attacks, but **recurrence is frequent and may lead to steroid-dependency**" (Ambrosini et al., Pain 2005).

`[PEER-REVIEWED]` Australian Prescriber: "Prolonged use should be minimised because of adverse effects" (Aust Prescr 2022).

This is the central problem with oral steroids in chronic CH. In episodic CH you take a two-week course and the bout ends anyway. In chronic CH there is no natural endpoint, so the patient hits the taper and the attacks come back — creating pressure for repeated or continuous courses, which is where avascular necrosis, osteoporosis, diabetes, weight gain and adrenal suppression live. **Oral steroids are a poor fit for chronic daily CH specifically because the disease does not stop when the course does.** This is the strongest argument for the injection route below.

`[CITIZEN-SCIENCE]` Interestingly, in the systematic review of survey studies, **corticosteroids were rated the most effective conventional prophylactic treatment, closely followed by verapamil** (Rusanen et al. 2022). Patients rate steroids highly — which is consistent both with them working and with them being

remembered fondly by people whose bouts ended.

2.3 Greater occipital nerve (GON) / suboccipital steroid injections

This is, in my reading, the most under-appreciated intervention in the whole acute-and-bridge space: **two positive randomised controlled trials, a clean safety record, and effect sizes that dwarf oral steroids.**

RCT 1 — Ambrosini (Italy/Belgium)

`[PEER-REVIEWED]` **Ambrosini A, Vandenheede M, Rossi P, Aloj F, Sauli E, Pierelli F, Schoenen J. "Suboccipital injection with a mixture of rapid- and long-acting steroids in cluster headache: a double-blind placebo-controlled study." Pain. 2005;118(1–2):92–6** (PMID 16202532, DOI 10.1016/j.pain.2005.07.015). Headache Clinic, INM Neuromed IRCCS, Pozzilli, Italy. *Italian/Belgian collaboration.*

23 outpatients (**16 episodic, 7 chronic**), one-week run-in, randomised to **13 verum / 10 placebo (physiological saline)**. Episodic patients were in a new bout of no more than one week's duration. Single **suboccipital injection of a mixture of long- and rapid-acting betamethasone, ipsilateral to the attacks, in the region of the greater occipital nerve.** Injections by three investigators; follow-up by four blinded investigators at 1 and 4 weeks.

| Outcome | Verum | Placebo | p | |—|—|—|—| | **Attack-free in the first week** | **11/13 (85%)** — including **3 chronic patients** | **0/10** | **0.0001** | | Remained attack-free at 4 weeks | 8 of those 11 | — | 0.0026 | | Remission lasting **4–26 months** | 5 patients | — | — |

Authors' conclusion: "A single suboccipital steroid injection completely suppresses attacks in more than 80% of CH patients," maintained for at least 4 weeks in the majority.

Placebo response was zero. In a disease where drug-trial placebo response runs **14–43%** (EAN 2023), a 0/10 placebo arm and an 85% verum arm is a striking separation — though with n=23 the confidence intervals are wide.

RCT 2 — Leroux (France)

`[PEER-REVIEWED]` **Leroux E, Valade D, Taifas I, Vicaut E, Chagnon M, Roos C, Ducros A. "Suboccipital steroid injections for transitional treatment of patients with more than two cluster headache attacks per day: a randomised, double-blind, placebo-controlled trial." Lancet Neurol. 2011;10(10):891–7** (PMID 21903477, DOI 10.1016/S1474-4422(11)70186-7, NCT00804895). Emergency Headache Centre, Lariboisière Hospital, Paris. *French source. Received no funding.* Editorial comment: PMID 21903478.

The eligibility criterion is precisely the population this chapter is about: adults aged 18–65 with more than two cluster headache attacks per day. 43 randomised (**15 chronic, 28 episodic**), stratified, blocks of four. Injectors were unblinded; patients and the evaluating physician were blinded. ITT analysis.

Intervention: three suboccipital injections of cortivazol 3.75 mg, 48–72 hours apart, as add-on to oral verapamil (episodic) or add-on prophylaxis (chronic). Primary outcome assessed over the 72 hours 2–4 days after the third injection.

Outcome	Cortivazol	Placebo	Effect
Mean ≤2 attacks/day after injections	**20/21**	**12/22**	**OR 14.5 (95% CI 1.8–116.9), p=0.012**
Mean attacks in first 15 days	**10.6 (95% CI 1.4–19.9)**	**30.3 (95% CI 21.4–39.3)**	**difference 19.7 (95% CI 6.8–32.6), p=0.004**
Serious adverse events	**none**	**none**	—
Other adverse events	18/21	14/22	32/43 (74%) overall, p=0.162

Most common adverse events: **injection-site neck pain and non-cluster headache.**

Authors' conclusion: "Suboccipital cortivazol injections can relieve cluster headaches rapidly in patients having frequent daily attacks, **irrespective of type (chronic or episodic)**."

That last clause is the important one. Unlike oxygen, unlike zolmitriptan, unlike oral steroids, the Leroux trial explicitly found the benefit did not depend on episodic vs chronic status. **A reduction from 30.3 to 10.6 attacks**

over 15 days is a two-thirds reduction in attack burden in a population averaging two attacks a day at baseline.

Contextual note: all episodic patients started verapamil at trial entry; mean verapamil dose was **420 mg (active) vs 564 mg (placebo)**, and additional prophylactics were used by **5% (active) vs 27% (placebo)** — the placebo group needed more of everything else.

Large prospective observational study — Germany

`[PEER-REVIEWED]` **Gaul C, Roguski J, Dresler T, Abbas H, Totzeck A, Görlinger K, Diener H-C, Weber R. "Efficacy and safety of a single occipital nerve blockade in episodic and chronic cluster headache: A prospective observational study." Cephalalgia. 2017;37(9)** (online 16 June 2016), DOI 10.1177/0333102416654886. *German source.* **n=101 (61 episodic, 40 chronic).** Single unilateral injection of **triamcinolone 10 mg + bupivacaine 0.5%**.

| Outcome | Result | |—|—| | Complete or partial response | **83.2%** | | Complete response (pain-free ≥1 day), **episodic** | **67.2%** | | Complete response, **chronic** | **50%** | | Overall duration of effect | **mean 27.3 ± 26.2 days; median 14 days** | | Pain-free duration, **episodic** | **33.6 ± 26.3 days** | | Pain-free duration, **chronic** | **14.3 ± 21.3 days** (p<0.001 vs episodic) | | Subjective benefit, episodic vs chronic | **70% vs 43%** (p<0.001) | | Side effects | **10.9%** — tension-type headache 4.6%, injection-site pain 1.8%, retro-orbital pain 1.8%, nausea 0.9%, pressure 0.9% | | Serious adverse events | **none** |

The most mechanistically interesting finding in this section: numbness occurred in **27.7%** (restricted to the GON/LON territory) and **41.6%** (more extended distribution), but there was **no association between numbness or local anaesthesia and treatment response (p=0.88)**.

That result argues strongly that the therapeutic agent is the steroid, not the nerve block. If blocking conduction in the greater

occipital nerve were the mechanism, patients with successful anaesthesia should do better. They don't. This aligns with Leroux & Ducros' conclusion that **anaesthetic-only injections are not supported** `[PEER-REVIEWED]` (Leroux & Ducros 2013). The implication is that "GON block" is a misleading name — it is really a **depot steroid injection in the suboccipital region**, and accurate nerve localisation may matter less than getting an adequate dose of long-acting steroid into the right tissue plane.

A conference-abstract version of this work appears at PMC3620288, DOI 10.1186/1129-2377-14-S1-P60.

Long-acting steroid, no anaesthetic — Italy

`[PEER-REVIEWED]` **Merli E, Asioli GM, Favoni V, Zenesini C, Mascarella D, Sartori A, Cortelli P, Cevoli S, Pierangeli G. "Great occipital nerve long-acting steroid injections in cluster headache therapy: an observational prospective study." J Neurol. 2022;269(4):2193–2199** (PMC8940833, DOI 10.1007/s00415-021-10884-0, PMID 34820736). IRCCS Bologna. *Italian source.* 60 enrolled, 58 analysed (**46 episodic, 12 chronic**).

Technique, described precisely: methylprednisolone 60 mg in 2 mL saline, NO local anaesthetic, 25-gauge needle, three injections on alternate days, ipsilateral. Injection point: **one-third laterally along the line from inion to mastoid, 2 cm below the occipital nuchal ridge; aspirate before injecting.**

| Outcome | All | Episodic | Chronic | |—| —|—|—| | **Complete responders** | **26/58 (44.8%)** | **22/46 (47.8%)** | **4/12 (33.3%)** | | Partial responders (≥50% reduction) | 9/58 (15.5%) | 10.8% | 33.3% | | **Combined** | **60.3%** | — | — |

Follow-up findings: - **50% of episodic complete responders were still pain-free at one year**; mean latency to recurrence **242 ± 130.49 days (~8 months)**. - **All chronic patients relapsed**; median pain-free duration **94 ± 7.85 days (~3 months)** — which the authors note is "**substantially longer than previously reported (13–65 days)**."

For a chronic daily patient, this is the most directly relevant number in the section: roughly three months of meaningful benefit per treatment course, in the third of chronic patients who respond completely, using a course of three injections without local anaesthetic. Three months is long enough to make this a repeatable strategy rather than a one-off.

Historical case series

`[PEER-REVIEWED]` / `[HISTORICAL/CULTURAL]` From the Leroux & Ducros review table (Leroux & Ducros 2013): - **Anthony 1985**, n=20: **depot methylprednisolone 120 mg + lignocaine 2%, 2–5 mL** → more than 20 headache-free days in **14/20**; repeat injections benefited 9/15. - **Anthony 2000**, n=20 chronic CH: **120 mg + lignocaine 1%, 3–4 mL** → good response reported.

Dosing and technique guidance

`[PEER-REVIEWED]` From Leroux & Ducros (source): - Recommended total: **80–160 mg methylprednisolone equivalent.** - Injection site: **medial third of the line between inion and mastoid, 2 cm under the ridge.** - **Feel the occipital bone** to avoid going too deep near the foramen magnum. - **Retract the plunger** to rule out vascular puncture. - **Anaesthetic-only injections are not supported.** - **Repeating three times per site per year is probably safe** — but note this is inferred from the intra-articular steroid literature, **not from trial data in CH**. `[PEER-REVIEWED]` label, but the safety claim itself is extrapolation and should be treated as such.

The dose-sparing argument, which is the clinical case for injection over tablets: the Leroux three-injection cortivazol regimen equals a **prednisone-equivalent of 187.5 mg**; the Ambrosini betamethasone regimen equals **135 mg**. A standard oral bridging course is **~500 mg or more** of prednisone equivalent (Leroux & Ducros 2013). **You get equal or better effect for roughly a quarter to a third of the systemic steroid exposure.** For anyone facing repeated bridging over years — i.e. anyone with

chronic CH — that ratio is the whole argument.

Where the guidelines land

`[PEER-REVIEWED]` **CNS Drugs 2020 names GON injection the first-choice transitional treatment** (Brandt et al. 2020, PMC7018790).

`[PEER-REVIEWED]` **Australian Prescriber** lists GON block with **local anaesthetic plus depot methylprednisolone** as an alternative bridging strategy which "can reduce attacks for an average of **four weeks**" and "avoids the adverse effects of a course of oral steroids" (Aust Prescr 2022).

One unresolved technical question, stated as such: Australian and German practice adds **local anaesthetic**; the Bologna group deliberately omits it; the German Gaul study found **no relationship between achieved anaesthesia and outcome**. **Whether local anaesthetic adds anything beyond immediate comfort is unknown.** It is not a reason to refuse an injection either way.

2.4 Bridge therapy — practical summary

Option	Best evidence	Typical effect	Duration	Main drawback
Oral prednisone/prednisolone	1 RCT, episodic only (Obermann 2021)	−2.4 attacks in week 1	~2–3 weeks, then recurrence on weaning	Systemic steroid load; recurrence; dependency risk
Suboccipital / GON steroid injection	**2 RCTs** (Ambrosini 2005; Leroux 2011) **+ 2 large prospective cohorts**	85% attack-free week 1; 30.3→10.6 attacks/15 days; 83% any response	mean 27 days (Gaul); ~94 days in chronic responders (Merli)	Needs a clinician who does the procedure; ~⅓ complete-response rate in chronic

If I were compressing this section to one sentence for a chronic daily patient: ask specifically about a course of suboccipital/GON steroid injections rather than accepting an oral prednisone taper by default, and cite Leroux 2011 — it is the trial that enrolled exactly people with more than two attacks a day.

3. Preventive Treatment

Preventive treatment aims to reduce attack frequency and severity over the course of a cluster period (episodic CH) or indefinitely (chronic CH). For chronic sufferers, this is the treatment category that matters most day-to-day, and it is also the category where the gap between trial evidence and real-world/community practice is widest — most of these drugs have never been tested in a properly powered chronic-CH-only RCT.

Before the drug-by-drug detail, three structural facts shape everything below.

1. The randomised evidence base for CH prevention is astonishingly thin. A 2022 German review states that *only* verapamil and lithium have evidence from randomised studies at all, and grades even those as `++` ("moderate evidence"), with topiramate `+` ("low"), and gabapentin and melatonin `(+)` ("questionable") (Drug Treatment of Cluster Headache, PMC8748342). **[PEER-REVIEWED]** The 2016 American Headache Society evidence-based guideline found that after a full systematic review, the **only** preventive treatment achieving a Level A recommendation was suboccipital steroid injection — not verapamil, not lithium (Robbins MS, Starling AJ, Pringsheim TM, Becker WJ, Schwedt TJ. *Headache* 2016;56(7):1093–1106, DOI 10.1111/head.12866, PMID 27432623). **[PEER-REVIEWED]**

2. Chronic CH is systematically worse-served than episodic CH. Every single agent below performs worse in chronic than episodic disease, and several drugs with positive episodic data have outright failed in chronic trials. This is the single most important pattern in this chapter for a daily-chronic patient, and it recurs so consistently that it is arguably a biological signal rather than a trial-design artefact.

3. The gap between guideline dosing and specialist/community practice is enormous — and the guidelines are, on the specific issue of verapamil dose, arguably the ones that are wrong. This is documented in an unusually explicit way in the German literature (see §1.6).

3.1 Verapamil

3.1.1 Status and why it is first-line

Verapamil is a non-dihydropyridine L-type calcium channel blocker, licensed for hypertension, angina and arrhythmia — **not** for cluster headache in most jurisdictions. It is nonetheless described as "the medication of choice" for CH prevention and "the most effective treatment with the best scientific evidence, followed by lithium" (PMC8748342). **[PEER-REVIEWED]**

Its efficacy in CH was first described by Meyer and Hardenberg in 1983 (Schmerzklinik Kiel, German-language). **[PEER-REVIEWED]** *(German-language source.)*

In 2025 the WHO Expert Committee on Selection and Use of Essential Medicines reviewed verapamil for CH prophylaxis and the reviewer "supports inclusion of verapamil for the prevention of cluster headache attacks, although the evidence supporting efficacy is limited" — the evidence base being *two small RCTs and three observational studies* (WHO 25th EML Expert Committee review). **[PREPRINT/TRIAL]** (WHO expert review document, not peer-reviewed journal publication.) Proposed EML formulations: immediate-release 40/80/120 mg, extended-release 120/180/240 mg.

Note the honest framing: the world's most-prescribed CH preventive rests on two small trials.

3.1.2 Efficacy — the actual numbers

The pivotal placebo-controlled trial

Leone M, D'Amico D, Frediani F, et al. *Verapamil in the prophylaxis of episodic cluster headache: a double-blind study versus placebo.* Neurology 2000;54(6):1382–1385, DOI 10.1212/WNL.54.6.1382. **[PEER-REVIEWED]**

Endpoint	Verapamil 360 mg/day	Placebo
n	30 total, randomised	—
Daily attack frequency	0.66 ± 0.88	1.65 ± 1.01
Daily analgesic consumption	0.5 ± 0.87	1.2 ± 1.03
≥50% reduction (week 2)	**80%**	**0%**
Attack-free	**27%**	—
p	<0.001 for attack frequency	—

Confirmed independently in the WHO review's reproduction of the same trial (WHO 2025). **[PREPRINT/TRIAL]**

Read that table carefully. An 80% responder rate sounds superb. But "responder" here means ≥50% reduction in attack frequency over two weeks in *episodic* CH — and only 27% became attack-free. Roughly three-quarters of even the responders were still having attacks. For a chronic daily patient, the 27% figure is the more honest anchor.

Verapamil vs lithium head-to-head

Bussone G, Leone M, Peccarisi C, et al. *Double blind comparison of lithium and verapamil in cluster headache prophylaxis.* Headache 1990;30(7):411–417, DOI 10.1111/j.1526-4610.1990.hed3007411.x. **[PEER-REVIEWED]** 23-week double-blind crossover, n=30 chronic CH, no placebo arm. Verapamil 360 mg/day vs lithium 900 mg/day. Headache Index reduction **50% (verapamil) vs 37% (lithium)**; Analgesic Consumption reduction 58% in both. Minor side effects **12% verapamil vs 29% lithium** (Spanish-hosted review of lithium literature, SciELO). **[PEER-REVIEWED]** *(Article in English, hosted on the Spanish SciELO platform, European Journal of Psychiatry 2009;23(1), Zaragoza.)*

Notice this trial had **no placebo arm**, so it establishes non-inferiority of two drugs to each other, not efficacy.

Open-label data — the optimistic end

- **Blau JN & Engel HO** open trial, n=72 (52 episodic, 18 chronic), starting 200 mg, most needing 200–480 mg, 12 patients needing 520–960 mg: complete relief in **49/52 episodic (94%)** and **10/18 chronic (55%)** (PMC8748342). **[PEER-REVIEWED]**
- Open study, n=84: **33/84 (69%)** improved by >75% in attack frequency (PMC8748342); the same 69%/>75% figure is cited by Schmerzklinik Kiel (German). **[PEER-REVIEWED]**
- Pair-wise meta-analysis of open-label studies: **87%** reached complete response or >50% reduction (PMC8748342). **[PEER-REVIEWED]**

Open-label data — the pessimistic end, and a genuine conflict

The WHO 2025 review reports **two different pooled figures within the same document**: the detailed section gives a pooled observational figure of **73% (95% CI 0.59–0.84)** reaching complete response or ≥50% reduction, while the reviewer summary states **87%** (WHO 2025). **[PREPRINT/TRIAL]** *This is an internal inconsistency in a WHO document, flagged here rather than resolved. Which figure the committee acted on is unknown.*

More importantly, **real-world clinic data are dramatically worse than trial data.** The Danish Cluster Headache Survey (n=400, tertiary headache centre, Rigshospitalet/Danish Headache Center) found only **44% of episodic and 34% of chronic** patients achieved >50% reduction on verapamil, and only **14%** achieved complete relief. A separate Danish cohort found a **20% response rate**. **[CITIZEN-SCIENCE / PEER-REVIEWED hybrid]** — this is a structured clinic-based patient survey published in the peer-reviewed literature; Petersen et al.'s Danish survey is one of the nine surveys catalogued in Rusanen SS, De S, Schindler EAD, Artto VA, Storvik M. *Curr Pain Headache Rep* 2022;26(8):623–637, PMC9436841.

The conflict is real and should not be smoothed over: open-label specialist trials report 69–94% response; a large Scandinavian real-world survey reports 34–44%. Likely contributors: responder-favourable publication in open series, differing definitions of "response", tertiary centres accumulating treatment-refractory patients, and the fact that early open trials predate modern ICHD diagnostic rigour. Which is closer to your likely experience is genuinely uncertain — but if you are chronic and attending a specialist centre, the Danish numbers are the better prior.

Time to effect

- EAN guideline: effect takes **14–21 days** (European Academy of Neurology guidelines on cluster headache, 2023, DOI 10.1111/ene.15956). **[PEER-REVIEWED]**
- German G-BA/Schmerzklinik Kiel: efficacy assessable "at the earliest after 1 week", onset dose-dependent (German). **[PEER-REVIEWED]**
- Gabai & Spierings: onset **1.7 weeks episodic, 5 weeks chronic** — chronic patients wait roughly three times as long. **[PEER-REVIEWED]**

This chronic/episodic latency difference matters practically: a chronic patient who abandons a dose after two weeks may be abandoning a dose that would have worked at week five.

3.1.3 Dosing and titration — four national protocols compared

There is no international consensus. Here are four, side by side.

Source	Start	Increment	Max	Notes
EAN 2023 (ene.15956)	80 mg TID or QID	+80 mg every 3–4 days	~1000 mg/day	Taper over 2–4 weeks on stopping
BASH (UK) (BASH verapamil regime)	320 mg/day (80/80/160)	Fixed 9-stage ladder, each stage held **2 weeks**, ECG before each step	**960 mg/day**	Explicitly "does not have a specific licence for a headache condition"
Australian Prescriber 2022 (Ray JC, Stark RJ, Hutton EJ. *Aust Prescr* 2022;45:15–20, DOI 10.18773/austprescr.2022.004)	80 mg TID for ≥2 weeks	+80 mg every 2 weeks	240–960 mg/day	Grade 1B
German G-BA (statutory) (Schmerzklinik Kiel, German)	**120 mg/day**	Not specified	**360 mg/day**	Above 360 mg = back into off-label
Schmerzklinik Kiel clinical practice (same page)	2 × 120 mg SR, 12 h apart; or 2 × 240 mg if severe	+step every 3–7 days	240–960 mg, up to **1200 mg** inpatient	Directly contradicts the G-BA limit

[PEER-REVIEWED] for EAN and *Australian Prescriber*; **[PREPRINT/TRIAL]** for BASH (clinical guidance document, not a peer-reviewed article) and the G-BA regulatory decision.

The full BASH 9-stage ladder (BASH): 80/80/160 (320) → 80/160/160 (400) → 160/160/160 (480) → 160/160/240 (560) → 160/240/240 (640) → 240/240/240 (720) → 240/240/320 (800) → 240/320/320 (880) → 320/320/320 (**960**). Each stage is held two weeks and requires a normal ECG before advancing. At that pace, reaching 960 mg takes ~18 weeks. **[PREPRINT/TRIAL]**

A Delphi consensus of headache specialists found the **mean highest verapamil dose used was 550 mg/day (range 240–960)** (Koppen H, et al. *Cephalalgia* 2016, DOI 10.1177/0333102416631968). **[PEER-REVIEWED]** So real specialist practice sits around 550 mg — well above the German statutory 360 mg cap and well below the 960 mg ceiling.

Immediate-release vs sustained-release: an unresolved and clinically important disagreement

- **Schmerzklinik Kiel (Germany)** states *only* sustained-release ("retardierte") 12-hour preparations should be used, because IR verapamil "produces fluctuations and gaps in plasma levels, reduces effectiveness, and allows the level to fall at night" — which matters given the nocturnal attack peak (German). **[PEER-REVIEWED]**
- The **G-BA decision itself does not state** whether IR or SR should be used (same source). **[PREPRINT/TRIAL]**
- The **patient community holds the exact opposite view** — see §1.5.

This is a genuine, unresolved conflict with no adequate head-to-head data. Unknown.

3.1.4 ECG monitoring: rationale and protocol

Why

Verapamil slows AV nodal conduction. In CH it is used at 2–4× cardiac doses, for years, in an otherwise healthy population. The observed harms are not theoretical.

Cohen AS, Matharu MS, Goadsby PJ — n=217, mean dose 512 mg/day: **19% developed arrhythmias**, PR prolongation the most common finding. **41% had never had an ECG at all. [PEER-REVIEWED]**

Lanteri-Minet M, et al. (French group), cardiac safety of very-high-dose verapamil (PMC3072493): of 200 CH patients, **29 (14.8%)** received high doses of 877 ± 227 mg/day. Among those 29: **ECG changes in 38% (11/29)**; **bradycardia in 7 (24%)** classed non-serious; **arrhythmia (heart block) in 4 (14%)** classed a **serious** adverse event. Mean dose in those with ECG changes **1003 ± 295 mg/day** vs **800 ± 143 mg/day** in those without. **[PEER-REVIEWED]**

Two findings from that study deserve emphasis because they break the intuitive mental model:

1. **Roughly three-quarters of cardiac adverse effects had markedly delayed onset — appearing after more than 2 years of treatment** (PMC3072493, summarised in German at Schmerzklinik Kiel). A clean ECG at month 3 does not buy you safety at year 3.
2. **Adverse events were reported as independent of dose level** (same source). BASH puts it even more bluntly: rhythm disturbances are "neither dose-dependent nor time-dependent" (BASH). **[PREPRINT/TRIAL]** This is why "I'm only on 240 mg so I don't need ECGs" is not a defensible position.

Australian Prescriber states plainly: **"one in five patients will develop an arrhythmia"** (Aust Prescr 2022;45:15–20). **[PEER-REVIEWED]**

Protocols

Source	Baseline	On titration	At stable dose
EAN 2023	Mandatory before treatment	Repeat with each +160 mg above 480 mg/day	—
BASH (UK)	Yes	**Before every dose step** (must be normal to advance)	**Every 6 months**
Australian Prescriber 2022	Yes	Every dose change	At stable dose after 10 days, then every 1–2 months, then every 6 months
Schmerzklinik Kiel (Germany)	Mandatory, assess **PQ interval**	**1–2 weeks after every dose increase**	Every 6 months if AV block unchanged; stop if worsening
Koppen Delphi (specialist actual practice)	82% do one	50% before increase; 60% after (mean 5 days, range 1–14)	Holter at ≥480 mg/day in 50%

Sources: EAN 2023, BASH, Aust Prescr 2022, Schmerzklinik Kiel, German, Koppen 2016 Delphi, DOI 10.1177/0333102416631968. **[PEER-REVIEWED]** except BASH **[PREPRINT/TRIAL]**.

The German source gives the most operationally precise thresholds available anywhere — worth quoting because most English-language guidance gives none (Schmerzklinik Kiel, German): **[PEER-REVIEWED]**

- **PQ > 0.20 s** = first-degree AV block → an *application restriction*, not an absolute contraindication; if there is a strict indication, first follow-up ECG at 1–2 weeks
- **PQ ≈ 0.25 s** → generally should not prescribe
- **PQ ≥ 0.30 s** → should in any case not prescribe
- **Second-degree AV block or higher** → absolute contraindication
- Suspected heart failure → contraindication
- **Beta-blockers must not be co-administered**
- Recommend interdisciplinary follow-up with a cardiologist
- No deaths during verapamil CH prophylaxis had been reported in the cited material; no embryotoxicity known

Full BASH contraindication list: acute porphyrias; atrial flutter/fibrillation with accessory pathway (e.g. WPW); bradycardia; cardiogenic shock; history of heart failure even if controlled; history of significantly impaired LV function even if controlled; hypotension; 2nd/3rd-degree AV block; sick sinus syndrome; sino-atrial block. Not recommended in pregnancy, planned pregnancy or breastfeeding (BASH). **[PREPRINT/TRIAL]**

Also: **slow tapering is strictly recommended** on discontinuation to avoid cardiac complications (WHO 2025; PMC8748342). EAN says taper over 2–4 weeks.

3.1.5 Side effects

Guideline/trial-derived: hypotension, fatigue, **constipation**, oedema, bradycardia, AV block (PMC8748342). **[PEER-REVIEWED]** Constipation and oedema can be dose-limiting; rare severe skin reactions (WHO 2025). **[PREPRINT/TRIAL]**

BASH's fuller patient-facing list adds: abnormal heartbeat, flushing, nausea, abdominal pain, dizziness, vertigo, **tinnitus**, tiredness, tremor, movement disorders, muscle weakness, joint/muscle aches, rash or itching, paraesthesia, **swollen gums**, numbness, **hair loss**, rare impotence, and rare galactorrhoea in males and females (reversible on cessation) (BASH). **[PREPRINT/TRIAL]** *Swollen gums (gingival hyperplasia) and hair loss are under-communicated in clinical practice and worth knowing about in advance.*

Comparative tolerability: minor side effects 12% verapamil vs 29% lithium in Bussone's head-to-head (SciELO review); Australian Prescriber similarly reports 29% lithium vs 12% verapamil (Aust Prescr 2022). **[PEER-REVIEWED]**

3.1.6 What the patient community says — verapamil

Drawn from three r/clusterheads threads (~40 identifiable participants total). **[COMMUNITY-REPORT]** throughout this subsection.

Doses actually used are frequently at or above the ceiling of most guidelines. Reported personal doses include 480 mg (thread), 600 mg (self-escalated without telling the doctor), 680 mg, 720 mg, 960 mg, and one patient on **3 × 340 mg = 1020 mg/day for seven years** (thread).

Time to effect, reported: "within a week" at 480 mg; ~1 week; "about two weeks to assess whether a dose is working"; one patient took **a full year** to titrate to 680 mg with an ECG between each step (thread).

Effectiveness is bimodal, not graded. Reports cluster into "largely stopped my attacks" and "did nothing":

> "After starting verapamil at a dosage of 480mg, I noticed a significant improvement—within a week, I was free from cluster headaches!" (r/clusterheads)

> "I've been taking it for about three years now and it has worked very well. Have gone from ~40 headaches a year to maybe 5 and haven't had side effects." (r/clusterheads)

> "It doesn't work for me." (r/clusterheads)

Side effects, community-weighted differently from the literature. Constipation dominates:

> "In a single word, my experience with Verapamil can be summed up as 'constipation.'" (r/clusterheads)

Also reported: bradycardia ("my heart rate is VERY slow. Resting Heart rate of an Olympic athlete" at 960 mg/day); fatigue and loss of motivation; ankle swelling; palpitations and light-headedness severe enough to stop the drug within a month; cold hands and feet; weight gain; hormonal imbalance; reduced sexual function; inability to raise heart rate during exercise, making exercise "impossible"; and one report of developing an allergy after several years (threads 1, 2, 3).

Four places where community experience diverges sharply from trial/guideline data

(a) ECG monitoring is frequently not happening. Guidelines are near-unanimous that ECGs are mandatory. Patients report otherwise:

> "I never had (or was told to have) ECGs, even though I mentioned heart symptoms during my annual check-up." (r/clusterheads)

Another reported severe palpitations and light-headedness and said the doctor "never tested them or checked the symptoms." Meanwhile Cohen's peer-reviewed series found **41% of 217 patients had never had an ECG** despite a mean dose of 512 mg/day — so the community observation and the published data agree exactly. **This convergence is the strongest signal in the chapter: monitoring failure is documented in both anecdote and peer-reviewed cohort data.**

(b) Immediate-release vs sustained-release — the community says the opposite of the German clinic. German specialists insist on SR for stable nocturnal levels. Multiple community members report the reverse:

> "Sustained-release verapamil is considered less effective for cluster prevention… dosing every 6–8 hours maintains a higher, more consistent blood concentration." — paraphrased community claim, presented as testimonials, not trial results (r/clusterheads)

Another simply: "the SR version did not work" (r/clusterheads). **This is an unresolved empirical question with no adequate trial. Neither side has good data. Contested.**

(c) Patients routinely self-escalate past doctor-imposed caps, and sometimes report benefit from doing so. One patient held at 440 mg because of an APC/ECG finding self-adjusted the regimen and reported "The result? My headaches disappeared" — the doctor was initially upset, then approved a modified regimen and documented the self-alteration in the notes (r/clusterheads). Another was capped at 480 mg despite reporting greater benefit at 600 mg. One explanation offered by a patient: their neurologist

"was kind but inexperienced with chronic cluster headache and the patient was the neurologist's first chronic case." **This is risky behaviour given the documented 14% serious-arrhythmia rate at high doses — but it is happening, and the German literature suggests the low caps may genuinely be wrong (see below).**

(d) One reported pattern with no trial correlate: episodic → chronic conversion on verapamil. A patient reported that after several treatment cycles it became impossible to stop verapamil without CH returning, that an initially episodic condition **became chronic while taking it**, and that after tapering off over nearly a year they became episodic again (r/clusterheads). **[COMMUNITY-REPORT]** — This is a single anecdote, entirely unverified, with an obvious confound (chronification is the natural history in a subset of episodic patients regardless of treatment). It is recorded here because it is the sort of minority observation that would never surface in a 2-week RCT, not because it is credible evidence. **Unknown.**

The German off-label paradox — worth understanding in detail

In Germany the G-BA (Federal Joint Committee) formally added verapamil to the Arzneimittel-Richtlinie for prophylaxis of episodic and chronic CH in adults ≥18, making it prescribable on statutory health insurance *beyond its licensed indication* — a real access win. But it fixed the dose at **initially 120 mg/day, maximum 360 mg/day**, set the treatment goal at **≥50% attack reduction**, said treatment should stop if that goal is not met, and stated episodic treatment generally lasts ~6 weeks (Schmerzklinik Kiel, German). **[PREPRINT/TRIAL]** (regulatory decision)

Reimbursement is further restricted to products from **1A/Hexal/Sandoz, Abbott, Aliud/Stada, Basics, Heumann and Wörwag** only — other manufacturers' verapamil may not be prescribed on a statutory prescription, because those companies did not submit statements and thus showed no interest in reimbursement eligibility (same source).

Hartmut Göbel's clinic then criticises the decision head-on, in terms rarely seen in official commentary: 120 mg/day is too low for many patients; effective treatment may require 2 × 240 mg or more; many severely affected patients respond only above 360 mg; the 360 mg cap therefore *returns those patients to off-label status*; up to 480 mg is already approved for hypertension; the standardisation is "incompatible with the scientific literature"; specialist centres can disregard the limit but are then off-label "quantitatively and qualitatively"; routine-care physicians are unlikely to attempt high-dose treatment; and prescribers face legal exposure if they prescribe against the authorisation (Schmerzklinik Kiel, German). **[PEER-REVIEWED]** (clinical commentary citing Göbel H, *Die Kopfschmerzen*, 3rd ed., Springer 2012)

Göbel also argues the **treatment goal itself is wrong** — that given the severity of cluster attacks, the goal should be complete freedom from attacks, not a 50% reduction. This is a substantive philosophical objection to how CH trials and reimbursement are framed, and it maps directly onto why the "80% responder rate" in Leone 2000 feels so much better on paper than in life.

3.1.7 2024–2026 updates

- **WHO 2025 EML review** recommended inclusion of verapamil (with prednisolone and subcutaneous sumatriptan) for CH, explicitly acknowledging limited evidence (WHO). **[PREPRINT/TRIAL]** If adopted, this is meaningful for global access, particularly in low- and middle-income countries.
- **A 2025 Czech-language review** (*Neurologie pro praxi* 2025;26(1):54–60) restates verapamil as first-line while explicitly acknowledging off-label status, recommending initiation as early as possible in the bout at **240 mg/day**, conditional on excluding contraindications and a normal ECG. **[PEER-REVIEWED]** *(Czech-language source — note the higher starting dose than the German G-BA's 120 mg.)*
- **Petersen AS et al. (2019, 2023)** reviews from the Danish Headache Center continue to emphasise the limitations of the verapamil evidence base (PMC10476341). **[PEER-REVIEWED]**
- **No new verapamil RCT has been published in 2024–2026.** The evidence base is still Leone 2000 and Bussone 1990. That is a 26-year gap in randomised evidence for the world's first-line CH preventive. Worth sitting with.

3.1.8 Australia specifically

Verapamil is available in Australia and cheap, but **off-label for CH** — there is no PBS indication for cluster headache. *Australian Prescriber* gives it Grade 1B and the titration/ECG schedule in §1.3–1.4 (Ray JC, Stark RJ, Hutton EJ. *Aust Prescr* 2022;45:15–20). **[PEER-REVIEWED]** Practical implication: your GP or neurologist can prescribe it, the cost is trivial, but the ECG monitoring burden falls on you to insist upon.

3.2 Lithium

3.2.1 Status

Second-line preventive; the only agent other than verapamil with any randomised evidence at all (PMC8748342, evidence level `++`). **[PEER-REVIEWED]** Historically the *first* drug shown to work in chronic CH — Ekbom's work in the 1970s. Notably, lithium has always been described as working **better in chronic than episodic CH**, which makes it the one drug in this chapter with a chronic-favouring profile.

3.2.2 Efficacy — the open-label record vs the one RCT

The Spanish-hosted English-language systematic review of lithium in CH (*Eur J Psychiatry* 2009;23(1), SciELO) catalogues the whole literature. **[PEER-REVIEWED]** Key studies:

Study	n	Dose / serum level	Result
Ekbom	5 (3 chronic, 2 episodic)	serum 0.7–1.2 mEq/L	Effective in all 5
Bussone et al.	20 chronic	900 mg – 2.2 g/day	All improved rapidly; headache returned **within 36 h** of stopping in some
Kudrow	32 chronic	serum <1.2 mEq/L	27 dramatic improvement; ineffective in 5
Mathew	31 (14 ep, 17 chr)	not stated	**80% responded**, 20% no improvement; effect **<1 week**; 55% mild side effects; 1 stopped
Peatfield	31	0.6–0.69 mmol/L	14 marked improvement in week 1; 10 lesser improvement
Ekbom 1981	19 (8 chr, 11 ep)	0.7–1.2 mmol/L	Immediate partial remission in **all** chronic cases; 4 episodic achieved complete suppression; rest slight/no benefit
Savoldi et al.	90 (68 ep, 22 chr)	600–1200 mg; plasma 0.3–0.8 (chr) / 0.3–0.7 (ep) mEq/L	**>80% of chronic improved by >90%** in week 2; ~3/4 of episodic improved by >60%
Manzoni et al.	90 (68 ep, 22 chr)	900 mg/day	Chronic: 11 (50%) definite improvement, 50% partial only; 9 relapsed on stopping. Episodic: 26 high response, 26 partial, 16 refractory
Damasio & Lyon	21 (9 ep, 12 chr)	not stated	52.4% absolute improvement; 23.8% partial; 23.8% none/temporary
Klimek et al.	15 (8 chr, 7 ep)	0.6–1.2 mmol/L	Symptoms disappeared in 5; significant improvement in 5; ineffective in 5

A meta-analysis of three open trials (n=103) found **77%** reached complete response or >50% reduction (PMC8748342). **[PEER-REVIEWED]** Early open studies averaged roughly **two-thirds responding** (same source).

The single placebo-controlled trial was negative

Steiner TJ, Hering R, Couturier EGM, Davies PTG, Whitmarsh TE. *Double-blind placebo-controlled trial of lithium in episodic cluster headache.* Cephalalgia 1997;17(6):673–675, PMID 9350389. **[PEER-REVIEWED]**

- n=27 episodic CH: 13 slow-release lithium carbonate 800 mg/day vs 14 placebo
- Cessation of bout: **15% lithium vs 14% placebo**
- Substantial improvement: **8/13 (62%) lithium vs 6/14 (43%) placebo — NS**
- **The trial was stopped because superiority of lithium could not be demonstrated**

Note the important qualifier: PMC8748342 states that in this placebo-controlled study "lithium concentrations were described as too low." **[PEER-REVIEWED]** So the negative result may be a dosing failure rather than a drug failure — but that is a post-hoc rescue argument and should be treated as such.

The conflict, stated plainly: dozens of open studies over 30 years report 50–80% response rates, especially in chronic CH; the only RCT was in *episodic* CH, was possibly underdosed, and was negative. The SciELO reviewers conclude lithium is effective in both chronic and episodic CH but that evidence in episodic CH "may be controversial" (SciELO). Given that the one RCT was in episodic CH and the strongest open data are in chronic CH, **the chronic-CH case for lithium has never actually been tested in a randomised trial.** That is a striking gap for a chronic daily patient.

3.2.3 Dosing, serum levels and monitoring

- **EAN 2023**: 600–1500 mg/day; serum level ≥0.4 mmol/L required; ideal **0.6–0.8 mmol/L**; never >1.2; **effect within 1 week** (EAN). **[PEER-REVIEWED]**
- **PMC8748342**: plasma 0.4–0.8 mEq/L; monitor plasma concentration, **kidney and thyroid function**; avoid concomitant **diuretics and NSAIDs**. **[PEER-REVIEWED]**
- **Contested:** the SciELO review notes explicit controversy — some authors require higher doses to reach 0.7–1.2 mmol/L; others find low doses producing 0.4–1.0 mmol/L adequate (SciELO). **[PEER-REVIEWED]**

The fast onset (<1 week, vs 2–3 weeks for verapamil) is lithium's distinctive practical advantage and is reported consistently across Mathew, Peatfield, Savoldi and the EAN guideline.

3.2.4 Side effects and contraindications

Short-term, generally tolerable: **fine hand tremor, polyuria, polydipsia** (SciELO). Longer term: **hypothyroid goitre and renal impairment**. Reversible goitre developed in 3 patients after 1–3 years in Manzoni's series. Mild side effects in 55% of Mathew's patients, with 1 discontinuation. **[PEER-REVIEWED]**

Table-level: tremor, acne, goitre, hypothyroidism, muscle weakness. Contraindications: heart failure, Addison disease, sodium balance disorders, low-salt diet, renal failure, pregnancy, lactation (PMC8748342). **[PEER-REVIEWED]** The same review states lithium has "more and potentially more dangerous adverse events than verapamil."

The SciELO review makes a point worth keeping: lithium-induced hypothyroidism **can be treated and should not by itself be a reason to stop lithium** in a stable patient. **[PEER-REVIEWED]**

3.2.5 Odd findings and minority observations

- **HLA association with lithium response.** Giacovazzo et al., among 35 episodic CH patients, identified 21 responders and 14 non-responders; responders had higher frequency of **HLA-B18 and HLA-A9**; non-responders had higher **HLA-A1** (SciELO). **[PEER-REVIEWED]** — A single small study, never replicated to my knowledge. If real, it would be the only pharmacogenomic predictor in CH. **Unknown / unreplicated.**
- **Lithium shifts melatonin.** In a preliminary report of lithium given at 19:00 daily for a week: melatonin amplitude decreased at day 0, then by day 7 melatonin secretion was delayed with a phase shift and a clear increase in acrophase; cortisol decreased (same source). **[PEER-REVIEWED]** This is a direct mechanistic bridge between lithium and the circadian story in §4 and is rarely mentioned in clinical guidance.
- **Proposed antiviral mechanism**, with a speculative CH–herpes simplex association (same source). **[PEER-REVIEWED]** but highly speculative. **Contested.**
- Other proposed mechanisms: effect on REM sleep, platelet serotonin and histamine, opiate-receptor affinity, correction of bilateral neuronal asymmetries, restoration of reduced erythrocyte choline, hypothalamic serotonin. The review concludes the exact mechanism of lithium's rapid effect **remains unclear**.
- **Tolerance:** some authors found decreased effectiveness after prolonged lithium use, possibly tolerance or non-compliance (same source). **[PEER-REVIEWED]**
- Case report: lithium produced complete recovery in a chronic CH patient on **haemodialysis** (Zuddas et al., same source). **[PEER-REVIEWED]**

3.2.6 Community view

The Rusanen citizen-science synthesis places lithium in an ambiguous position. In the Sewell et al. survey, omitting "partially effective" responses made **verapamil and lithium appear to underperform** relative to other surveys; the reviewers state that reassigning those partial responses to "effective" would have matched other surveys almost exactly (Rusanen et al. 2022, PMC9436841). **[CITIZEN-SCIENCE]** Lithium features far less in r/clusterheads discussion than verapamil or Emgality, appearing mostly in "drugs I've already failed" lists (e.g. Peres & Rozen case 1's history of failed lithium 900 mg). This under-discussion may reflect genuine declining use, monitoring burden, or the drug's psychiatric associations — unknown.

3.3 Topiramate

3.3.1 Status

Third-line/tertiary option. Evidence level `+` = "low evidence"; "a possible alternative when verapamil or lithium is ineffective or not tolerated"; data "only from open observational studies" (PMC8748342). **[PEER-REVIEWED] There has never been a randomised placebo-controlled trial of topiramate in cluster headache.**

3.3.2 Efficacy — and a big internal inconsistency in the literature

Leone M, Dodick D, Rigamonti A, et al. open trial, *Cephalalgia* 2003, DOI 10.1046/j.1468-2982.2003.00665.x. **[PEER-REVIEWED]** n=33 analysed: only **21% (7/33)** achieved >50% reduction — **26% of episodic, 10% of chronic**. Seven patients took ≥200 mg/day for 15 days with **zero improvement**. p=0.3.

Other open series (PMC8748342): **[PEER-REVIEWED]**

Study	n	Dose	Result
Initial open-label	10	not stated	Positive effect within 3 weeks
Open, consecutive	36 (26 ep, 10 chr)	100–150 mg/day	**7/33** >50% reduction
Open	12	not stated	**9/12** good or moderate effect
Prospective, Spain	26 (12 ep, 14 chr)	max 200 mg	**15/26** remission of cluster period; 6/26 >50% reduction; mean time to remission 2 weeks

These results do not agree with each other. 7/33 (21%) vs 9/12 (75%) vs 15/26 remission (58%) in studies of the same drug at similar doses. No adequate explanation exists; the differences are most likely small-sample noise, differing outcome definitions, and open-label expectation effects. **Contested.**

2026 update

Shafiyev J, Gahramanov I. *The Evaluation of Topiramate as a First-Line Medication for Cluster Headache Prophylaxis: A Prospective Observational Cohort Study.* Clin Neuropharmacol 2026 Feb 23, online ahead of print, DOI 10.1097/WNF.0000000000000678, PMID 41805259. **[PEER-REVIEWED]** Prospective observational, Central Military Hospital, Baku, **Azerbaijan**, Oct 2023–Dec 2024. n=51 adults (64.7% male, mean age 38.6), episodic and chronic, topiramate monotherapy 25 mg/day titrated weekly to max 100 mg. Significant reductions in VAS and HIT-6 over time in all patients. **Chronic patients started with higher HIT-6 and improved more slowly than episodic.** Somnolence 19.6%; no discontinuations.

Be sceptical of this one. The title frames topiramate as *first-line*, which no guideline supports. The study is observational with no control group, no randomisation, no blinding, and — critically — **reports no attack-frequency outcome at all**, only VAS and HIT-6, with no exact values, no p-values and no confidence intervals published in the abstract. For a condition where placebo

response in prophylaxis trials is well documented (Nilsson Remahl AIM, Laudon Meyer E, Cordonnier C, Goadsby PJ. *Placebo Response in Cluster Headache Trials: A Review*, Cephalalgia 2003), an uncontrolled cohort showing "significant improvement over time" is close to uninformative. It is included for completeness, not because it changes anything.

3.3.3 Dosing and side effects

Start 25 mg/day, increase by **25 mg per week** (slow titration explicitly reduces side-effect rate), target **100–150 mg/day**, up to 200 mg (PMC8748342; Leone 2003). **[PEER-REVIEWED]**

Adverse events: cognitive dysfunction, fatigue, dizziness, paraesthesia, mood swings, anxiety, weight loss, hair loss. Contraindications: kidney stones, glaucoma, hypercalcaemia, dose adjustment in renal impairment, pregnancy (PMC8748342).

One warning deserves to be pulled out of the table. That review states topiramate can cause mood swings and depression, and explicitly flags this as relevant "because of the increased risk of suicide in patients with cluster headache." **[PEER-REVIEWED]** Given CH's grim nickname and documented suicidality, prescribing a mood-destabilising drug to this population is a real trade-off, not a footnote. If you try topiramate, have someone who will notice mood change before you do.

The cognitive effects ("dopamax" in community parlance) are the most common reason for discontinuation in practice.

3.3.4 Community view

Topiramate is not among the drugs the Rusanen synthesis singles out for either high or low self-reported efficacy — it is neither in the high-efficacy clade (LSD, psilocybin, ergoline alkaloids, methysergide, verapamil, corticosteroids) nor explicitly in the low clade (melatonin, valproic acid, gabapentin, amitriptyline, propranolol) (PMC9436841). **[CITIZEN-SCIENCE]** The survey paper describes topiramate and melatonin as "usually recommended as tertiary options." Community discussion is dominated by the cognitive side effects rather than by efficacy claims in either direction. **[COMMUNITY-REPORT]**

3.4 Melatonin

3.4.1 Why melatonin at all: the circadian rationale

This is the drug with the strongest *mechanistic* story and the weakest *evidence*. That mismatch is the whole point of this section.

The circadian biology of CH

Benkli B, Kim SY, Koike N, et al. *Circadian Features of Cluster Headache and Migraine: A Systematic Review, Meta-analysis, and Genetic Analysis.* Neurology 2023;100(22):e2224–e2236, DOI 10.1212/WNL.0000000000207240, PMID 36990725, PMC10259280. PROSPERO CRD42021234238. 72 studies. **[PEER-REVIEWED]** This is the definitive quantitative account:

- **70.5% (3,490/4,953)** of CH patients have a circadian pattern of attacks (16 studies)
- **Clear peak between 21:00 and 03:00** — the 7 consecutive hours 21:00–03:00 comprise all 7 highest hourly values
- **Single most likely hour: 02:00** (6.5%, 508/8,856)
- Peak months: **March, April, September, October, November** (53.8%, 1,882/3,495); most common season **autumn** (30.7%)
- Longitudinal stability: over ≥2 headache cycles, **52.5%** retained the same pattern (n=139); over ≥5 years, **78.4%** retained it (n=42)

The melatonin-specific findings

From the same meta-analysis (8 studies reporting corticosteroid or melatonin data):

- **Nocturnal urinary melatonin LOWER than controls in 5 studies**
- **Plasma melatonin LOWER than controls in 1 study**
- Corticosteroid blood levels higher than controls in 3 studies, unchanged in 1

- Association between CH and ***CLOCK*** SNV **rs12649507** reported — but *no* association with rs1801260, rs11932595 or rs12649507 in other analyses (i.e. **the CLOCK finding does not replicate consistently — contested**)
- Lower ***REV-ERBα*** RNA in lymphoblasts of CH patients vs controls
- No association with *PERIOD3* VNTR polymorphisms

Supporting mechanism from an earlier review (Gooriah R, Buture A, Ahmed F. *Ther Clin Risk Manag* 2015;11:1687–1696, DOI 10.2147/TCRM.S94193, PMC4646474): **[PEER-REVIEWED]** a **suppressed nocturnal melatonin peak is seen during the active phase** of CH; melatonin production is regulated by a multisynaptic pathway from the suprachiasmatic nucleus to the pineal gland; **smokers with CH have lower melatonin than non-smoking CH patients**; corticosteroid administration *increases* nocturnal urinary 6-sulfatoxymelatonin (the stable melatonin metabolite); disordered circadian rhythms of cortisol, luteinizing hormone, growth hormone and prolactin; reduced TRH stimulation; lower testosterone during attacks; and PET demonstrating highly specific hypothalamic grey matter activation in both nitroglycerine-induced and spontaneous CH.

So the rationale is genuinely strong: CH is a disorder with a hypothalamic pacemaker signature, a 02:00 attack peak, seasonal equinox-linked bouts, and measurably suppressed endogenous melatonin. Replacing melatonin is a rational hypothesis, not a wellness fad.

3.4.2 Efficacy — the positive trial

Leone M, D'Amico D, Moschiano F, Fraschini F, Bussone G. *Melatonin versus placebo in the prophylaxis of cluster headache: a double-blind pilot study with parallel groups.* Cephalalgia 1996;16(7):494–496, PMID 8933994, DOI 10.1046/j.1468-2982.1996.1607494.x. **[PEER-REVIEWED]**

- n=20 (**18 episodic, 2 chronic**), melatonin **10 mg nightly × 14 days** vs placebo, parallel groups
- Attack frequency significantly reduced, **p<0.03**
- Analgesic use reduced, **p<0.06** (i.e. did not reach conventional significance)
- **5/10 (50%) responders on melatonin vs 0/10 on placebo**
- **Neither of the two chronic patients responded**
- **No side effects**

That last-but-one point is the one that matters most for a chronic daily patient, and it is almost never quoted: **in the only positive randomised trial of melatonin in CH, both chronic patients failed to respond.** Confirmed independently: "melatonin rapidly alleviated cluster attacks only in episodic cluster patients in the Leone et al. report. Two chronic cluster headache patients in the trial did not respond" (Peres MFP & Rozen TD, Cephalalgia 2001, DOI 10.1046/j.1468-2982.2001.00307.x). **[PEER-REVIEWED]**

3.4.3 Efficacy — the negative trial

Pringsheim T, Magnoux E, Dobson CF, Hamel E, Aubé M. *Melatonin as adjunctive therapy in the prophylaxis of cluster headache: a pilot study.* Headache 2002;42(8):787–792, DOI 10.1046/j.1526-4610.2002.02181.x, PMID 12390642. **[PEER-REVIEWED]**

- n=9 (**6 chronic, 3 episodic**), single-blind, melatonin added to existing prophylaxis in patients with incomplete relief
- Chronic patients: 1 month baseline diary → 1 month melatonin → 1 month placebo. Episodic: placebo then melatonin.
- Primary endpoint mean headaches/day: **no significant differences between melatonin, placebo and baseline months**
- All secondary endpoints (analgesic consumption, % mild/moderate/severe headaches): **no significant differences**
- No side effects
- Authors' conclusion: patients with chronic CH, or episodic CH uncontrolled on conventional therapy, "did not appear to gain therapeutically from adding melatonin to their usual treatment regimens"

The authors offer a face-saving hypothesis worth taking seriously: melatonin's phase-shifting properties might mediate its effect in *episodic* CH, and **treatment from the very beginning of the bout might be necessary to reset the circadian pacemaker**. That is a testable claim that has never been tested. **Unknown.**

3.4.4 The contradictory case reports

Peres MFP & Rozen TD. *Melatonin in the preventive treatment of chronic cluster headache.* Cephalalgia 2001;21(10):993–995, DOI 10.1046/j.1468-2982.2001.00307.x. **[PEER-REVIEWED]**

Two **chronic** CH patients, melatonin **9 mg at bedtime** (9 rather than Leone's 10 mg simply because 3 mg tablets were what was available in the US), added to verapamil.

- **Case 1**: 38-year-old man, 20-year history, 6–7 attacks/day *despite verapamil 640 mg*, headache reliably 1 hour after falling asleep, naps also triggered attacks, never a headache-free period >14 days, had failed steroid tapers, valproic acid 2000 mg, verapamil 640 mg and lithium 900 mg. On melatonin: **significant improvement within 2 days, became headache-free, remained so for 6 months**, sleep no longer disrupted, no side effects.
- **Case 2**: 40-year-old man, 8-year history, 3 attacks/day, one always 40 minutes after sleep onset. On melatonin: **immediate pain relief, daytime and nocturnal headaches completely abated, headache-free for 8 months**, did not want to discontinue.

The authors themselves note a placebo response or spontaneous remission could account for this, though they considered a therapeutic effect most likely, and called for a double-blind placebo-controlled trial in chronic CH. **That trial has still not been done, 25 years later.**

The conflict is direct and unresolved. Leone 1996: 2/2 chronic patients failed. Pringsheim 2002: 6 chronic patients, no benefit. Peres & Rozen 2001: 2/2 chronic patients became headache-free within days. n=10 chronic patients total across the entire randomised-ish literature. This is not enough evidence to conclude anything. **Unknown.**

3.4.5 Dosing and safety

- Table dose **10 mg**; evidence level `(+)` = **questionable**; adverse events daytime sleepiness, headache, dizziness, hypothermia; contraindications **depression, coagulation disorders**; "very good tolerability" (PMC8748342). **[PEER-REVIEWED]**
- **Australian Prescriber**: Grade **2C**; start **4 mg**, titrate to **8–10 mg** (Aust Prescr 2022;45:15–20). **[PEER-REVIEWED]** *Note: in Australia, 2 mg modified-release melatonin (Circadin) is the registered product; 10 mg immediate-release generally requires compounding or import, which is a practical access wrinkle.*
- Recommended as an option for patients who don't tolerate lithium or verapamil (PMC8748342).

The honest summary of melatonin's appeal: it is cheap, essentially free of serious side effects across every study cited above, and mechanistically well-motivated. It is also probably not very effective, and probably least effective in exactly the population reading this. Its main virtue is a superb risk-benefit ratio at low expected benefit — a reasonable add-on, a poor primary strategy.

3.4.6 Community view — the sharpest divergence in the chapter

Melatonin sits in the LOW self-reported efficacy clade in the largest citizen-science synthesis available, grouped with valproic acid, gabapentin, amitriptyline and propranolol (Rusanen et al. 2022, PMC9436841). **[CITIZEN-SCIENCE]**

This is a notable divergence: melatonin has a *positive randomised trial* (Leone 1996) and yet patients rank it alongside drugs with no evidence at all. Three readings, all plausible: (a) patients are right and the 1996 pilot was a small-n false positive; (b) patients are mostly chronic or treatment-refractory, exactly the group Leone's trial showed doesn't respond; (c) patients are using 3–5 mg supermarket melatonin, not 10 mg at a fixed nightly time, and are effectively testing a different intervention. I cannot distinguish these from available data. **Contested.**

3.5 Other Weaker-Evidence Preventives

Grouped roughly from "has a positive RCT" down to "has a case series and a hope."

3.5.1 Warfarin / anticoagulation — the surprising one

Hakim SM. *Warfarin for refractory chronic cluster headache: a randomized pilot study.* Headache 2011;51(5):713–725, PMID 21395575. **[PEER-REVIEWED]**

- n=34, randomised **crossover**, refractory **chronic** CH
- Warfarin titrated to **INR 1.5–1.9** (deliberately sub-therapeutic by cardiac standards)
- Remission ≥4 weeks: **50% (warfarin) vs 11.8% (placebo), p=0.004**
- Absolute risk reduction **0.38 (95% CI 0.18–0.58)**
- **NNT 2.6 (95% CI 1.7–5.5)**
- Hazard ratio **5.26 (95% CI 2.13–13.03)**

This is, on paper, the single best NNT in this entire chapter — better than verapamil's, in a refractory chronic population, from a randomised crossover design. The AHS 2016 guideline acknowledged it as a newly evaluated treatment with a **positive** study, but graded it only **Level C** (Robbins et al. 2016, PMID 27432623). **[PEER-REVIEWED]**

Why isn't everyone on warfarin? Because n=34, single-centre, never replicated in 15 years; because the mechanism is unexplained (possibly anti-inflammatory or endothelial rather than anticoagulant, since the target INR is low); and because indefinite anticoagulation in a young population carries real bleeding risk. But the near-total silence on this finding is odd, and it is the clearest example in this chapter of a positive result that the field simply did not pursue. **A genuine unexplained gap.**

3.5.2 Civamide / capsaicin (intranasal, TRPV1 desensitisation)

Saper JR, Klapper J, Mathew NT, Rapoport A, Phillips SB, Bernstein JE. *Intranasal civamide for the treatment of episodic cluster headaches.* Arch Neurol 2002;59(6):990–994, PMID 12056936. **[PEER-REVIEWED]** n=28, civamide 50 µg/day intranasal × 7 days. Attack reduction **−55.5% vs −25.9%, p=0.03**. Adverse effects: **nasal burning in 14/18**, lacrimation in 9/18.

Marks DR, Rapoport A, Padla D, Weeks R, Rosum R, Sheftell F, Arrowsmith F. *A double-blind placebo-controlled trial of intranasal capsaicin for cluster headache.* Cephalalgia 1993;13(2):114–116, DOI 10.1046/j.1468-2982.1993.1302114.x, PMID 8495452. **[PEER-REVIEWED]** Capsaicin in the ipsilateral nostril × 7 days, severity recorded 15 days. On **days 8–15** headaches were significantly less severe with capsaicin than placebo; within the capsaicin group severity significantly decreased days 8–15 vs days 1–7; **no significant decrease in the placebo group**. **Episodic patients appeared to benefit more than chronic patients.** Sample size, capsaicin concentration, exact p-values and CIs are not reported in the abstract. Rationale: topical capsaicin desensitises sensory neurons by depleting nerve terminals of substance P.

Two positive randomised trials for the same mechanism, 9 years apart, and neither drug is in routine use. Civamide was never commercialised for CH. The nasal burning (14/18) is presumably why. Note again the episodic > chronic pattern.

3.5.3 Sodium valproate / divalproex — negative RCT, positive open studies

El Amrani M, Massiou H, Bousser MG. *A negative trial of sodium valproate in cluster headache: methodological issues.* Cephalalgia 2002;22(3):205–208, PMID 12047460. **[PEER-REVIEWED]** *(Direct PubMed fetch failed with an NCBI access block; the trial details below come from the review that reproduces them.)*

Per PMC8748342: **[PEER-REVIEWED]** - Randomised, double-blind, placebo-controlled: **n=96 (50 valproate, 46 placebo; 17 chronic)**, 1000–2000 mg/day × 2 weeks. Primary endpoint ≥50% reduction in mean weekly attacks: **no statistical difference vs placebo** - Open-label study: 73% experienced pain reduction - Open study n=15, 600–2000 mg/day: 11/15 treatment success, 9/15 cessation of attacks

The review's verdict is blunt: **"there is no scientific evidence that sodium valproate is effective in cluster headache."** Treatment of **women of childbearing age is contraindicated** (teratogenicity/neurodevelopmental risk). No valproate row appears in that review's summary table. Note the internal inconsistency the review itself flags: its own abstract and key points describe divalproex as "possibly effective based on open trials" while the detailed section says there is no evidence. **A contradiction within a single peer-reviewed paper — flagged, not resolved.**

Community data agree with the negative RCT: **valproic acid is in the low self-reported efficacy clade** (Rusanen 2022, PMC9436841). **[CITIZEN-SCIENCE]** This is a case where trial data and community experience converge cleanly on "no."

3.5.4 Gabapentin

Vuković V, Lovrenčić-Huzjan A, Budišić M, Demarin V. *Gabapentin in the prophylaxis of cluster headache: an observational open label study.* Acta Clin Croat 2009;48(3):311–314, PMID 20055254. **[PEER-REVIEWED]** *(Croatian institution — Sestre milosrdnice University Hospital, Zagreb — published in English.)*

n=14 (9 M, 5 F, mean age 42±15), maintenance 900–2400 mg/day (900 mg n=6, 1200 mg n=2, 1800 mg n=4, 2400 mg n=2), mean treatment 3.5 months (2–5). Response reported within **1–2 weeks**.

- Headache days/4 weeks: **378 → 210 total; mean 27 → 15**; a reduction of 12 headache days per 4 weeks = **44.94%**
- Pain intensity: 25% reduction in 1 (7.14%), **50% reduction in 8 (57.14%)**, 75% reduction in 3 (21.4%), **non-responders 2 (14.28%)**
- No recurrent headaches after completing therapy
- Adverse events in **8/14 (57.14%)**, mild-moderate: drowsiness, dizziness, slowness, constipation. **Zero drop-outs.**
- **No p-values, no confidence intervals, no control group reported**

Other data (PMC8748342): a case report of refractory chronic CH becoming symptom-free on 1800 mg/day after lithium, verapamil and pizotifen failed; a small Italian study n=12 (8 ep, 4 chr) at 1000 mg showing significant reduction in cluster period length; an open-label study in refractory chronic CH n=8 with 6/8 responding.

Evidence level `(+)` = **questionable**; dose 1000–1800 mg; AEs dizziness, somnolence, peripheral oedema; contraindications suicidal thoughts, depression, myasthenia gravis, decreased lung function, COPD, chronic kidney disease.

Gabapentin is in the LOW self-reported efficacy clade in the community synthesis (PMC9436841), and one r/clusterheads user reported skipping gabapentin entirely on the basis that "many people had not responded well to gabapentin" (r/clusterheads NHS thread); another said flatly that gabapentin "did not help" (same thread). **[CITIZEN-SCIENCE / COMMUNITY-REPORT]** Again, community and evidence converge on "probably not."

3.5.5 Baclofen

Hering-Hanit R, Gadoth N. *The use of baclofen in cluster headache.* Curr Pain Headache Rep 2001;5(1):79–82, DOI 10.1007/s11916-001-0014-1, PMID 11252142. Meir General Hospital, Sapir Medical Center, Kfar Saba, **Israel**. **[PEER-REVIEWED]**

Pilot study, **n=16 symptomatic patients**, baclofen **15–30 mg daily in three divided doses**, given through the cluster period plus 2 weeks after. No comparator, no randomisation or blinding stated, episodic/chronic split not stated.

- **12 patients reported cessation of attacks within 1 week**
- 1 further patient substantially better, attack-free by end of the following week
- **3 patients' attacks WORSENED** — corticosteroids prescribed for all three, one also given verapamil
- 3 patients had a subsequent cluster period which cleared with a second course
- No adverse-event rate, no p-values, no CIs, no responder percentages reported
- Authors: baclofen "seemed to be effective, safe, and well tolerated"

13/16 apparent responses is a striking-looking result, but with no control group in a condition with a large documented placebo response and spontaneous bout termination, it means very little. That **3/16 got worse** is at least as interesting and is essentially never mentioned when baclofen is listed as an option. No baclofen row appears in the PMC8748342 summary table. This trial has not been replicated in 25 years. **Unknown.**

3.5.6 Clonidine (transdermal)

D'Andrea G, Perini F, Granella F, Cananzi A, Sergi A. *Efficacy of transdermal clonidine in short-term treatment of cluster headache: a pilot study.* Cephalalgia 1995;15(5):430–433, DOI 10.1046/j.1468-2982.1995.1505430.x, PMID 8536305. Este Hospital USL 22, Este, **Italy**. **[PEER-REVIEWED]**

Open pilot, no control, n=13 (**8 episodic, 5 chronic**), transdermal clonidine **5–7.5 mg for 1 week** after a run-in week:

Endpoint	Before	During	p
Weekly attack frequency	17.7 ± 7.0	**8.7 ± 6.6**	**0.0005**
Pain intensity (VAS, mm)	98.0 ± 7.2	**41.1 ± 36.1**	**0.001**
Attack duration (min)	59.3 ± 21.9	**34.3 ± 24.6**	**0.02**

Rationale: reduced noradrenergic tone in both active and remission phases of CH; sharp sympathetic fluctuations as attack triggers; clonidine as an α2-presynaptic agonist producing central sympathoinhibition. **No adverse-event data reported at all** — which for a drug that causes sedation and hypotension is a conspicuous omission. No responder rate, no NNT, no episodic-vs-chronic breakdown, no follow-up beyond one week.

A 50% attack reduction with p=0.0005 looks impressive until you remember there was no placebo arm and CH attack frequency fluctuates enormously week to week. **Unreplicated, 30 years old, no clonidine row in modern summary tables. Unknown.**

3.5.7 Pizotifen

Pizotifen (a 5-HT2 antagonist, still available in Australia and the UK, unavailable in the US) has essentially **no modern CH evidence**. The only CH-specific data traceable is **Ekbom 1969, pizotifen up to 2.5 mg/day, n=28**, catalogued in the placebo-response review (Nilsson Remahl AIM, Laudon Meyer E, Cordonnier C, Goadsby PJ. *Placebo Response in Cluster Headache Trials: A Review*, Cephalalgia 2003, DOI 10.1046/j.1468-2982.2003.00531.x). **[PEER-REVIEWED]** It appears in the Rusanen review's list of drugs with "positive clinical studies" for CH prophylaxis (PMC9436841) but with no numbers attached. It also appears in the literature as a drug that had *failed* before gabapentin worked in a refractory case (PMC8748342).

Most contemporary pizotifen evidence is for migraine, not CH, and even there certainty is very low (systematic review and meta-analysis, *Headache Medicine*). **[PEER-REVIEWED]** No pizotifen row appears in any modern CH summary table reviewed here. **Verdict: essentially unevidenced in CH. If offered it, ask what the evidence is.**

3.5.8 Botulinum toxin

Three distinct approaches, none established:

Sphenopalatine ganglion injection — Trondheim pilot, PMC4853809, NCT02019017. **[PEER-REVIEWED]** n=10, 25 or 50 IU onabotulinumtoxinA: attacks/week **18±12 → 11±14, p=0.038**. But **7/10 had adverse events, including one severe posterior epistaxis**. n=10, open-label, wide standard deviations — the p-value should not be over-read.

Other data (PMC8748342): **[PEER-REVIEWED]** - Open trial in chronic CH, 17 male completers, 28 weeks: **59%** achieved >50% reduction in cumulative headache minutes - Open-label, n=10, injections toward the **otic ganglion**: **no statistically significant reduction** in attacks/week at month 2 vs baseline - A further SPG trial listed as ongoing

No botulinum toxin row appears in that review's summary table. Rationale is CGRP-linked: botulinum toxin reduces plasma CGRP levels in chronic migraine, and CGRP is elevated in CH (PMC4646474). **[PEER-REVIEWED]** Given §6, that rationale now looks shakier than it did.

Verdict: promising signal in SPG injection, meaningful procedural risk, no controlled evidence. Unknown.

3.5.9 Briefly: agents evaluated and found negative

From the AHS 2016 guideline (PMID 27432623): **[PEER-REVIEWED]**

Treatment	Level	Study direction
Suboccipital steroid injection	**A**	Positive (2nd Class I study added) — the only Level A preventive
Deep brain stimulation	B	**Negative**
Warfarin	C	Positive
Cimetidine/chlorpheniramine	C	**Negative**
Candesartan	C	**Negative**
Frovatriptan	U	Not characterised

Also negative or unevidenced elsewhere: methysergide has **no placebo-controlled trials**, benefit 20–73% across open studies, more effective in episodic CH, and carries long-term risk of retroperitoneal, pulmonary, cardiac and pleural fibrosis — the manufacturer ceased production (PMC4646474). **[PEER-REVIEWED]** Amitriptyline, propranolol and indomethacin all sit in the **low self-reported efficacy clade** and none are recommended in current guidance (PMC9436841). **[CITIZEN-SCIENCE]**

3.6 CGRP Monoclonal Antibodies

This is the most consequential and most confusing section, and it is where the trial-vs-community gap is widest. *(Editor's note: the registry-level trial-by-trial view, including erenumab/CHERUB01, is tabulated in Part VII, §5.1.1; the contested CGRP biology is in Part II, §3.4.)*

3.6.1 CGAL: galcanezumab in episodic CH — the one positive trial

Goadsby PJ, Dodick DW, Leone M, et al. *Trial of Galcanezumab in Prevention of Episodic Cluster Headache.* N Engl J Med 2019;381(2):132–141, DOI 10.1056/NEJMoa1813440, NCT02397473. **[PEER-REVIEWED]**

Item	Detail
n	106 randomised (49 galcanezumab, 57 placebo)
Dose	**300 mg SC** at month 0 and month 1 (note: 300 mg, not the 120 mg migraine dose)
Primary endpoint	Mean change in weekly attack frequency, **weeks 1–3**
Result	**−8.7 ± 1.4 vs −5.2 ± 1.3**; difference **3.5 (95% CI 0.2–6.7), p=0.04**
Mean % reduction	**52% vs 27%**
Week-3 ≥50% responders	**71% vs 53%, p=0.046, OR 2.4 (95% CI 1.0–5.7)**
Adverse events	43% vs 33%; **no serious AEs**; injection-site pain 8%
Recruitment	**Halted early due to enrolment difficulty**

Read the confidence intervals. The primary difference CI is **0.2 to 6.7** — the lower bound almost touches zero. The responder OR CI is **1.0 to 5.7** — the lower bound *is* 1.0. This is a trial that scraped over the significance line, in a population smaller than planned, in **episodic** CH only.

Critically: the effect converged with placebo after week 4 — by week 5 the odds ratio was **0.3** (i.e. numerically favouring placebo). The drug's apparent benefit is concentrated in the first three weeks, in a condition where episodic bouts spontaneously remit. This is the single most important caveat about CGAL and it is rarely mentioned.

Regulatory divergence — a genuine conflict. The FDA approved galcanezumab (Emgality) 300 mg for episodic CH in the US on the basis of this trial. The **EMA rejected it**, stating superiority "not convincingly demonstrated." **[PREPRINT/TRIAL]** Two competent regulators looked at the same single trial and reached opposite conclusions. That should tell you how marginal the result

is.

Note also that PMC8748342's summary table lists galcanezumab for episodic CH as **"120 mg s.c. once monthly"** with evidence level `+`. **This appears to be an error** — CGAL used 300 mg, and 120 mg is the migraine dose. A patient or prescriber relying on that table would underdose by 60%. Flagged as a documented discrepancy in a peer-reviewed review.

3.6.2 The chronic CH galcanezumab trial — the failure

Dodick DW, Goadsby PJ, Lucas C, et al. *Phase 3 randomized, placebo-controlled study of galcanezumab in patients with chronic cluster headache: Results from 3-month double-blind treatment.* Cephalalgia 2020;40(9):935–948, DOI 10.1177/0333102420905321, PMID 32050782, NCT02438826. **[PEER-REVIEWED]**

- n=237 (117 galcanezumab 300 mg monthly, 120 placebo)
- Weekly attack frequency change: **−5.4 vs −4.6, p=0.334**
- **Primary AND key secondary endpoints not met**

Larger trial, longer treatment, same drug, same dose — and it failed outright in chronic CH.

An important factual correction that circulates wrongly: the chronic trial was **completed**, not stopped for futility. This was explicitly corrected in the literature by **Wenzel R, et al.**, *Neurol Sci* 2020;41:2641, PMID 32266593, PMC7419360. **[PEER-REVIEWED]** If you see "the chronic trial was stopped for futility," that is wrong.

Why did it fail in chronic CH? Competing hypotheses

None of these are established. All are labelled as hypotheses.

1. **CGRP may not be the driver in chronic CH.** A prospective controlled study (n=297, *Cephalalgia* 2024) found **plasma CGRP is LOWER in CH patients than in controls** — the opposite of the assumption underpinning the whole drug class. **[PEER-REVIEWED]** This directly undercuts the mechanistic rationale. Note this conflicts with older data showing elevated CGRP in the external jugular vein *during attacks* and elevated interictal CGRP during bouts in episodic CH (PMC4646474). **[PEER-REVIEWED]** Possible reconciliation: CGRP elevation may be attack-associated and episodic-bout-associated rather than a chronic-state feature. **Contested.**
2. **PACAP** (pituitary adenylate cyclase-activating polypeptide) may be the more relevant target in CH than CGRP. **[PREPRINT/TRIAL]** — hypothesis stage.
3. **Regression to the mean in episodic CH.** The episodic trial's effect was concentrated in weeks 1–3 and vanished by week 5. Bouts end on their own. Chronic CH has no bout to end, so no spontaneous-remission tailwind for the drug to ride. Under this reading, **CGAL's positive result may be substantially an artefact of episodic natural history** — and the chronic failure is the more honest measurement of the drug. This is a hypothesis, but it fits the data uncomfortably well.
4. **Dose/exposure**: the same 300 mg dose that worked marginally in episodic may be insufficient for a continuously active pathophysiology. Unresolved.

3.6.3 Fremanezumab — both trials terminated

Fremanezumab was trialled in **both** episodic and chronic CH. **Both trials were terminated early for futility.** The chronic trial was **NCT02964338** (EU CTR 2016-003278-42). **There is no journal publication of the results. [PREPRINT/TRIAL]**

This is a meaningful and under-discussed fact: a full anti-CGRP ligand antibody programme in CH was abandoned, and the data were never published in the peer-reviewed literature. Publication bias in this field runs in the direction you would expect.

3.6.4 Eptinezumab: ALLEVIATE and CHRONICLE

ALLEVIATE — failed

Jensen RH, Tassorelli C, Tepper SJ, et al. *Eptinezumab for the Preventive Treatment of Episodic Cluster Headache: The ALLEVIATE Randomized Clinical Trial.* JAMA Neurol 2025;82(7):706–714, DOI 10.1001/jamaneurol.2025.1317, NCT04688775. **[PEER-REVIEWED]**

- n=231, eptinezumab **400 mg IV**
- Primary endpoint, change in weekly attacks weeks 1–2: **−4.0 vs −4.6**; difference **0.7 (95% CI −1.3 to 2.6), p=.50**
- **FAILED. Stopped for futility at interim analysis.**

Note the direction: the placebo group did *numerically better* than the drug group.

A documented discrepancy worth knowing about

In 2024, Lundbeck issued a press release stating that **"VYEPTI met its primary endpoint"** in cluster headache (Lundbeck newsroom, 2024). **[PREPRINT/TRIAL]** The peer-reviewed publication a year later reports a failed primary endpoint (p=.50) and a trial stopped for futility. I have not been able to reconcile these two statements from the material gathered — the press release may refer to a different analysis, a different endpoint definition, or a different study population. **This is flagged as a documented discrepancy between a company communication and the subsequent peer-reviewed publication, not as an established finding of misrepresentation. Contested / unresolved.** It is, however, an excellent reason to treat pharmaceutical press releases about CH as advertising until the paper appears.

CHRONICLE — open-label, no control

Tassorelli C, Jensen RH, Goadsby PJ, et al. Lancet Neurol 2025;24(5):429–440, DOI 10.1016/S1474-4422(25)00065-1, PMID 40252664, NCT05064397. **[PEER-REVIEWED]** Open-label, n=131, 400 mg IV every 12 weeks over 60 weeks. TEAEs **81%**; 4 withdrawals; **no treatment-related serious adverse events**; "consistent improvements" in attack frequency — **but there is no placebo control**, so the efficacy statement carries essentially no weight. The study is a safety/tolerability result, and on that narrow question it is reassuring.

A German-language summary of CHRONICLE is available at Thieme. **[PEER-REVIEWED]** *(German-language source.)*

3.6.5 The 2026 meta-analyses: do they genuinely conflict?

Two meta-analyses published within months of each other in 2026 appear to reach opposite conclusions. **They do partially conflict — but the conflict is smaller and more interesting than it looks.**

Meta-analysis A — network meta-analysis, negative

Muneer et al. *Neurol Sci* 2026;47(6):488, DOI 10.1007/s10072-026-09078-1, PMID 42118310. **[PEER-REVIEWED]** 5 RCTs, ~1000 patients. Outcome: **weekly attack frequency**. Result: **no agent statistically significant.** Galcanezumab −0.81, fremanezumab pooled −0.27, eptinezumab −0.17 weekly attacks; fremanezumab 675/225 mg **+0.71 (numerically worse than placebo)**.

Meta-analysis B — systematic review and meta-analysis, positive in episodic only

Kolakowski L, Kleinsorge MT, Wegener S, Pohl H. *Efficacy and effectiveness of anti-CGRP monoclonal antibodies treatment in the prevention of cluster headache attacks: A systematic review and meta-analysis.* Cephalalgia 2026;46(4):3331024261434209, DOI 10.1177/03331024261434209, PMID 41961550. PROSPERO CRD420250609351. **[PEER-REVIEWED]** *(Swiss group — Zurich.)*

Searched Embase, Medline, Cochrane CENTRAL, Web of Science; 734 records → 25 articles, **1,587 patients**; RoB 2 and ROBINS-I; random-effects, odds ratios. Primary emphasis: **≥50% responder rate closest to 4 weeks** (chosen because it was reported in almost all studies).

Population	Effect	95% CI	p
Episodic CH	**OR 1.65**	**1.07–2.55**	**0.02 — significant**
Chronic CH	OR 1.07	0.78–1.48	0.68 — **not significant**

Galcanezumab 300 mg and eptinezumab 400 mg were both identified as more effective than placebo on the ≥50% responder endpoint in episodic CH. For **weekly attack frequency at week 4**, a significant mean reduction was seen **only for galcanezumab 300 mg (p=0.04)** — effect size and CI not stated in the abstract.

Adjudication

They agree completely on chronic CH: no effect. OR 1.07 (0.78–1.48), p=0.68 in one; no significant agent in the other. **For a chronic daily patient, both 2026 meta-analyses say the same thing, and it is not encouraging.**

They disagree on episodic CH — but on different endpoints. Meta-analysis A used **weekly attack frequency** (a continuous measure) and found nothing. Meta-analysis B used **≥50% responder rate at 4 weeks** (a dichotomised measure) and found OR 1.65. Meta-analysis B *also* found weekly attack frequency significant for galcanezumab specifically (p=0.04), which is closer to B's endpoint and closer to A's galcanezumab point estimate of −0.81.

So the conflict is **partly a genuine disagreement about galcanezumab in episodic CH, and partly an endpoint-selection artefact.** Responder-rate analyses are more sensitive to a small subgroup of strong responders; continuous mean-difference analyses are diluted by non-responders. Both are defensible; they answer slightly different questions. B also included non-randomised evidence (case series, case reports) alongside RCTs, which A did not — a further source of divergence, and a reason to weight A more heavily for a strictly causal question.

My reading, stated as a judgement rather than a finding: anti-CGRP mAbs probably produce a real but modest benefit in a minority of episodic CH patients, concentrated early, and probably produce nothing detectable in chronic CH. Both meta-analyses are consistent with that. **Neither meta-analysis reports NNT.** Meta-analysis B reports no adverse-event data, no GRADE assessment and no certainty-of-evidence rating at abstract level.

3.6.6 The real-world data — where the community and the trials diverge hardest

Lamas Pérez R, Millán-Vázquez M, González-Oria C, et al. Cephalalgia 2024;44(3):3331024231226181, DOI 10.1177/03331024231226181, PMID 38501892. Seville, **Spain**. **[PEER-REVIEWED]** *(Spanish research team; published in English.)*

n=21 refractory chronic CH — exactly the population the RCT said galcanezumab doesn't help — treated off-label at 240 mg:

- Median monthly attacks **60 → 31 at 1 month, p=0.003**
- **≥50% reduction: 47.6% at 1 month, 46.6% at 3 months**
- **≥75% reduction: 19% at 1 month, 26.6% at 3 months**
- Adverse events 52%, mostly mild

A ~47% responder rate in refractory chronic CH, from the drug that failed its chronic RCT. This is the crux of the trial-vs-real-world gap. **Both cannot be straightforwardly true.** Candidate explanations: (a) open-label expectation effects in an uncontrolled study — the most likely single explanation; (b) regression to the mean, since patients start the drug when they are at their worst; (c) a genuine responder subgroup that a 3-month parallel-group RCT diluted; (d) the different dose (240 mg vs 300 mg) — unlikely to explain a benefit at a *lower* dose. Note that the 2026 Kolakowski meta-analysis explicitly acknowledges that "some non-randomised trials reported findings suggesting an effect in chronic cluster headache" while its own pooled randomised estimate was null (PMID 41961550). **[PEER-REVIEWED]** The field is aware of this tension and has not resolved it. **Contested.**

3.6.7 What the community says about Emgality — in detail

From three r/clusterheads threads. **[COMMUNITY-REPORT]** throughout.

Doses used are far above label

Reported: “3 × 100 mg monthly”, “three injections each month”, “three Emgality shots per month”, “300 mg each month, all at once”, “three injections at the start of a cluster” (Emgality for chronic CH thread; How long for Emgality to kick in). One patient noted the regular migraine dose “worked but wore off after two weeks” and moved to 300 mg dosing. Several described the effect “wearing off towards the end of the month.”

This end-of-month wearing-off pattern is reported repeatedly and has no counterpart in the trial literature, which used monthly dosing and did not report within-cycle fluctuation. If real, it argues for more frequent dosing or higher trough levels — an entirely untested hypothesis generated by patients. Worth noting as a legitimate research question that came from the community, not the clinic.

Time to effect — much longer than trials suggest

Trials measured the primary endpoint at weeks 1–3. Patients report:

> “Truthfully I’d say it was in month three or so that I noticed a change in the intensity and a small change in frequency.” (r/clusterheads)

Others: “the pain was gone after a week”; “a difference within a few days”; one commenter asserted it “may take up to five months for chronic sufferers to achieve full benefit” (no source cited). One reported **headaches WORSENING for a couple of weeks after starting** before benefit arrived (r/clusterheads).

Divergence: CGAL’s whole positive result lives in weeks 1–3. Much of the community reports benefit arriving at months 3–5. If the community is right, CGAL measured the wrong window. If the trials are right, the late “responses” are regression to the mean or bout cycling. Unresolved, but the disagreement is stark.

Effectiveness in chronic CH — bimodal and often time-limited

Reported outcomes from one thread of ~12 participants (r/clusterheads):

Reported outcome	Count
No benefit at 6 months	1
No benefit at 7 months	1
Worked ~6 months then stopped completely	1
Worked 6–12 months then stopped	1
Worked 12 months (then refills discontinued)	1
Worked 2 years then stopped after daylight saving began	1
Ongoing benefit	2

> “I was chronic, and Emgality has helped me return to a normal lifestyle.” — headaches went from multiple daily at 8–10/10 to 4–5/10

> “It worked well for roughly six months, achieving over 90% effectiveness.” — and this from someone who said it was “the only preventive that provided more than 10–20% efficacy during nearly seven years of chronic illness,” before ceasing to work entirely

> "I tried the 6-month course, but it caused hair loss and didn't help my chronic headaches."

> "starting was tough—my headaches actually worsened for a couple of weeks—but since then I haven't had any cluster attacks, except when I miss an injection."

Two patterns here have no trial correlate whatsoever and deserve flagging as unexplained:

1. **Tachyphylaxis.** Multiple independent reports of excellent response for 6–24 months followed by complete and permanent loss of effect. The trials ran 3 months (chronic) and 8 weeks (episodic) — **structurally incapable of detecting this**. The Seville real-world study ran 3 months. Nobody has looked. **Unknown, and important.**
2. **One patient reported Emgality stopped working "after daylight saving time began"** (r/clusterheads). **[COMMUNITY-REPORT]** — n=1, almost certainly coincidence. Recorded only because CH has a documented seasonal/circadian structure (§4.1: peaks in March/April and September/October/November, i.e. around the equinoxes and around DST transitions in both hemispheres), which makes it the one coincidence in this chapter with a non-absurd mechanism. **Unverified, almost certainly noise, but noted.**

Side effects patients report that trials don't emphasise

- **Hair loss** — reported independently in three separate threads by at least four different people (1, 2, 3). "I started noticing more hair in my comb each morning." One described "severe hair loss" that vitamins did not help. **CGAL reported no serious AEs and 8% injection-site pain; alopecia is not a labelled galcanezumab adverse effect.** This is one of the clearest examples in the chapter of a community signal absent from trial data. Whether it is causal is **unknown** — but four independent reports across three threads is above the noise floor for an anecdotal source, and post-marketing alopecia reports for CGRP mAbs do exist in the wider migraine community.
- **Weight gain** — reported by at least two people, one estimating 5–10 lb over two years and considering it a fair trade.
- **Frequent urination** in the first two weeks after injection, described as "pretty ridiculous."
- **Sluggishness** in the first few days post-injection.
- Injection-site appearance "like a punched stomach."

The trial-reported profile (injection-site pain, no serious AEs) and the community-reported profile (hair loss, weight gain, urinary frequency) barely overlap. Trials of 8 weeks to 3 months in ~340 patients total are not powered to detect uncommon or slow-onset effects.

Access is a major, under-documented barrier

UK/NHS (r/clusterheads NHS thread):

> "If you want it through the NHS, your neurologist must apply for external funding."

The neurologist must demonstrate "all other options have been exhausted"; the patient must have tried "nearly every other NHS drug"; and one refractory chronic patient was "only permitted a three-month trial." No commenter in that thread confirmed successfully obtaining it long-term.

US: "exhausted from battling insurance"; one patient's refills were **discontinued after 12 months** despite the drug working, with no reason given — they switched to Qulipta (atogepant), reporting daily clusters fell from four to one or two (r/clusterheads). **[COMMUNITY-REPORT]** *(Atogepant in CH is off-label with no trial evidence; this is a single anecdote.)*

Australia: galcanezumab (Emgality) is TGA-approved and PBS-listed, but **only for chronic migraine and high-frequency episodic migraine — not for cluster headache** (PBS galcanezumab listing; Australian Government Department of Health announcement on expanded Emgality PBS listing). **[PREPRINT/TRIAL]** (government/regulatory documents) Migraine Australia describes it as "on PBS for a very limited criteria of people, available through a discount program for others," and is actively campaigning for expanded criteria (Migraine Australia). **[COMMUNITY-REPORT]** (patient advocacy organisation) Headache Australia notes the PBAC recommended galcanezumab for chronic migraine in July 2019 after failure of at least three preventives (Headache Australia). **[COMMUNITY-REPORT]**

Practical implication for an Australian chronic CH patient: there is no PBS pathway for Emgality in cluster headache. Private cost is substantial (the PBS DPMQ for a single 120 mg pen is listed at **$523.36** — and the CH dose is 300 mg, i.e. multiple pens). Realistic routes are a compassionate/discount access programme, private purchase, or a specialist arguing the case individually. **Given that both 2026 meta-analyses found no significant effect in chronic CH, spending that money on a chronic-CH indication is a decision to make with clear eyes about the evidence.**

3.6.8 Summary judgement on CGRP mAbs

Question	Answer	Confidence
Works in episodic CH?	Marginally, early, in a subset	Low-moderate; one trial scraped p=0.04, EMA rejected it, meta-analyses split by endpoint
Works in chronic CH?	**No detectable effect in randomised data**	Moderate-high; one adequately sized negative RCT plus two concordant 2026 meta-analyses
Real-world chronic response ~47%?	Reported, uncontrolled, plausibly inflated	Low
Tachyphylaxis after 6–24 months?	Repeatedly reported by patients, **never studied**	Unknown
Hair loss?	Repeatedly reported by patients, not a labelled AE	Unknown
Safe?	Yes, on available data — no treatment-related SAEs across CGAL, chronic trial and CHRONICLE	Moderate-high

---

4. Neuromodulation & Procedures

This category covers non-invasive and implanted devices, and surgical procedures, generally reserved for people who have failed multiple preventive drug trials — refractory chronic CH. Response rates here are inflated relative to the general CH population by design, because trial cohorts are pre-selected for having already failed everything else; that caveat applies to every efficacy figure in this section.

4.0 Framing note: what "refractory chronic CH" means, and why it matters here

Every device and procedure in this chapter is aimed at a specific population, and it is worth being precise about the entry criteria, because response rates are quoted for people who have already failed everything else.

[PEER-REVIEWED] The European Headache Federation consensus defines refractory chronic cluster headache (rCCH) as: "a situation that fulfills the criteria of ICHD-3 beta for CCH with at least three severe attacks per week despite at least three consecutive trials of adequate preventive treatments" (Mitsikostas DD, Edvinsson L, Jensen RH, Katsarava Z, Lampl C, Negro A, Osipova V, Paemeleire K, Siva A, Valade D, Martelletti P. *J Headache Pain* 2014;15(1):79. DOI 10.1186/1129-2377-15-79, PMID 25430992).

The formal criteria are (verbatim from that consensus):

- **A.** “Headache attacks fulfilling the ICHD-3 beta criteria for chronic cluster headache (CCH), or probable cluster headache (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 CCH 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.”

[PEER-REVIEWED] The same consensus lists the preventives that count towards criterion C: “verapamil, lithium, oral or iv steroids, greater occipital nerve infiltration, topiramate, methysergide, ergots, civamide and long acting triptans. Among them verapamil has better documentation. Some agents may be not available across all European countries” (EHF consensus 2014). It also cautions that the indomethacin test should be used to exclude paroxysmal hemicrania, and that SUNA/SUNCT, cluster-tic syndrome and persistent idiopathic facial pain should be ruled out first.

[PEER-REVIEWED] The consensus was cautious about this whole chapter’s subject matter: “The new frontier for the treatment of the subset of patients with rCCH could be neuromodulation, an interesting approach but still not sufficiently validated” (EHF consensus 2014). That was 2014; the picture in 2026 is somewhat better evidenced but commercially worse.

[PEER-REVIEWED] A 2021 narrative review of all neurostimulation methods in chronic CH landed on a blunt summary: “Altogether, only nVNS and SPG stimulation are supported by at least one positive sham-controlled clinical trial for preventive and acute attack (only SPG stimulation) treatment… The evidence for these neurostimulation methods in the treatment of chronic cluster headache is poor and in part contradictive. However, except deep brain stimulation, tolerability and safety of these methods are good so that in refractory situations application might be justified in individual cases” (Neurostimulation Treatment in Chronic Cluster Headache — a Narrative Review, *Neurol Ther* / PMC8665918, 2021).

[PEER-REVIEWED] An important methodological caveat from that same review, and one that is rarely stated aloud: “The real efficacy of the stimulation techniques remains also unknown since only refractory patients were treated (and included in trials). It might be that patients responding to oral drugs also respond to stimulation techniques” (PMC8665918, 2021). In other words: nobody knows what these devices would do in a less pre-selected population.

4.1 Non-invasive vagus nerve stimulation (nVNS / gammaCore)

4.1.1 What it is

A hand-held device held against the side of the neck over the cervical vagus nerve, delivering a 2-minute low-voltage electrical stimulation. No surgery, no implant. Used both acutely (at attack onset) and preventively (fixed daily doses).

[PREPRINT/TRIAL] In Australia, the device is the rechargeable **gammaCore Sapphire**, supplied non-sterile as a single-patient-use device. Each stimulation lasts 2 minutes; the device permits up to 30 stimulations per 24-hour period but the label instructs users not to exceed 24 per 24 hours, because “use of more than 24 stimulations per day has not been evaluated in controlled clinical trials”. Preventive use is two 2-minute stimulations morning and night; acute use is two 2-minute stimulations on the same side of the neck as needed, repeated if pain persists (Medistar Australia — gammaCore for Patients). The device is activated by a **refill card** that loads a fixed number of therapy days; “the course of therapy decreases by 1 day as every 24-hour period passes after activation” whether or not you use it (Medistar). That last detail matters financially — the clock runs even on good days.

4.1.2 ACT1 — the first sham-controlled acute trial

[PEER-REVIEWED] ACT1: Silberstein SD et al., *Headache* 2016;56(8):1317-1332, DOI 10.1111/head.12896, PMID 27593728, NCT01792817. Randomised, double-blind, sham-controlled, US multicentre.

- 150 randomised; ITT population 133 (nVNS 60, sham 73). Of these, 85 had episodic CH (eCH) and 48 chronic CH (cCH).
- **Primary endpoint:** response defined as pain intensity 0 or 1 at 15 minutes for the *first* treated attack, with no rescue medication through 60 minutes.

Population	nVNS	Sham	p
All patients (primary endpoint)	**26.7% (16/60)**	**15.1% (11/73)**	**0.10 — NOT MET**
Episodic CH	34.2% (13/38)	10.6% (5/47)	<0.01
Chronic CH	13.6% (3/22)	23.1% (6/26)	0.48

[PEER-REVIEWED] So ACT1 **failed its primary endpoint** in the overall population. The episodic subgroup was clearly positive; the chronic subgroup was **numerically worse than sham** (13.6% vs 23.1%), though not significantly so. Sustained response favoured nVNS in eCH (p=.008) and in the total population (p=.04) (Silberstein 2016, PMID 27593728).

[PEER-REVIEWED] ACT1 double-blind-period safety: ≥1 adverse event in 18 (24.7%) nVNS vs 31 (40.3%) sham; adverse device effects in 11 (15.1%) nVNS vs 24 (31.2%) sham. Lip/facial drooping, pulling or twitching occurred in 8 (11.0%) nVNS patients and 0 sham. **No serious device-related adverse events** (Silberstein 2016). Notably, the *sham* device produced more adverse events than the active device — the sham delivered a perceptible low-frequency current, which is relevant to interpreting the blinding.

4.1.3 ACT2 — the trial that made the episodic/chronic split undeniable

[PEER-REVIEWED] ACT2: Goadsby PJ et al., *Cephalalgia* 2018;38(5):959-969, DOI 10.1177/0333102417744362, NCT01958125. European, randomised, double-blind, sham-controlled.

- 102 randomised; efficacy population 92 (nVNS 48, sham 44). eCH 14/13; **cCH 34/31 — i.e. 70.6% of the efficacy population had chronic CH**, the reverse of ACT1's composition.
- **Primary endpoint:** proportion of all treated attacks achieving pain-free status at 15 minutes.

Endpoint	Population	nVNS	Sham	p
Primary — % attacks pain-free at 15 min	**All**	—	—	**0.71 — NOT MET**
% attacks pain-free at 15 min	**Episodic**	**48%**	**6%**	**<0.01**
% attacks pain-free at 15 min	**Chronic**	**5%**	**13%**	**0.13**
≥50% of attacks pain-free at 15 min	All	23%	15%	0.15
≥50% of attacks pain-free at 15 min	Episodic	36%	8%	0.16
≥50% of attacks pain-free at 15 min	Chronic	9%	7%	1.00
Responder (≥50% of attacks)	All	40%	14%	<0.01
Responder (≥50% of attacks)	**Episodic**	**64%**	**15%**	**<0.01**
Responder (≥50% of attacks)	Chronic	29%	13%	0.11

[PEER-REVIEWED] The **interaction term between CH subtype and treatment was significant (p=0.04)** (Goadsby 2018, DOI 10.1177/0333102417744362). This is the key statistical fact: the difference between episodic and chronic responders was not just a subgroup eyeball — the trial formally demonstrated that treatment effect depended on subtype.

This is the single most important number in this section for a person with chronic daily CH. In ACT2, chronic patients got 5% of attacks pain-free at 15 minutes on active nVNS versus 13% on sham. In ACT1, chronic patients got 13.6% response versus 23.1% on sham. In both trials the chronic subgroup's point estimate was *numerically below sham*. Neither difference was statistically significant, and both subgroups were small (48 and 65 chronic patients respectively), so the honest reading is "no detectable acute benefit in chronic CH", not "harmful". But it is not a near-miss; it is a flat line.

4.1.4 Pooled analysis of ACT1 + ACT2

[PEER-REVIEWED] de Coo IF, Marin JC, Silberstein SD, Friedman DI, Gaul C, McClure CK, Tyagi A, Liebler EJ, Načinović Đ, Ferrari MD, Goadsby PJ. *Cephalalgia* 2019;39(8):967-977, DOI 10.1177/0333102419856607, PMID 31246132 / PMC6637721. Pooled n=225 (eCH 112, cCH 113).

- Episodic CH: absolute difference vs sham of **+27%** on the ACT1 endpoint and **+22%** on the ACT2 endpoint, both p<0.01.
- Interaction between subtype and treatment: **p=0.0052** (ACT1 endpoint), **p=0.0025** (ACT2 endpoint).
- **"No treatment difference in cCH for any endpoint."**
- Pooled safety: ≥1 AE in 38 (31%) nVNS vs 45 (35%) sham; serious AEs 2 (2%) vs 1 (1%), **none device-related**; perioral myokymia 8 (7%) nVNS vs 0 sham; dysgeusia 0 vs 8 (6%) sham; application-site erythema 0 vs 9 (7%) sham. No serious adverse device effects (de Coo 2019).

4.1.5 PREVA — nVNS as a *preventive* in chronic CH (the one positive chronic trial)

[PEER-REVIEWED] PREVA: Gaul C et al., *Cephalalgia* 2016;36(6):534-546, DOI 10.1177/0333102415607070. Prospective, **open-label** (not sham-controlled), randomised: 97 patients with chronic CH, nVNS + standard of care (n=48) vs standard of care alone (n=49); 92 continued into an extension phase.

- Reduction in attacks per week: **−5.9 (nVNS+SoC) vs −2.1 (SoC)**, p=.02; **therapeutic gain 4.2 attacks/week**.
- **≥50% responder rate: 40% vs 8.3%, p<.001.**
- 57% decrease in abortive medication use, p<.001.

- 100% response (attack-free): 8% vs 0%.
- ≥25% response p<0.001; ≥75% response p=0.009.
- Adverse events ≥5%: headache 8%, dizziness 6%, neck pain 6%. No serious treatment-related AEs.

[PEER-REVIEWED] Post hoc analysis: Gaul C et al., *J Headache Pain* 2017;18(1):22, DOI 10.1186/s10194-017-0731-4, PMID 28197844 / PMC5309191.

The tension to hold in mind: nVNS is a *failed acute treatment in chronic CH* and a *positive preventive treatment in chronic CH*, and the preventive evidence comes from a single open-label trial where patients knew they were getting the device. Both statements are true simultaneously. The 2021 narrative review's evidence table records exactly this: preventive nVNS — "one trial positive"; acute nVNS — "two trials negative" (PMC8665918).

4.1.6 Real-world open-label data in refractory chronic CH

[PEER-REVIEWED] Simmonds L et al., *Front Neurol* 2023;14:1100426, DOI 10.3389/fneur.2023.1100426 — UCL/National Hospital for Neurology and Neurosurgery, London; 40 patients with refractory chronic CH:

- **43% (17/40)** achieved ≥50% reduction in attack frequency at 3 months.
- Attacks fell from 124±67 to 79±63 per month (mean reduction 44.7, 95% CI 25.1–64.3, p<0.001).
- Severity fell by 1.2 points on a verbal rating scale (p=0.001).
- **2 patients achieved complete remission; 5 had no benefit; 2 worsened.**

[PEER-REVIEWED] A separate retrospective UK observational series reported mean chronic CH attack frequency falling from 26.6±17.1 to 9.5±11.0 attacks/week (p<0.01), with reduced attack duration, severity and abortive use (summarised in PMC8665918, 2021).

Minority observation, clearly labelled as such: the Simmonds series is one of the very few places in this literature that reports patients getting *worse* on a treatment (2/40, 5%). Most device papers do not report deterioration as a category at all. Take the near-universal absence of "worsened" rows in these tables as a reporting artefact rather than evidence that it doesn't happen.

4.1.7 Guideline positions

[PEER-REVIEWED] European Academy of Neurology guideline: May A, Evers S, Goadsby PJ, Leone M, Manzoni GC, Pascual J, et al. "European Academy of Neurology guidelines on the treatment of cluster headache." *Eur J Neurol* 2023;30(10):2955-2979, DOI 10.1111/ene.15956, PMID 37515405; full PDF.

- **Acute treatment:** STRONG recommendation, LOW quality evidence, for nVNS in acute attacks **in episodic but not chronic CH**. Guideline Table 11: 131 participants, RR 4.4 (95% CI 2.7–7.2) in eCH. Table 12: 122 participants, cCH **RR 0.4 (95% CI 0.2–0.6)** — i.e. the pooled chronic estimate points *away* from benefit.
- **Preventive treatment in chronic CH (PREVA):** WEAK recommendation, low/very low evidence; mean 3.9 fewer attacks per week (95% CI 0.5–7.2).
- Consensus statement: "nVNS and SPG stimulation are the most promising approaches and should be discussed with the individual patient."

[PREPRINT/TRIAL] NICE (UK) Medical Technologies Guidance MTG46 reviewed 8 studies covering 410 patients and concluded that gammaCore "worked better acutely for episodic than chronic CH", noting studies were not powered for subgroup analysis and that no serious device-related adverse events were reported. NICE recommends stopping treatment if there is no reduction in the first 3 months (NICE MTG46, evidence chapter). NICE's committee also concluded gammaCore "appears to be effective in some but not all people" (NICE HTG533 committee discussion).

[PEER-REVIEWED] NICE health-economic analysis: *PharmacoEconomics Open* 2021;5(4):577-586, DOI 10.1007/s41669-021-00276-5, PMID 34322861 / PMC8611122 — "Evidence suggests that gammaCore reduces the intensity and frequency of cluster headaches and that the addition of gammaCore to standard care is cost saving."

[PREPRINT/TRIAL] Direct conflict, stated plainly. Ontario Health's 2025 HTA reached the opposite conclusion for acute treatment: "no statistically significant improvement in overall response, pain freedom, or duration", GRADE **Very low**. It recomputed ACT1 as RR 1.77 (95% CI 0.89–3.52), p=.10; ACT2 absolute difference 15.1%, p=.05; combined ≥50%-of-attacks endpoint RR 1.85 (0.84–4.07), not significant (*Ont Health Technol Assess Ser* 2025;25(2):1-177, PMID 40496978 / PMC12148001).

So: **NICE says adopt it and it saves money; Ontario Health says the acute evidence is very low quality and not significant; EAN says strong-but-low-evidence yes for episodic, and no for chronic acute.** All three read essentially the same two trials. The disagreement is about how much weight to give a subgroup finding from a trial that missed its primary endpoint.

4.1.8 Regulatory status

[PREPRINT/TRIAL] United States (FDA): - April 2017 — released for acute treatment of pain associated with **episodic** cluster headache in adults. - June 2017 — gammaCore-S 510(k) clearance (K173442). - January 2018 — acute treatment of migraine. - **28 November 2018 — FDA clearance for adjunctive preventive treatment of cluster headache** (NeurologyLive). - The label explicitly states: "The safety and effectiveness … has not been established in the acute treatment of chronic cluster headache." The FDA has essentially codified the ACT1/ACT2 subgroup finding into the labelling.

[PREPRINT/TRIAL] Europe: CE-marked; gammaCore-S available in the EU since 2015.

[PREPRINT/TRIAL] Australia (TGA): listed on the **ARTG as entry 355575**, sponsor **Medistar 2 Pty Ltd (trading as Medistar)**. The TGA granted a s42DF restricted-representation advertising approval on **23 October 2023** (TGA advertising permissions — Medistar 2 Pty Ltd, gammaCore).

The Australian indication is broader than the US one. Medistar states gammaCore is indicated in Australia "for the treatment and/or prevention of primary headache: migraine, cluster headache, and hemicrania continua, and medication overuse headache in adults", available "on authorisation by a registered healthcare professional" (Medistar patient page). Migraine Australia confirms: "gammaCore is a Vagus Nerve Stimulator (VNS) device that is TGA approved for the management of primary headache conditions such as cluster headache and migraine… available by prescription only… Under Australian law, this device is restricted to sale by or on the order of a licenced healthcare provider" (Migraine Australia — Devices).

Worth flagging honestly: the Australian indication covers chronic cluster headache without the US carve-out, even though the underlying trial evidence for acute chronic CH is null. Regulatory indication breadth is not evidence.

4.1.9 Cost and access — Australia specifically

[PREPRINT/TRIAL] Medistar's own prescriber document states: **"At this time, there is no available subsidy for gammaCore Sapphire"** (Medistar — How to prescribe gammaCore in AU). Kits are supplied as 31-day and 93-day Starter/Refill options.

[PREPRINT/TRIAL] No AUD price is published on any Medistar page I could fetch. The patient page says only that the healthcare professional "will provide the initial costs" and "ongoing costs", and that Medistar contacts the patient "regarding payment and shipment" (Medistar patient page). Migraine Australia likewise lists no price (Migraine Australia). **The Australian out-of-pocket cost is therefore effectively unpublished — you have to go through a prescriber to find out.** That is an access barrier in itself.

[PREPRINT/TRIAL] For a reference point, the Ontario Health HTA records the North American cash price: "the device costs $650 (plus tax) for a 93-day kit, and 93-day refills cost an additional $650", with patients obtaining it "through out-of-pocket payment or through private insurance plans" (Ontario Health HTA 2025). At roughly quarterly refills, that is on the order of AU$4,000/year equivalent before shipping — treat as an indicative order of magnitude only, not an Australian quote.

[PREPRINT/TRIAL] Elsewhere: the NHS in England supports adoption under NICE MTG46. electroCore reported 2025 revenue of $32.0M, up 27%, and announced a reimbursement approval in September 2025 (electroCore investor release). The company is commercially alive, which — as the rest of this chapter shows — is not a given in this field.

4.1.10 Patient community experience and sentiment

[COMMUNITY-REPORT] On the ClusterBusters forum, the only substantive post in the "Has anyone used / had success with GammaCore?" thread is the original question, from user *Baby Moth* (23 April 2024): "Has anyone used / had success with GammaCore? I am thinking of getting a prescription, but it's VERY expensive and not covered by insurance. Wanted to see if anyone had experiences with this in the community." (ClusterBusters forum thread). **The thread received no reported user experiences.** That silence is itself a data point about penetration in the community.

[COMMUNITY-REPORT] On r/ClusterHeadaches, a 2025 nVNS thread contains discussion but **no commenter states that they personally used gammaCore**. User *Designer_Training_74* wrote: "The gammaCore Sapphire is effective for migraines; if you can obtain coverage, it's worth trying. The Truvaga Plus is the original gammaCore model, so it may be your next best option." User *Andimatic* noted that "GammaCore is specifically designed for cluster headaches" while considering the cheaper consumer device Pulsetto instead (r/ClusterHeadaches — vagus nerve stimulation).

[COMMUNITY-REPORT] Odd finding, minority, flagged as such: in that same thread, user *JoeyLongHots* reported that the consumer vagus device Pulsetto "seemed to trigger attacks". Pulsetto is a wellness device, not gammaCore, and is not TGA/FDA cleared for cluster headache — but the report of a vagus-targeting device apparently *provoking* attacks is worth noting rather than discarding (r/ClusterHeadaches).

[COMMUNITY-REPORT] Another thread member, *Sir_Pervert369*, described self-triggering the gag reflex to stimulate the vagus nerve and stop attacks, noting "it requires repeated attempts" (r/ClusterHeadaches). Purely anecdotal, no supporting evidence, included because it is a recurring folk technique in the community rather than because it is validated.

[PEER-REVIEWED / registry] A manufacturer-linked prospective registry ("gammaCore Patient Registry", GPR) exists for episodic CH — Am J Manag Care 2020;26(1 Suppl):S15-S19, PMID 32109020. Treat as sponsor-adjacent evidence with the usual selection caveats.

[COMMUNITY-REPORT] electroCore's own testimonial page carries uniformly positive quotes ("gammaCore was awesome, and gave me immediate pain relief") (gammaCore reviews). Curated marketing testimonials; no sentiment weight should be assigned to them.

Sentiment summary, honestly stated: community sentiment towards gammaCore is **thin rather than negative**. The recurring themes in what does exist are cost and lack of reimbursement, not reports of failure. There is no ClusterBusters or OUCH-run structured survey of gammaCore outcomes that I could locate — so there is **no [CITIZEN-SCIENCE] tier evidence for nVNS**, only trials at one end and scattered anecdote at the other.

4.2 Sphenopalatine ganglion (SPG) stimulation — Pulsante / Pathway CH-1 and CH-2

4.2.1 What it is

A miniature implanted neurostimulator placed via a trans-oral, gingival-buccal approach into the pterygopalatine fossa, with a lead abutting the sphenopalatine ganglion. It has no battery: the patient holds a hand-held remote controller against the cheek, which powers the implant by radiofrequency and delivers on-demand stimulation during an attack. **[PEER-REVIEWED]** The SPG was targeted because of its role in the trigemino-autonomic reflex producing lacrimation, nasal congestion and rhinorrhoea; high-frequency stimulation is thought to block parasympathetic outflow (PMC8665918, 2021).

[HISTORICAL/CULTURAL] SPG *blockade* (not stimulation) is much older — "SPG blockades had been used to terminate cluster headache since the early 1900s", though they were "clinically difficult to perform" and never widely adopted. Devoghel reported 120 blocks with an 85% response rate; Pipolo et al. reported 15 endoscopic SPG blocks with 54% complete remission lasting 1–28 months (Trigeminal Autonomic Cephalalgias: Beyond the Conventional Treatments, *Curr Pain Headache Rep* 2014;18(8):438 / PMC4119587).

4.2.2 Pathway CH-1 — the pivotal European trial

[PEER-REVIEWED] Schoenen J, Jensen RH, Lantéri-Minet M, Láinez MJA, Gaul C, Goodman AM, Caparso A, May A. "Stimulation of the sphenopalatine ganglion (SPG) for cluster headache treatment. Pathway CH-1: a randomized, sham-controlled study." *Cephalalgia* 2013;33(10):816-830, DOI 10.1177/0333102412473667, PMID 23314784 / PMC3724276, NCT01255813. Funded by Autonomic Technologies Inc (ATI).

- 32 patients with refractory chronic CH implanted; 28 completed the experimental period. Each attack randomised to full, sub-perception, or sham stimulation.

Outcome at 15 min	Full stimulation	Sham	p
Pain relief	**67.1%**	7.4%	<0.0001
Pain freedom	**34.1%**	1.5%	<0.0001
Sub-perception stimulation (pain relief)	7.3%	—	0.96 vs sham

- **Acute responders: 9/28 (32%)** — 9 of 14 eligible patients, 64%.
- **Frequency responders: 12/28 (43%)**, with a mean 88% reduction in attack frequency.
- **Therapeutic responders (acute and/or frequency): 19/28 (68%).**
- Rescue medication use 31.0% (stimulation) vs 77.4% (sham).

The sub-perception arm is an underappreciated strength of this trial: it provides an active-but-imperceptible control, which is very hard to achieve in neuromodulation and largely rules out a pure paraesthesia-expectation effect.

[PEER-REVIEWED] CH-1 safety — and this is where the honesty is required: - **Sensory disturbance in 26/32 patients (81%)**; localised loss of sensation in 19/32. - Resolution averaged 82–97 days (range 12–259 days); **6 cases had not resolved**. - Pain 12/32 (38%); trismus 5 (16%); swelling 7 (22%); infection 2; paresis 2. - **5 device- or procedure-related serious adverse events**; 5 late-onset explants or lead revisions (Schoenen 2013).

An 81% rate of facial sensory disturbance, mostly transient but permanent in some, is a real cost. The 2014 review characterises it the same way: "81% reported transient facial sensory disturbance. Five cases required surgical revision for lead migration or explantation" (PMC4119587).

4.2.3 Pathway CH-2 — the US confirmatory trial

[PEER-REVIEWED] Goadsby PJ, Sahai-Srivastava S, Kezirian EJ, Calhoun AH, Matthews DC, McAllister PJ, Costantino PD, Friedman DI, Zuniga JR, Mechtler LL, Popat SR, Rezai AR, Dodick DW. "Safety and efficacy of sphenopalatine ganglion stimulation for chronic cluster headache: a double-blind, randomised controlled trial." *Lancet Neurol* 2019;18(12):1081-1090, DOI 10.1016/S1474-4422(19)30322-9, PMID 31701891, NCT02168764.

- 21 US centres; 93 randomised (45 SPG, 48 control); enrolment July 2014 – February 2017.
- **Pain relief at 15 minutes: 62.46% (95% CI 49.15–74.12) with SPG stimulation vs 38.87% (95% CI 28.60–50.25) control; OR 2.62 (95% CI 1.28–5.34), p=0.008.**
- 9 serious adverse events by the end of the open-label phase: 3 procedure-related (aspiration during intubation, nausea/vomiting, venous injury), 1 both device- and procedure-related (infection), 5 unrelated.

Note the sham response: 38.87% pain relief in the control arm of CH-2, versus 7.4% in CH-1. That is an enormous difference in control-arm performance between two trials of the same device, and it substantially narrows the treatment effect in the US trial. The absolute gain in CH-2 is about 24 percentage points; in CH-1 it was about 60. Contested — but the most likely explanation is a different control condition and a different (US, higher-expectation) population, not a different device.

4.2.4 Pathway R-1 — the European registry (non-Anglophone-led)

[PEER-REVIEWED] Barloese M, Petersen A, Stude P, Jürgens T, Jensen RH, May A. "Sphenopalatine ganglion stimulation for cluster headache, results from a large, open-label European registry." *J Headache Pain* 2018;19(1):6, DOI 10.1186/s10194-017-0828-9, PMID 29349561 / PMC5773459.

Explicitly non-Anglophone: 12 centres — 10 in Germany, 1 in Denmark (Danish Headache Center/Rigshospitalet lineage, Barloese and Jensen), 1 in Austria. This is the German/Danish/Austrian real-world dataset.

- 97 enrolled (88 chronic, 9 episodic), implanted September 2012 – March 2015; 85 evaluated at 12 months (78 chronic, 7 episodic).
- **Chronic CH frequency responders: 55% (43/78).**
- **23/78 (29%) were attack-free at 12 months.**
- Acute responders: 32% (27/85).
- 13,600 attacks treated: effective therapy in 39%, pain freedom in 26%.
- **Therapeutic responders (chronic): 65% (51/78)**; ≥75% response 47% (37/78); ≥30% response 74% (58/78).
- 74% were able to stop, reduce, or remain off all preventive medication (summarised in PMC8665918).
- 8 lead repositions; 4 initial implant failures.

[PEER-REVIEWED] Long-term data: Jürgens TP et al., *Cephalalgia* 2017 — 18-month outcomes (SAGE); and Barloese M et al., *J Headache Pain* 2016;17(1):67, DOI 10.1186/s10194-016-0658-1 — 24-month outcomes: of 33 chronic CH patients followed 24 months, **30% experienced at least one period of attack remission**, beginning after approximately 3.5 months of treatment, with HIT-6 improving by a mean 12.5 points (PMC4961666; as summarised in PMC8665918). At 24 months: acute responders 45%, frequency responders 33%, total response 61%.

This is the most interesting biological finding in the SPG literature: a device designed purely as an *acute* abortive turned out to have a *preventive* effect that emerged over months. That was not the hypothesis.

4.2.5 Guideline position

[PEER-REVIEWED] The EAN 2023 guideline gives SPG stimulation a **STRONG recommendation with MODERATE quality evidence** — the strongest evidence grade of any device in this chapter — citing pain relief in approximately 65% of attacks and stating it is "efficacious in 60%–70% of patients". And then, in the same document: **"The method is not available at the time of writing."** Table 18 records: "At the time of publishing, not available in Europe" (EAN guideline 2023, PDF).

[PEER-REVIEWED] The American Headache Society's 2016 CH treatment guideline (Robbins MS et al., *Headache* 2016) assigned SPG stimulation a Level B recommendation. (Wiley's site blocks automated retrieval; this citation is included for completeness but I was **not able to fetch and verify the AHS text directly** — treat the Level B grading as unverified in this document.)

[PREPRINT/TRIAL] NHS England declined routine commissioning of SPG stimulation for refractory chronic CH in adults in 2018 (NHS England clinical commissioning policy document).

4.2.6 The commercial collapse — and why this section matters more than the efficacy numbers

[PREPRINT/TRIAL] Autonomic Technologies Inc (ATI), of Redwood City / Mountain View, California, received European approval to market the Pulsante SPG Microstimulator in **February 2012** and **collapsed by the end of 2019**. Its UK subsidiary, Autonomic Technology Limited, was formally dissolved on **11 May 2021** (UK Companies House, company 07239097).

[PEER-REVIEWED — journalism in *Nature*] The consequences were documented in detail by Liam Drew in *Nature*'s immersive feature "Abandoned: the human cost of neurotechnology failure":

- **“More than 700 other people”** were left with an implanted ATI device and no manufacturer support (*Nature* — Abandoned).
- After ATI’s closure, “users and physicians could no longer access the proprietary software needed to recalibrate the device and maintain its effectiveness.”
- The featured patient, **Markus Möllmann-Bohle** (German; first cluster headache 1987 at age 22, chronic from 2006, up to 8 hour-long attacks per day, implanted 2013), used stimulation about an hour at a time, 5 or 6 times daily, which was “enough to prevent attacks from becoming debilitating”. He said: **“There is still no medication reliable enough to help me live a pain-free life without the device.”**
- He replaced the hand-held unit’s battery several times, repaired a faulty charging port himself, sourced replacement batteries from a US firm which then stopped making them, and had his most recent battery **custom-made by a Chinese company**. The battery “was never intended to be accessible to the user”. He stated the stimulator had to be replaced every few months, and after one year at the latest, because of battery failure.
- A second patient, **Timothy White**, credited the device with allowing him to complete his medical training; after ATI’s bankruptcy he switched to a migraine drug at **triple the recommended dose**. He noted that after the company closed, **“no one was collecting data on security, safety, complications, or side effects.”**

[COMMUNITY-REPORT / HISTORICAL] This is the clearest documented case in the CH field of patients being stranded by a company failure, and it is the central fact a patient should weigh before consenting to any implanted CH device. It is not unique: *Nature* documents Nuvectra (bankruptcy 2019, ≥3,000 spinal-cord stimulator implants, replacement surgery around US$40,000), Second Sight (2020, ~350 retinal implant users), and Stimwave (*Nature* — Abandoned). Neurotech Reports has separately catalogued the pattern of headache-device market failures (Neurotech Reports).

4.2.7 Current status, 2025–2026

[PREPRINT/TRIAL] ATI’s intellectual property was acquired in late 2020 by **Unity HA** of Effingham, Illinois, which renamed itself **Realeve** in August 2021 with Jon J. Snyder as CEO (BusinessWire, 18 August 2021).

[PREPRINT/TRIAL] In **April 2021** the company obtained **FDA Breakthrough Device designation** for the Pulsante SPG Microstimulator System for “treatment of acute headache pain associated with chronic cluster headaches”. Its own materials describe Pulsante as **“a development stage therapy”** and state that “the Pulsante SPG Microstimulator has treated over 700 patients in the US and EU to date” (Realeve / Unity HA Breakthrough Device announcement).

Breakthrough Device designation is not approval. It is an expedited-review pathway. As of the material I could retrieve, **Pulsante is not FDA-approved and not CE-marked**.

[PREPRINT/TRIAL] Snyder told *Nature* in July (2022): **“Since we do not have FDA or CE mark approval yet, we are unable to market the therapy and provide support.”** Snyder subsequently departed and a consulting firm took temporary control; interim CEO Peter Donato said Realeve had gained approval **in Denmark** to distribute replacement devices and software to existing users, hoping deliveries could begin in the second half of 2023, with talks underway with three other European countries. ***Nature* does not state that deliveries began** (*Nature* — Abandoned).

[PREPRINT/TRIAL] Company activity is ongoing but has broadened away from cluster headache. In September 2023 Realeve announced a multimillion-dollar grant supporting a Cleveland Clinic post-stroke recovery study (BusinessWire, 20 September 2023). In **May 2025**, manufacturing partner Promex announced that it and Realeve had been recognised by MedTech Breakthrough for the Pulsante Micro-Neurostimulator System (Promex Industries, 8 May 2025) — evidence that the device is still in active development and manufacturing engineering as of 2025. Realeve’s founder and CEO is now listed as **Dr Peter Bonutti** (Realeve, January 2025).

Bottom line as of this writing (2026): SPG stimulation has the **best trial evidence of any invasive CH neuromodulation** — two positive sham-controlled RCTs plus a positive registry — and is **commercially unavailable in Europe, the US and Australia**. There is no route for an Australian patient to obtain it. Its resumption is unknown; Realeve has been “about to relaunch” since 2021.

4.2.8 Community sentiment

[COMMUNITY-REPORT] Community sentiment on SPG stimulation is bifurcated in a specific way: strongly positive about the *therapy*, deeply bitter about the *company*. Möllmann-Bohle continued to jury-rig batteries for years rather than give up the device (*Nature*). That combination — a therapy patients will hand-build batteries to keep using, made by a company that dissolved and left them without software — is the defining story of SPG stimulation, and it should carry more weight in a personal decision than the CH-1 response rates.

4.3 Occipital nerve stimulation (ONS)

4.3.1 What it is

Subcutaneous electrodes placed across the back of the head at the level of the greater occipital nerves (usually bilaterally), connected to an implanted pulse generator, typically below the clavicle. Unlike SPG stimulation this is a *preventive*, continuous therapy, not an abortive one.

[PEER-REVIEWED] Uniquely among invasive CH options, "Occipital nerve stimulation for refractory CCH is the only available invasive approach with a Conformité Européenne (CE) mark" (PMC8665918, 2021). This is important: it is the only implantable CH device you can actually get in Europe. It is also — see below — the one guidelines are most negative about.

4.3.2 Early evidence base — open-label case series

[PEER-REVIEWED] ONS with implanted electrodes in CCH was first reported in **2007** in a case series of 8 patients, with attack-frequency reductions ranging from 25% to 95% (summarised in PMC8665918). Other early series:

Series	n	Result
Burns et al.	14	10 reported benefit; 3 >90%; 3 >40% (PMC4119587)
Magis et al.	14	11 with ≥90% attack reduction at mean 37 months (PMC4119587)
Unnamed series	13	Mean attack frequency −68%, intensity −49%; 1 infection requiring hardware removal (PMC8665918)
Miller et al. 2016	51	**≥50% improvement in attack frequency in 53%** (PMC8665918)
Long-term observational	—	Median follow-up 6.1 years; **67% responders (≥50% reduction in attacks/day)**; of those, 40% had only sporadic attacks (PMC8665918)
Large observational	**105**	**>50% attack reduction in 69%**; mean weekly attacks 22.5 → 9.9; preventive and abortive medication significantly reduced; efficacy sustained at 1 year and last follow-up (PMC8665918)
EAN-cited uncontrolled study	35	59% responders (≥50% frequency reduction), mean follow-up 48.8 months (EAN 2023)

These open-label numbers (53–69% responders) are the ones patients usually hear. The controlled trials below tell a much more complicated story.

4.3.3 ICON — the phase 3 dose-controlled trial

[PEER-REVIEWED] Wilbrink LA, de Coo IF, Doesborg PGG, Mulleners WM, Teernstra OPM, Bartels EC, Burger K, Wille F, van Dongen RTM, Kurt E, Spincemaille GH, Haan J, van Zwet EW, Huygen FJPM, Ferrari MD, ICON study group. "Safety and efficacy of occipital nerve stimulation for attack prevention in medically intractable chronic cluster headache (ICON): a randomised, double-blind, multicentre, phase 3, electrical dose-controlled trial." *Lancet Neurol* 2021;20(7):515-525, DOI 10.1016/S1474-4422(21)00101-0, PMID 34146510, NCT01151631.

Design — and this is the crux. Because ONS causes paraesthesia, a true sham is impossible. ICON therefore randomised patients to **100% versus 30%** of the individually determined range between paraesthesia threshold and near-discomfort, hypothesising similar paraesthesia but different efficacy. 150 enrolled, 131 randomised (65 at 100%, 66 at 30%, one not implanted). Sites: four hospitals in the Netherlands, one each in Belgium, Germany and Hungary. Enrolment Oct 2010 – Dec 2017. Funded by the Netherlands Organisation for Scientific Research, the Dutch Ministry of Health, the NutsOhra Foundation, and Medtronic.

Group	Baseline weekly attacks (median, IQR)	Weeks 21–24	Median change
All	15.75 (9.44–24.75)	7.38 (2.50–18.50)	**−5.21 (IQR −11.18 to −0.19), p<0.0001**
100% ONS	17.58 (9.83–29.33)	9.50 (3.00–21.25)	−4.08 (−11.92 to −0.25)
30% ONS	15.00 (9.25–22.33)	6.75 (1.50–16.50)	−6.50 (−10.83 to −0.08)

Between-group difference: −2.42 (95% CI −5.17 to 3.33) — no difference between doses.

[PEER-REVIEWED] The 30% "low-dose" arm did just as well as the 100% arm. As the L-ICON authors put it: "The 30% stimulation was assumed to be clinically ineffective or much less effective… [it] was found to be as effective as the 100% stimulation" and "because there was no difference between treatment groups, a placebo response could not be formally ruled out, but was considered highly unlikely by the authors" (L-ICON, *eBioMedicine* 2023, DOI 10.1016/j.ebiom.2023.104895, PMC10755111).

State the conflict explicitly: the trialists interpret the equal-dose result as "low-dose ONS is also therapeutic". The alternative interpretation — that both arms reflect regression to the mean plus placebo in an unblindable procedure — cannot be excluded by this design. The EAN guideline, reading the same data, sided with scepticism (§3.6). Reasonable experts genuinely disagree here.

[PEER-REVIEWED] ICON masked-phase safety: 129 adverse events with 100% ONS versus 95 with 30%; **17 versus 8 serious adverse events**, requiring brief hospital admission for minor hardware-related issues. Named event types: local pain, impaired wound healing, neck stiffness, hardware damage (Wilbrink 2021).

4.3.4 L-ICON — long-term extension (2–8 years)

[PEER-REVIEWED] Brandt RB, Wilbrink LA, De Coo IF, Haan J, Mulleners WM, Huygen FJPM, van Zwet EW, Ferrari MD, ICON study group. "A prospective open label 2–8 year extension of the randomised controlled ICON trial on the long-term efficacy and safety of occipital nerve stimulation in medically intractable chronic cluster headache." *eBioMedicine* 2023, DOI 10.1016/j.ebiom.2023.104895, PMC10755111.

- 88/103 eligible Dutch participants started L-ICON; mean follow-up 4.2±2.2 years; 370 person-years observed (84% of potential).
- Followed ≥2 years: 73/88 (83%); ≥3 years: 61/88 (69%); ≥5 years: 33/88 (38%); ≥8.5 years: 3/88 (3%).

Efficacy:

Time point	Pooled geometric mean weekly attacks	95% CI
Baseline	16.2	14.4–18.3
1 year	4.2	2.8–6.3
2 years	5.1	3.5–7.6
5 years	4.1	3.0–5.5

Responder analysis	n/N	%
≥50% responders at end of ICON	49/88	56%
Retained ≥50% response for ≥half of L-ICON follow-up	35/49 or 36/49	**71% or 73%**
ICON non-responders who *became* ≥50% responders	15/39	38%
All L-ICON participants with ≥50% response for ≥half of follow-up	**52/88**	**59%**
≥30% responders at end of ICON	57/88	65%
Retained ≥30% response	47/57	82%
≥75% responders at end of ICON	36/88	41%
Retained ≥75% response	24/36	67%

Minor internal inconsistency, flagged: the paper reports 35/49 (71%) in its Summary and 36/49 (73%) in its Results for the same quantity (PMC10755111). Trivial, but worth noting for a source-of-truth document.

Patient-reported outcomes at last follow-up: 69/88 (78%, 95% CI 68–86%) reported subjective improvement; 9/88 (10%) no change; **4/88 (5%) worsening**; 6/88 (7%) could not answer. **70/88 (81%) would recommend ONS to other patients**; 2/88 (2%) would not (PMC10755111).

Long-term safety — the number that should govern the decision:

Category	Events	Participants	%	Incidence rate (per person-year)	95% CI
All serious adverse events	**202**	**63/88**	**72%**	**0.62**	0.54–0.71
Hardware-related SAEs	122	48/88	55%	0.37	0.31–0.45
Non-hardware-related SAEs	79	40/88	45%	0.24	0.19–0.30
All hardware-related AEs	**593**	**71/88**	**81%**	**1.83**	1.68–1.98

- **112/122 (92%) of hardware-related SAEs required additional surgery, affecting 44/88 participants (50%)**, at 0.35 per person-year. Two-thirds were lead replacements, one-third battery replacements (PMC10755111).
- Follow-up was prematurely terminated in 34/88 (39%): explantation 8, device switched off for lack of efficacy 3, lost to follow-up 10, personal reasons 4, **death from another disease 4**, attack freedom 3, “no effect but scared to stop ongoing stimulation” 2.
- The authors state that **“no biological SAEs occurred”** — no infections, no neurological injury. All SAEs were hardware/hospitalisation events.

Read that honestly: half of long-term ONS patients needed at least one further operation, and 81% had some hardware-related adverse event, but essentially none of it was biologically dangerous. It is a high-nuisance, low-catastrophe profile — the opposite of DBS. The authors' own conclusion is that ONS is "safe, well-tolerated and long-term effective". A patient may reasonably weigh "50% chance of repeat surgery" differently from how the authors do.

4.3.5 Fogh-Andersen 2026 — the placebo-controlled Danish trial (newest evidence)

[PEER-REVIEWED] Fogh-Andersen IS, Sørensen JCH, Petersen AS, Jensen RH, Meier K. "Safety and efficacy of occipital nerve stimulation as treatment of chronic cluster headache: an investigator-initiated, double-blind, randomized, placebo-controlled study." *J Headache Pain* 2026 Mar 9;27(1):77, DOI 10.1186/s10194-026-02312-3, PMID 41803706 / PMC12980930, NCT05023460. Aarhus University Hospital + Danish Headache Center; funded by the Novo Nordisk Foundation. **Danish, non-Anglophone-led.**

Design: 4-week baseline → 12 weeks open-label TENS → ONS implantation → 14-day grace period → **12 weeks double-blind burst ONS (n=19) vs placebo/no stimulation (n=19)** → 12 weeks open-label tonic ONS. Primary endpoint: proportion achieving ≥30% reduction in attack frequency.

Endpoint	Burst ONS	Placebo
≥30% responders, randomised phase	**18.81% (95% CI 0.28–37.89)**	**50.02% (95% CI 26.87–73.09)**
≥30% responders, open-label tonic phase	42.09% (19.91–64.34)	51.11% (27.32–74.88)

The chance of achieving ≥30% reduction was 31.20% HIGHER in the placebo group (95% CI 1.29–61.23), p=0.042. In the open-label phase there was no difference (p=0.63) (Fogh-Andersen 2026).

Weekly attack frequency did fall in both arms — burst ONS from 20.57 to 13.87 (−31.10% from baseline, 95% CI −56.78 to +10.14); placebo from 12.75 to 6.67 (−44.32%, 95% CI −64.69 to −12.13). PGIC "much/very much improved": 4 (21%) burst vs 9 (50%) placebo in the randomised phase; 11 (58%) vs 13 (72%) in the open-label phase.

[PEER-REVIEWED] The authors' conclusion: both burst and tonic ONS reduced attack frequency, but **burst ONS was not superior to placebo** (Fogh-Andersen 2026).

This is the most important recent result in the ONS literature and it deserves emphasis. In a properly blinded, placebo-controlled design — the implant present but switched off — the placebo arm *outperformed* the active arm on the primary endpoint. Combined with ICON's finding that 30% dose equals 100% dose, there are now two independent controlled designs in which varying or removing the actual stimulation made no difference to outcome, while outcomes improved substantially from baseline in everyone.

The most parsimonious reading: **a large part of the benefit patients experience from ONS may come from implantation, expectation, regression to the mean and intensive specialist care, rather than from the electrical stimulation itself.** That reading is contested — burst stimulation specifically may simply be the wrong waveform, the trial was small (38 patients), and the groups were imbalanced at baseline (burst arm had 20.6 attacks/week versus placebo 12.8). But it cannot be waved away.

4.3.6 Complication rates across the wider literature

Different series report wildly different complication rates, largely reflecting era and surgical technique.

[PEER-REVIEWED] Falowski S, Wang D, Sabesan A, Sharan A. "Occipital Nerve Stimulator Systems: Review of Complications and Surgical Techniques." *Neuromodulation* 2010;13(2):121-125, DOI 10.1111/j.1525-1403.2009.00261.x. Retrospective single-centre chart review, 28 patients implanted 2003–2007, mean follow-up 21 months (range 2–60):

- **Average 2.1 surgeries per patient; 59 total surgeries, 41 lead-related; 1–5 surgeries per patient over 60 months.**
- Lead migration in **7/28 patients (25%)**; 13 lead-migration revisions (**32%** of procedures in that series).

- Average time to revision for lead migration 26 weeks; 54% of revisions within 8 weeks, 39% within 4 weeks, 31% within 2 weeks.
- Cited from Schwedt et al.: lead migration **33% at 6 months, 60% at 2 years, 100% at 3 years** (Falowski 2010).

[PEER-REVIEWED] The 105-patient observational series recorded: **67 patients experienced at least one complication; 29 required additional surgery.** Infection 6%, lead migration 12%, lead fracture 4.5%, hardware dysfunction 8.2% (PMC8665918).

[PEER-REVIEWED] Modern technique looks markedly better. Meier K, Fogh-Andersen IS, Sørensen JCH. "Occipital nerve stimulation: A detailed description of a surgical approach and a discussion on implantation techniques." *Pain Pract* 2025;25(1):e13444, DOI 10.1111/papr.13444, PMID 39607056. Aarhus, Denmark; 45 CCH patients implanted March 2018 – June 2024; 86.3 patient-years:

- **22 adverse events in 17 patients; 9 required revision surgery.**
- **No lead migration. No lead breakage. No muscle/neck stiffness.**
- Most frequent non-surgical AE: temporary occipital dysaesthesia, resolving spontaneously within weeks.
- **Serious adverse event rate: one per 9.6 patient-years.**
- 6 patients had the system explanted for lack of efficacy.

The contrast between Falowski's 25% lead migration (2003–2007, older leads, single lead anchoring) and Meier's zero lead migrations (2018–2024, tined leads, single lead from behind the ear across the back of the head, IPG below the right clavicle, sleep-awake anaesthetic with perioperative patient feedback) is one of the more encouraging findings in this chapter. The L-ICON authors say the same: more flexible electrodes reduced fracture risk and tined leads reduced dislocation risk (PMC10755111). **Old complication rates in reviews and patient forums substantially overstate the risk of a modern implant.**

Battery depletion: **[PEER-REVIEWED]** originally a major driver of reoperation, "overcome by the introduction of rechargeable batteries" (PMC4119587). ICON used non-rechargeable IPGs; rechargeables were used for replacements during follow-up (PMC10755111).

Side-shift: **[PEER-REVIEWED]** some series reported a shift of attacks to the other side when unilateral stimulation was used, which is why **bilateral lead placement became standard** (PMC4119587). The modern Danish technique uses a single lead crossing the back of the head (Meier 2025).

4.3.7 Guideline position — the most negative in this chapter

[PEER-REVIEWED] The EAN 2023 guideline: **"No recommendation for greater ONS based on a very low level of evidence"**, and states ONS is **"not recommended due to side effect profile"**. Table 18 records the expert consensus that ONS is a "method of third choice" with an "unfavourable efficacy/side-effect profile" — while also conceding it "could be discussed with patients before DBS is planned". The evidence base cited is 181 participants (Miller 2016 n=51; Wilbrink 2021 n=130) (EAN 2023 PDF).

[PEER-REVIEWED] A 2021 review is blunter about the practicalities: "GON stimulation for the treatment of refractory CCH and chronic migraine has been regarded as a cost-intensive treatment option with a significant complication rate" and "the highest rate of technical problems after implantation has been reported for GON stimulation" (PMC8665918).

So: ONS is the only implantable CH device you can actually obtain in Europe, and it is the one the European guideline declines to recommend. That is an uncomfortable but accurate summary of the current position.

4.3.8 Community experience

[COMMUNITY-REPORT] Community reports on ONS specifically for cluster headache are sparse. One r/migraine poster who has both chronic cluster headaches and migraines reported on a 60-day trial of a *percutaneous* occipital stimulator (SPRINT PNS, a temporary system, not a permanent implant): "about a 50% decrease in the intensity" (r/migraine — Experience with occipital nerve stimulation?). A 2025 r/ClusterHeadaches nVNS thread contains **no ONS reports at all** (r/ClusterHeadaches).

[PEER-REVIEWED — patient-reported, closest thing to structured patient sentiment] The strongest structured patient-sentiment data for ONS is inside L-ICON: **81% would recommend it to other patients, 78% reported subjective improvement, 2% would not recommend, 5% reported worsening** (PMC10755111). Two participants continued stimulation despite "no effect but scared to stop ongoing stimulation" — a small, human, and telling category that almost never appears in trial reporting.

Note the gap: **81% of ONS patients would recommend it, and the European guideline does not recommend it.** Both are defensible. The patients are reporting on their own experience of a package that includes implantation, intensive follow-up, and possibly placebo; the guideline is reporting on whether the electricity is proven to be the active ingredient.

4.4 Deep brain stimulation (DBS) of the posterior hypothalamus

4.4.1 History and rationale

[HISTORICAL/CULTURAL] + [PEER-REVIEWED] DBS for CH grew directly out of functional imaging: PET showed the posterior hypothalamus becoming active during cluster attacks. **Massimo Leone and colleagues in Milan, Italy published the first case in 2001** — Leone M et al., *N Engl J Med* 2001;345:1428-1429 (cited in Leone & Proietti Cecchini, *Cephalalgia* 2016, DOI 10.1177/0333102415607176; also Karger systematic review). Leone's review states DBS of the posterior hypothalamic area "was first introduced in 2000 to treat drug-refractory chronic cluster headache".

Leone (Istituto Neurologico Carlo Besta, Milan) is the field's central figure; the Italian series is by far the largest and longest-followed. **This is an Italian-origin therapy** and much of the foundational work is non-Anglophone in origin, though published in English.

4.4.2 Leone's pooled series — 79 patients

[PEER-REVIEWED] Leone M, Proietti Cecchini A. "Deep brain stimulation in headache." *Cephalalgia* 2016 (online 7 December 2015), DOI 10.1177/0333102415607176 (SAGE full text).

- **79 patients** with hypothalamic stimulation, 88.6% chronic cluster headache; remainder SUNCT, one paroxysmal hemicrania, one symptomatic trigeminal neuralgia, one symptomatic CH-like syndrome.
- Mean follow-up 2.2 years.
- **≥50% improvement in headache frequency and/or intensity: 55 patients (69.6%).**
- In the study-by-study table totals: pain-free 24 (30.4%), ≥50% improvement 31 (39.2%).

Note an internal discrepancy in the source: the abstract states 69.6% (55/79) achieved ≥50% improvement, while the compiled table totals give 24 pain-free (30.4%) plus 31 with ≥50% improvement (39.2%) — 55 patients combined, i.e. the 69.6% figure counts pain-free patients within the responder group. Read the 69.6% as "pain-free OR ≥50% improved" (Leone & Proietti Cecchini 2016).

[PEER-REVIEWED] The remarkable long-term finding. Leone's own longest-followed cohort: 17 drug-resistant chronic CH patients at a **median follow-up of 8.7 years** — improvement in **70% (12/17)**; six almost pain-free; six transformed into episodic CH. Critically: **"Improvement could be maintained with the stimulators off but only after years of continuous stimulation"**, which the authors say "suggested that hypothalamic stimulation can change disease course" (Leone & Proietti Cecchini 2016).

That claim — that DBS may be *disease-modifying* rather than merely suppressive — is unique in the CH literature and comes from a single uncontrolled series by the group that invented the therapy. It is the strongest reason DBS has not been abandoned, and it remains unreplicated. Treat as intriguing and unproven.

4.4.3 Series-by-series results and adverse events

[PEER-REVIEWED] From Leone & Proietti Cecchini's compiled table (SAGE):

Series	n	Follow-up (yrs)	Pain-free	≥50% improved	Side effects / complications
Leone (2001/2004/2006/2013)	19	8.7	6	6	Electrode displacement ×2; infection ×4; electrode malpositioning ×1; transient non-symptomatic third-ventricle haemorrhage ×1; slight unilateral muscle weakness ×1; seizure ×1
Schoenen (2005)	**6**	**4**	**2**	**1**	**Fatal haemorrhage; panic attack; oculomotor disturbances**
D'Andrea (2006)	3	2.5	2	0	—
Benabid (2006)	1	1	1	0	—
Starr (2007)	4	1	0	2	Transient ischaemic attack
Owen (2007)	1	0.7	1	0	—
Mateos (2007)	2	1	1	1	—
Black (2007)	2	2.6	0	2	—
Bartsch (2008)	6	1.4	2	1	—
Piacentino (2008)	4	0.4	3	1	—
Fontaine (2010) — RCT	**11**	**1**	**3**	**3**	Subcutaneous infection; transient loss of consciousness with hemiparesis; micturition syncopes
Hidding & May (2011)	1	NR	0	0	Headache; high-frequency tremor
Seijo (2011)	5	2.8	2	3	Euphoria; well-being; dizziness and oculomotor disturbances; concentration difficulties; headache; cervical dystonia; increased appetite
Kovacs (2014)	2	2	NR	2	Disrupted sleep pattern in both
Total (all indications)	**79**	**2.2**	**24 (30.4%)**	**31 (39.2%)**	

4.4.4 The death — Schoenen 2005

[PEER-REVIEWED] Schoenen J, Di Clemente L, Vandenheede M, Fumal A, De Pasqua V, Mouchamps M, Remacle JM, de Noordhout AM. "Hypothalamic stimulation in chronic cluster headache: a pilot study of efficacy and mode of action." *Brain* 2005;128(Pt 4):940-947, PMID 15689358.

Six patients with refractory chronic CH, ipsilateral ventroposterior hypothalamic stimulation, mean follow-up 14.5 months, mean voltage 3.28V with "diplopia being the major factor limiting its increase".

- Clinical outcome excellent in 3: **two pain-free**, one with fewer than three attacks per month.
- One patient had only transient remissions.
- **"Another patient died" of "an intracerebral haemorrhage."**
- In one pain-free patient, switching the stimulator off led to attacks resuming after 3 months, until it was switched on again.

This is the index death in the CH DBS literature and it happened in a six-patient pilot study. It is the single fact that most shapes how this therapy is regarded.

4.4.5 Systematic review and meta-analysis — 108 cases

[PEER-REVIEWED] "Deep Brain Stimulation for Chronic Cluster Headaches." *Stereotact Funct Neurosurg* 2023;101(4):232-243 (Karger). PRISMA 2020 systematic review and random-effects meta-analysis; PubMed + Scopus searched 3 January 2022; 797 records screened → 16 included studies → **108 unique cases**. All reports graded "good" on the Newcastle-Ottawa Scale.

Population: average age 46.6 (range 24–71); 76.9% male (n=83); 86.3% unilateral headaches; baseline 33.8 attacks/week (SD 16.7); baseline intensity 8.5/10 (SD 1.8); mean 9.5 years (SD 6.7) from diagnosis to DBS.

Targets: posterior hypothalamus 58.3% (n=63); ventral tegmental area 21.3% (n=23); pre-rubral tegmentum/mammillothalamic tract 13.9% (n=15); posterior inferior third-ventricle floor 6.5% (n=7). Unilateral leads 82.4%; local anaesthesia with minimal sedation 82.4%.

Efficacy:

Outcome	Result
Attack frequency before → after	33.8/week → 10.1/week (**−70.1%**)
Intensity before → after	8.5 → 4.2 (**−50.6%**)
Responders (≥50% improvement in frequency)	**78/105 (74.3%)**
Frequency mean difference (meta-analysis)	MD 20.97, 95% CI 13.58–27.01, p=0.0001
Intensity mean difference (meta-analysis)	MD 5.00, 95% CI 3.16–6.84, p<0.0001
Overall follow-up	Mean 45.4 months (SD 38.7), range 1–144
Feasibility	>99% of cases

Complications — the definitive numbers:

Category	Rate	n
Mortality	**<1%**	**1/108 — intracerebral haemorrhage, death on postoperative day 3, "due to catastrophic bleeding after MER"**
Major complications, total	**16.67%**	18
Electrode misplacement or breakage	7.41%	8 (4 migration/misplacement requiring replacement; 4 intracranial breakage requiring revision)
Surgical-site infection requiring additional surgery	4.63%	5
Neurological deficits	3.70%	4 (seizure — resolved; intraoperative TIA with ipsilateral hemiplegia — resolved in 5 min; **irreversible dysarthria — not resolved**; **persistent diplopia — not resolved**)
Contralateral / side-shift cluster attacks	2.8%	3
Intracerebral haemorrhage	0.93%	1
Minor complications, total	**4.63%**	5 (infection resolved with antibiotics 2.78%; asymptomatic third-ventricle-wall haemorrhage 0.93%; micturition syncope 0.93%)
Transient stimulation-related — diplopia	**22.2%**	24
Transient — changes in satiety/hunger, sexual drive/hormones	17.6%	19
Transient — vertigo or dizziness	6.5%	7

Transient stimulation-related effects were amplitude-related and mostly resolved with lower intensity (Karger 2023).

[PEER-REVIEWED] An interesting technical finding: microelectrode recording (MER) was associated with better postoperative intensity scores (3.05±2.53 with MER vs 5.18±3.17 without, p=0.006) — but **the single fatality was caused by bleeding after MER** (Karger 2023). Better targeting, higher haemorrhage risk. That trade-off is unresolved.

[PEER-REVIEWED] Conflicting haemorrhage estimates, stated explicitly: the Karger meta-analysis gives intracerebral haemorrhage at 0.93% (1/108). The EAN 2023 guideline states a **bleeding risk of approximately 2%** (EAN 2023). A 2014 review put "the collated risk of serious hemorrhage for DBS in CCH" at **3%**, noting this was within the range reported for DBS in movement disorders (PMC4119587). The true figure is probably somewhere in 1–3%; the range is honest uncertainty from small numbers, not a discrepancy anyone has resolved.

4.4.6 The negative randomised trial

[PEER-REVIEWED] Fontaine et al. (2010) ran the only randomised, prospective, crossover, double-blind study: 11 patients with severe refractory CCH, **no significant difference between active and sham stimulation** during the randomised phase; three serious adverse events (subcutaneous infection, transient loss of consciousness, micturition syncopes) (summarised in PMC8665918; table in Leone & Proietti Cecchini 2016).

[PEER-REVIEWED] Leone's defence of the negative result: "There is only one double-blind, randomised, controlled study investigating DBS efficacy in chronic CH… the short blind period, one month, [is] too short to give clinically significant information on DBS efficacy" (Leone & Proietti Cecchini 2016). Other reviews agree the negative result likely reflects the short blinded phase, because reported delays to response range from 1 to 86 days, with a mean delay of ~42 days (PMC4119587).

[PEER-REVIEWED] The EAN also notes that a randomised trial of **endoventricular tegmental stimulation** was negative (EAN 2023).

So the state of evidence is: ~70–75% responder rates across 108 uncontrolled cases with long follow-up, and the only controlled trial was negative. This is precisely the pattern that ONS also shows. The difference is that DBS carries a ~1% mortality and ~17% major complication rate, so the burden of proof is much higher.

4.4.7 Acute use — doesn't work

[PEER-REVIEWED] In a larger case series only **23% of attacks** improved with direct DBS stimulation during an attack, so DBS "cannot be regarded as effective in the treatment of attacks" (PMC8665918). DBS is purely preventive.

4.4.8 Current status and guideline position

[PEER-REVIEWED] The EAN 2023 guideline makes **no formal recommendation** on DBS. It records that a **death has been reported**, states a bleeding risk of approximately 2%, notes reports of secondary worsening, notes the negative endoventricular tegmental RCT, and states that **ONS should be attempted before DBS is planned** (EAN 2023 PDF).

[PEER-REVIEWED] The 2021 narrative review's caution is the sharpest sentence in this chapter: "Only DBS electrodes should be implanted with very high caution since fatal outcome of the operation has been reported" (PMC8665918).

[PEER-REVIEWED] The European Headache Federation has recommended that neuromodulation be considered only after all other medical treatments have failed, performed by tertiary headache centres, using **the least invasive methods before considering DBS** (PMC4119587).

How rare is it now? No source I could retrieve gives an annual worldwide figure. What can be said with confidence: the cumulative published world literature to a 2022 search date is **108 cases across roughly 22 years** (Karger 2023) — under five published cases per year globally. It is performed at a handful of tertiary centres (Milan, Liège, Oxford, Grenoble, Oviedo, Barcelona, Hannover). Whether it continues in routine use anywhere in 2026 is **unknown from the sources I could verify**; the direction of travel in guidelines is clearly away from it. **There is no realistic Australian pathway to hypothalamic DBS for cluster headache.**

4.4.9 Community experience

[COMMUNITY-REPORT] I found no substantive patient-community discussion of hypothalamic DBS for cluster headache in the sources retrieved — no Reddit threads, no ClusterBusters threads, no patient blogs surfaced in searching. Given roughly 108 published patients worldwide, this is unsurprising, but it means **there is effectively no community sentiment data for DBS**, and any claim otherwise should be treated with suspicion. The absence should not be read as either endorsement or condemnation.

4.5 Surgical history — what was tried, and why most of it was abandoned

4.5.1 Timeline

[HISTORICAL/CULTURAL] + [PEER-REVIEWED] Approximate chronology, assembled from the sources below:

Period	Development
Early 1900s	Sphenopalatine ganglion blockade used to terminate cluster attacks; “clinically difficult to perform”, never widely adopted (PMC4119587)
Mid–late 20th century	Destructive trigeminal procedures explored: gangliorhizolysis, rhizotomy, nerve section, glycerol/alcohol injection
1988	Mathew NT, Hurt W. “Percutaneous radiofrequency trigeminal gangliorhizolysis in intractable cluster headache.” *Headache* 1988;28:328-331 (cited in Leone, IHS)
1993	Kirkpatrick PJ, O’Brien MD, MacCabe JJ. “Trigeminal nerve section for chronic migrainous neuralgia.” *Br J Neurosurg* 1993;7:483-490 (cited in Leone, IHS)
1998	Lovely TJ, Kotsiakis X, Jannetta PJ — microvascular decompression series, *Headache* 1998;38:590-594 (PMID 11398301)
1998	Ford et al. — first report of gamma knife radiosurgery of the trigeminal nerve for chronic CH (cited in JNNP gamma knife trial)
2000–2001	Leone and colleagues, Milan: first hypothalamic DBS (Karger 2023) — the pivot from destructive to neuromodulatory surgery
2002	Peres MF et al. — greater occipital nerve blockade series, *Cephalalgia* 2002;22:520-522 (cited in Leone, IHS)
2003	Jarrar RG, Black DF, Dodick DW, Davis DH — trigeminal nerve section outcomes, *Neurology* 2003 (PMID 12707445)
2005	Donnet et al. — prospective gamma knife trial, negative and toxic (JNNP 2005;76(2):218)
2007	First implanted ONS series in CCH (PMC8665918)
2012–2013	SPG microstimulator: European approval Feb 2012; Pathway CH-1 published 2013
2019	Pathway CH-2 published; ATI collapses
2021–2026	ICON, L-ICON, Fogh-Andersen; SPG device commercially unavailable; destructive surgery essentially historical

4.5.2 Trigeminal nerve section / rhizotomy

[PEER-REVIEWED] Jarrar RG, Black DF, Dodick DW, Davis DH. “Outcome of trigeminal nerve section in the treatment of chronic cluster headache.” *Neurology* 2003 Apr 22;60(8):1360-1362, DOI 10.1212/01.WNL.0000055902.23139.16, PMID 12707445. 17 patients with intractable chronic CH. The abstract’s conclusion is favourable: trigeminal nerve section “is an effective treatment with acceptable morbidity for a carefully selected group of patients.”

[PEER-REVIEWED] But the outcome data tell a harsher story. A later review reports on the same series: **76% of the 17 patients experienced “long-term full or near complete pain relief”** — “However, adverse effects were dramatic, with **one death**, cerebrospinal-fluid leaks, [and] a case of meningitis.” **In the Jarrar series, two patients needed surgery for corneal anaesthesia to prevent blindness.** The review also notes: “Other groups have reported negative outcomes with CH continuing after trigeminal nerve root section” (*Curr Pain Headache Rep* 2014;18(8):438 / PMC4119587).

One death and two sight-threatening corneal complications in a 17-patient series. The primary paper’s phrase “acceptable morbidity” and the review’s phrase “adverse effects were dramatic” describe the same data. That conflict is worth seeing clearly, and I have not smoothed it: the surgical literature of this era routinely used framing that a modern patient would not accept.

[PEER-REVIEWED] Leone's IHS history chapter lists the complications of destructive trigeminal procedures generally: **diplopia, hyperacusis, jaw deviation, corneal anaesthesia, and anaesthesia dolorosa**. It notes that **complete trigeminal analgesia is necessary to obtain good results** — i.e. you must deliberately deaden the whole face to have a chance of success — and that **"the risk of a contralateral recurrence after surgery is rather high"** in patients whose attacks alternate sides. Long-term ophthalmic follow-up is "highly recommended to avoid corneal ulcers" (Leone M, IHS chapter on non-pharmacological treatment).

Why abandoned: three converging reasons, per Leone: **"few destructive procedures are associated with long-lasting benefit"**, "side effects can be severely debilitating", and candidates must be restricted to "chronically intractable patients with unilateral headaches and no history of side shift" (Leone, IHS). Add anaesthesia dolorosa — an intractable deafferentation pain in a numb face that is arguably worse than what you started with — and the arrival of non-destructive neuromodulation from 2001, and the procedure had no remaining rationale.

4.5.3 Percutaneous radiofrequency trigeminal gangliorhizolysis

[PEER-REVIEWED] Mathew NT, Hurt W, *Headache* 1988;28:328-331. Leone's review lists this among procedures "sometimes reported to be successful", subject to the same requirement for complete trigeminal analgesia, the same complication list (diplopia, hyperacusis, jaw deviation, corneal anaesthesia, anaesthesia dolorosa), and the same high contralateral recurrence risk in side-shifting patients (Leone, IHS). No numerical success or complication rates are given in the sources I could retrieve — a gap, honestly noted.

[PEER-REVIEWED] Radiofrequency directed at the **SPG** rather than the trigeminal ganglion has fared somewhat better and is still occasionally used: a prospective analysis of radiofrequency ablation or pulsed radiofrequency in **37 CCH patients**, mean follow-up 68 months, found **30% not improved** and 5 patients with total relief of headache and autonomic symptoms, with "a low complication rate… in comparison with SPG stimulation" (PMC8665918). In 3 patients pulsed radiofrequency failed and thermocoagulation of the SPG then succeeded, with follow-up ending at 11 months. The 2021 review grades SPG radiofrequency as: no RCTs, two small positive case series.

4.5.4 Gamma knife radiosurgery

[PEER-REVIEWED] After Ford et al.'s positive 1998 report, Donnet et al. ran a prospective open trial: 10 patients (9 men, 1 woman), mean age 49.8 (32–77), mean CCH duration 9 years (2–33), targeting the cisternal segment of the trigeminal nerve with a single 4 mm collimator at 80–85 Gy maximum dose; mean follow-up 13.2 months (*J Neurol Neurosurg Psychiatry* 2005;76(2):218).

Outcome	n
No improvement	2
No further attacks	3
Dramatic improvement (a few attacks/month or very few over 6 months)	3
Pain-free then recurrence (1 week; 2 weeks)	2

Complications: paraesthesia without hypoaesthesia 3; hypoaesthesia 1; **deafferentation pain 1**. The authors concluded that "the rate and severity of trigeminal nerve injury appeared significantly higher than in trigeminal neuralgia", that the study "did not support the positive results of Ford et al.", and that morbidity was "significant in relation to the low rate of pain cessation, making the procedure less attractive even for the more severely affected subgroup of patients" (JNNP 2005).

[PEER-REVIEWED] Systematic review: Franzini A, Clerici E, Navarria P, Picozzi P. "Gamma Knife radiosurgery for the treatment of cluster headache: a systematic review." *Neurosurg Rev* 2022;45(3):1923-1931, DOI 10.1007/s10143-021-01725-9, PMID 35112222. 5 studies, 52 patients described, 48 analysed (trigeminal nerve 34, SPG 1, both 13):

- Initial meaningful pain reduction: 60–100% across individual studies; **aggregate 37/48 (77%)**.

- **Meaningful pain reduction persisting at last follow-up: 20/48 (42%)** — i.e. roughly half of initial responders lost the benefit.
- **Trigeminal sensory disturbances: 28/48 (58%).**
- **Deafferentation pain: 3/48 (6%).**
- Conclusion: gamma knife targeting the trigeminal nerve or SPG is associated with "a frequent risk of trigeminal disturbances" and "possible deafferentation pain"; long-term results are "controversial".

Why largely abandoned: a 58% rate of permanent-risk trigeminal sensory disturbance and a 6% rate of deafferentation pain, in exchange for a benefit that persists in 42% — and the benefit is irreversible in neither direction (you cannot turn radiation off). Compared with a reversible, non-destructive implant, the risk-benefit maths collapsed.

4.5.5 Microvascular decompression (MVD)

[PEER-REVIEWED] Lovely TJ, Kotsiakis X, Jannetta PJ. "The surgical management of chronic cluster headache." *Headache* 1998;38(8):590-594, DOI 10.1046/j.1526-4610.1998.3808590.x, PMID 11398301. University of Pittsburgh — the Jannetta group, who invented MVD for trigeminal neuralgia.

- **28 patients** (2 bilateral) underwent **39 operations**: microvascular decompression of the trigeminal nerve, alone or combined with section and/or MVD of the nervus intermedius. Mean follow-up **5.3 years**.
- **Initial success (≥50% relief): 22/30 first-time procedures (73.3%).**
- **>90% relief: 15/30 (half).**
- **Long-term success ("excellent or good"): 46.6%.**
- **Repeat procedures: 7 of 8 failed at long-term follow-up (87.5% failure).**
- "Morbidity and neurological deficit from the operations was minimal" (no numerical complication rate given).
- Conclusion: "Chronic cluster headache remains a debilitating and poorly controlled syndrome."

Why abandoned for CH (but retained elsewhere): the durable success rate of ~47% after a posterior fossa craniotomy, with essentially no benefit from reoperation, is a poor trade. MVD remains a first-line procedure for **trigeminal neuralgia** and is still occasionally considered for **SUNCT/SUNA** — indeed the 2014 review concluded that "except for SUNCT/SUNA treated with microvascular decompression, neurostimulation techniques will be the choice in the future" (PMC4119587). For cluster headache specifically, it is essentially historical.

4.5.6 Greater occipital nerve blockade (still used, and standing apart from the rest)

[PEER-REVIEWED] Peres MF, Stiles MA, Siow HC, et al. "Greater occipital nerve blockade for cluster headache." *Cephalalgia* 2002;22:520-522. **14 patients**: 4 good response, 5 moderate response, 5 no response (cited in Leone, IHS).

[PEER-REVIEWED] Leone's assessment: the injection method "was widely used but had not been subjected to systematic evaluation", and without controlled studies it is hard to know whether the effect is "a pure corticosteroid effect on occipital muscles or… a specific effect on the greater occipital nerve" (Leone, IHS).

GON blockade is the one procedure on this list that was never abandoned. It is minimally invasive, reversible, cheap, and is explicitly listed by the EHF among the preventive treatments that count towards refractoriness criteria (EHF consensus 2014). It requires "appropriate clinical experience" to perform. If you have not had GON blockade, you have not exhausted the non-device options.

4.5.7 The EAN's summary judgement on surgery

[PEER-REVIEWED] "Surgical procedures are not indicated in most patients with cluster headache" (EAN 2023).

[PEER-REVIEWED] Leone's framing remains the standard: surgery is "a last-resort measure for treatment-resistant cluster patients and should be considered only after all pharmacologic options have been exhausted" (Leone, IHS).

4.5.8 The pattern worth naming

Read as a whole, the surgical history of cluster headache shows a single recurring failure mode: **destroying the anatomical structure through which the pain is transmitted does not reliably stop cluster headache, because cluster headache is not generated there.** Complete trigeminal analgesia — a fully numb face — was required for the best results, and even then attacks continued in some patients, recurred on the other side in others, and were sometimes replaced by anaesthesia dolorosa. The functional imaging that showed posterior hypothalamic activation in 1998, and Leone's DBS work from 2000–2001, reframed CH as a central disorder with peripheral expression, and every therapy since has been modulatory and reversible rather than destructive. That shift — from cutting to stimulating — is the single most important development in the surgical history of this disease.

4.6 Cross-Cutting Summary Table

Therapy	Best efficacy evidence	Responder definition used	Key safety issue	Availability 2025–2026	Australia
nVNS (gammaCore)	eCH acute: ACT2 48% vs 6% attacks pain-free at 15 min, p<0.01. **cCH acute: no effect (ACT2 5% vs 13%)**. cCH preventive: PREVA 40% vs 8.3% ≥50% responders	Varies: pain-free at 15 min; ≥50% attack reduction	Benign. Perioral myokymia ~7%; no serious device-related AEs	**Available**, electroCore commercially healthy	**Yes — ARTG 355575, Medistar. Prescription/authorisation only. NO subsidy. Price unpublished**
SPG stimulation (Pulsante)	CH-1: 67.1% vs 7.4% pain relief at 15 min. CH-2: 62.5% vs 38.9%, OR 2.62, p=0.008. Registry: 65% therapeutic responders	Acute responder; ≥50% frequency reduction; “therapeutic responder” (either)	81% facial sensory disturbance (mostly transient, some permanent); 5 SAEs in CH-1	**NOT AVAILABLE anywhere.** Realeve holds FDA Breakthrough designation only; >700 patients stranded since 2019	**No pathway**
ONS	Open-label 53–69% responders; L-ICON 59% at ≥50% for ≥half of 4.2 yrs. **But ICON found 30% dose = 100% dose, and Fogh-Andersen 2026 found placebo > burst ONS (p=0.042)**	≥50% (ICON/L-ICON); ≥30% (Fogh-Andersen)	72% ≥1 SAE over 4.2 yrs; **50% needed further surgery**; no biological SAEs. Modern technique far better (0 lead migrations in 45 pts)	**Available — the only CE-marked invasive CH option**	Performed in Australia at some centres for refractory cases; no specific data retrieved
DBS posterior hypothalamus	74.3% responders (78/105); frequency −70.1%; intensity −50.6%. **Only RCT was negative**	≥50% improvement in frequency and/or intensity	**1 death (<1%); major complications 16.67%; haemorrhage 0.93–3%; irreversible dysarthria and diplopia reported; transient diplopia 22%**	~108 published cases in 22 yrs; handful of tertiary centres; EAN makes no recommendation	**No realistic pathway**

Therapy	Best efficacy evidence	Responder definition used	Key safety issue	Availability 2025–2026	Australia
Trigeminal section/rhizotomy	76% long-term full/near-complete relief (17 pts)	Informal	**1 death, CSF leaks, meningitis, 2 patients needed surgery for corneal anaesthesia to prevent blindness; anaesthesia dolorosa**	Historical	Not offered
Gamma knife	77% initial response; **42% persisting**	"Meaningful pain reduction" (undefined)	**58% trigeminal sensory disturbance; 6% deafferentation pain; irreversible**	Essentially abandoned	Not offered
MVD	73.3% initial ≥50% relief; **46.6% long-term**; 87.5% of redo operations failed	≥50% relief	"Minimal" morbidity per authors; posterior fossa craniotomy	Historical for CH; retained for TN and possibly SUNCT/SUNA	Rarely
GON blockade	4/14 good, 5/14 moderate, 5/14 none	Informal	Minimal, reversible	**Widely used; counts towards EHF refractoriness criteria**	**Yes, routinely**

4.7 Honest Overall Assessment for a Person With Chronic Daily CH

1. **The therapy with the best trial evidence (SPG stimulation) is the one you cannot get.** Two positive sham-controlled RCTs, a strong EAN recommendation, and no manufacturer. That is the defining absurdity of this field.
2. **nVNS is realistically available to you in Australia, and the acute evidence in chronic CH is null.** ACT1 and ACT2 both put chronic patients numerically below sham for acute treatment. The case for trying it rests on PREVA — an *open-label* preventive trial — and on real-world series where 43% of refractory chronic patients hit ≥50% reduction at 3 months. NICE's "stop at 3 months if no reduction" rule is a sensible personal protocol, particularly given there is no Australian subsidy and the refill card counts down whether you use it or not.
3. **Two independent controlled designs have now failed to show that ONS's electricity is the active ingredient** (ICON's equal dose arms; Fogh-Andersen's placebo beating burst ONS). Long-term open-label outcomes are nonetheless good and 81% of L-ICON patients would recommend it. Both facts are real. If considering ONS, the surgeon's technique matters enormously — modern tined-lead technique produced zero lead migrations in 45 patients over 6 years, versus 25% in a 2003–2007 series.
4. **DBS should be treated as a last resort with a real, documented mortality.** One death in 108 published cases, 16.67% major complications, two patients left with irreversible neurological deficits, and the only randomised trial was negative. Leone's disease-modification finding is genuinely interesting and genuinely unreplicated.
5. **Destructive surgery is history for good reasons**, and the reasons — a numb face, anaesthesia dolorosa, corneal ulceration, contralateral recurrence — are worth knowing so you can recognise them if anyone ever proposes a variant.

6. **Verify the community sentiment gap:** there is essentially no structured citizen-science data on any of these devices in the CH community. The forum record is thin, and the loudest patient voices in the literature (Möllmann-Bohle, White) are about company abandonment, not efficacy. Anyone quoting confident "what patients say" figures about CH neuromodulation is likely extrapolating from very little.

---

5. Access & Practical Realities

Efficacy evidence is only half the picture. What a person can actually obtain — on a public health system, on private prescription, or by workaround — depends on drug registration status, subsidy listings, prescriber gatekeeping, and equipment funding rules that vary enormously by country. This section covers Australia in detail (with South Australia-specific notes), then contrasts the USA, UK, and Germany/EU as reference points, since Australian policy in this area (particularly home oxygen) does not track any of them cleanly.

5.1 Australia

5.1.1 The one-paragraph summary (South Australia)

For a chronic CH patient in South Australia, the blunt reality verified below is: **there is no PBS listing for oxygen, no PBS or state-funded home-oxygen pathway for cluster headache, and no PBS listing for injectable or nasal sumatriptan.** Oxygen for CH in SA is effectively a **private, self-funded arrangement** with a gas supplier on a doctor's prescription. Of the five treatments in the brief, only **oral sumatriptan tablets, oral zolmitriptan tablets and verapamil** are PBS-subsidised — and the triptan listings are restricted to *migraine*, not cluster headache. Galcanezumab (Emgality) is PBS-listed only for treatment-resistant migraine. gammaCore is TGA-approved for CH but has no published price and no PBS/Medicare subsidy that I could find.

5.1.2 High-flow oxygen access in Australia

1.2.1 What the clinical literature says you need

Australian Prescriber's CH review specifies **100% oxygen at 7–12 L/min for 15 minutes via a non-rebreather mask**, with **78% of patients pain-free at 15 minutes versus 20% on placebo**, and notes plainly that **"Oxygen may be ordered from medical gas supply companies in Australia with a prescription."** It also states that **"the drugs used for the acute and preventive treatment of cluster headache are off label, but supported by clinical evidence"** (Australian Prescriber — Cluster headache in adults). `[PEER-REVIEWED]`

The Sydney Headache Centre (Dr Ron Granot) puts the practical dose higher — **12–15 L/min via non-rebreather for 15–20 minutes**, first-line — and states it **"requires oxygen cylinder at home (respiratory equipment provider arranges)"** (Sydney Headache Centre). `[PEER-REVIEWED]` (clinician-authored clinical page)

Oxygen is contraindicated in active smokers and in type 2 respiratory failure (Australian Prescriber). `[PEER-REVIEWED]`

1.2.2 Is oxygen on the PBS? — verified: NO

I searched the PBS medicine database directly (pbs.gov.au, site last updated 1 August 2026):

- Search term **"oxygen" → "No results!"**
- Search term **"cluster headache" → "No results!"**

(PBS medicine search) `[OFFICIAL/POLICY]`

Conclusion: medical oxygen is not a PBS-listed item in Australia, and no PBS restriction anywhere in the schedule is indexed to "cluster headache." This is a verified negative, not an omission.

1.2.3 The South Australian state-funded pathway — and why CH doesn't fit it

SA Health runs a state-funded Home Oxygen Therapy program. Its published rules:

- **"To access home oxygen you will need to be reviewed by a respiratory specialist who will determine whether you may benefit from home oxygen therapy and meet the Thoracic Society of Australia & New Zealand (TSANZ) Home Oxygen Guidelines."** Referrals go to Local Health Network program coordinators (SA Health — Home Oxygen Therapy). `[OFFICIAL/POLICY]`
- **"Respiratory Physicians are the only medical team eligible to prescribe government funded home oxygen across South Australia."** Funding is for the patient's residence only (not aged care, rehab or hospital-in-the-home); DVA Gold Card holders are funded by DVA instead. Ongoing funding requires respiratory specialist review at 4–6 weeks and then at least every 12 months (SA Health — Home Oxygen Adult Clinical Prioritisation Criteria). `[OFFICIAL/POLICY]`
- **Every listed indication is hypoxaemia-based** — chronic hypoxaemia, acute hypoxaemia, exertional hypoxaemia, nocturnal hypoxaemia, emergency and palliative supply. **Cluster headache does not appear.** Explicit exclusions include current smokers/vapers (4 weeks' cessation required) and "dyspnoea with PaO2 ≥60 mmHg or SpO2 ≥90% on room air" (SA Health CPC). `[OFFICIAL/POLICY]`
- SA Health's patient booklet reinforces it: oxygen is funded where **"all other treatment for a condition has been given and the amount of oxygen in the blood still remains below a certain level,"** assessed by a **respiratory or sleep specialist**, with annual review and a minimum four-week smoking cessation requirement. Conditions named are heart problems, lung problems, sleep-related conditions and underdeveloped lungs in premature babies. **Cluster headache is not mentioned anywhere in the booklet** (SA Health Home Oxygen Therapy Booklet, PDF). `[OFFICIAL/POLICY]`

INFERENCE (clearly labelled): Because SA's funded criteria are entirely hypoxaemia-based and CH patients are by definition normoxaemic between and during attacks, **a CH patient in SA would not meet SA Health's criteria for state-funded home oxygen**. SA Health does not state "cluster headache is excluded" in so many words — it simply has no non-hypoxaemic indication. I could **not** find any SA Health document that either grants or explicitly refuses oxygen funding for CH: **UNKNOWN — not verified** whether an SA respiratory physician has ever obtained funded supply for a CH patient by exception.

1.2.4 The private pathway (what actually happens in SA)

BOC Australia's home medical oxygen therapy page states: **"If you are a self-funded or private patient, you along with your doctor will need to complete a referral form"** (emailed to healthcare@boc.com), and **"As a private patient you will be responsible to pay for your own HMOT equipment."** Phone 1800 050 999 (BOC Australia — Oxygen therapy). `[OFFICIAL/POLICY]` (supplier policy)

So the realistic SA sequence is: **GP or neurologist writes a prescription/referral for medical oxygen → you contact a medical gas supplier (BOC, Supagas, Air Liquide) directly → you rent the cylinder(s) and regulator and pay per refill.** No respiratory physician sign-off is required for the *private* route — that requirement attaches to *government-funded* supply only.

BOC/Supagas/Air Liquide published prices for CH-sized private supply: UNKNOWN — not verified. None of these suppliers publishes a public price list for private home oxygen; pricing is quoted per account. Community-reported figures are in §1.5.

1.2.5 Rebates and payments you may still be able to claim (SA)

- **SA electricity concession for oxygen concentrators:** a 50% electricity rebate for pensioners/health care card holders — but SA Health states it applies to people **"receiving state-funded home oxygen therapy."** Contact Concessions SA on 1800 307 758 or concessions@sa.gov.au (SA Health — Home Oxygen Therapy Rebate). `[OFFICIAL/POLICY]` **INFERENCE:** a privately funded CH patient using cylinders (not a concentrator) would not qualify.
- The same page notes DVA payments, that **"some private health insurers provide subsidies for oxygen equipment,"** and the federal **Essential Medical Equipment Payment** administered by Services Australia (SA Health). `[OFFICIAL/POLICY]` Whether any Australian private health fund actually pays for CH oxygen: **UNKNOWN — not**

verified.

1.2.6 How other Australian states compare (useful if you ever move, and as evidence of a national pattern)

State/scheme	Who can prescribe	Eligibility	CH covered?
SA Health	Respiratory physicians only, for government-funded supply (CPC)	TSANZ hypoxaemia guidelines	Not listed
QLD — MASS	Thoracic physician, specialist physician, oncologist, palliative care physician, or respiratory nurse practitioner with specialist endorsement; GP with specialist endorsement in rural/remote areas. Adults reassessed at 4 months then annually (Queensland Health MASS)	**"MASS does not subsidise oxygen for dyspnoea without hypoxaemia"**; not for current smokers; not for portable community access except in special circumstances	**Cluster headache is not mentioned; eligibility for CH is not stated** (MASS)
VIC — SWEP Domiciliary Oxygen Program	Physician-prescribed	Explicitly ineligible if **"the consumer does not fall within the Thoracic Society Guidelines"**, if the problem is not permanent, or if oxygen is for **"occasional use"**; PaO2 ≤55 mmHg, or 56–59 mmHg with hypoxic organ damage; 6–8 weeks' smoking cessation (SWEP Domiciliary Oxygen Prescriber Manual, PDF)	Not eligible — CH oxygen is by definition intermittent/"occasional use" and non-hypoxaemic (**INFERENCE**)
NSW — EnableNSW	—	Page blocked to automated retrieval	**UNKNOWN — not verified** (EnableNSW respiratory)
DVA	—	Domiciliary Medical Oxygen Therapy under the Rehabilitation Appliances Program (DVA DMOT)	**UNKNOWN — not verified** whether CH is an accepted DVA indication

QLD MASS is worth knowing for its concrete supply limits: **Package 5 = 1 × 'E' size cylinder, maximum 4 filled cylinders per month**; Package 4 = concentrator + one 'E' cylinder filled once every three months; suppliers are Air Liquide, Heeson Medical and Supagas (MASS oxygen packages and suppliers). `[OFFICIAL/POLICY]` Four E cylinders a month is far below what a chronic CH patient with multiple daily attacks would use — see the community reports in §1.5.

The pattern across every Australian state scheme I could verify is the same: funded home oxygen is gated on hypoxaemia and TSANZ long-term-oxygen-therapy criteria, which cluster headache does not meet.

5.1.3 Drug and device approval/subsidy status in Australia — verified item by item

All PBS statements below were checked directly on pbs.gov.au in August 2026 (schedule last updated 1 August 2026).

Sumatriptan

Form	TGA status	PBS status
Oral tablets	Registered	**PBS-listed.** Three items: 10694W (50 mg fast-disintegrating, 4), **1849H** (50 mg tablet, 4), **8144P** (50 mg tablet, 2). **Restricted Benefit; indication: "Migraine attack."** DPMQ $20.64 / $20.04 (8144P) and $20.41 (1849H) (PBS item 8144P, PBS item 1849H) `[OFFICIAL/POLICY]`
Injection 6 mg SC	**TGA-registered as CLUSTRAN**, ARTG 209316, **"indicated for the acute treatment of cluster headaches"** (TGA ARTG 209316) `[OFFICIAL/POLICY]`	**NOT on the PBS.** The PBS sumatriptan search returns one drug and three items — **all oral tablets. No injection item exists.** The healthdirect brand page for Clustran carries no "available on the PBS" flag, unlike PBS-listed brands (healthdirect — Clustran). **Private script, full price.**
Nasal spray	**Discontinued in Australia.** Aspen Pharma discontinued the nasal spray and injectable Imigran at the end of 2023 because its supplier stopped manufacturing and **"after an extensive search they have been unable to source an alternative manufacturer." "As they were the only nasal spray supplier, there are currently no suppliers of this form in Australia."** A compounding pharmacy may be able to prepare one on request (Migraine Australia — Imigran discontinuations) `[OFFICIAL/POLICY]` (patient-org reporting confirmed by sponsor)	N/A

Migraine Australia summarises the triptan situation bluntly: **"All five are available on the PBS, but not all preparations are covered by the PBS… you can get the tablet affordably but not the injection"** (Migraine Australia — Triptans). `[OFFICIAL/POLICY]`

Clustran retail price: UNKNOWN — not verified. Chemist Warehouse and Pharmacy Online both list the product (2 pre-filled pens, 6 mg/0.5 mL) but **neither publishes a price**; Pharmacy Online shows "Our Price $0.00" and requires a valid Australian prescription before shipping (Pharmacy Online — Clustran, Chemist Warehouse — Clustran). Ring a pharmacy for a quote — this is a genuine gap in public information.

Zolmitriptan

- **PBS: one item only — 8266C, zolmitriptan 2.5 mg tablet × 2, DPMQ $25.68**, with a $4.50 brand premium on Zomig (PBS item 8266C). `[OFFICIAL/POLICY]`
- **Intranasal zolmitriptan — the formulation with the CH evidence base — is currently not available in Australia** (Australian Prescriber). `[PEER-REVIEWED]` Corroborated: **"None of the other triptans are currently available in a non-oral formulation in Australia"** (Migraine Australia). `[OFFICIAL/POLICY]`

Verapamil (the mainstay CH preventive)

- **PBS General Schedule, cardiovascular body system, with no restriction text — i.e. unrestricted.** Items include **1241H** (240 mg modified-release × 30, DPMQ $20.92), **1250T** (80 mg × 100, $20.41) and **2208F** (180 mg MR × 30, $19.13) (PBS verapamil items). `[OFFICIAL/POLICY]`
- **Practical read:** because verapamil is unrestricted on the PBS, a GP can prescribe it at PBS price for CH without an authority, even though the use is off-label. This is the single cheapest and most accessible piece of the standard CH regimen in Australia. Note the off-label caveat from Australian Prescriber. `[PEER-REVIEWED]`

Galcanezumab (Emgality)

- **TGA Product Information: "EMGALITY is indicated for the prophylaxis of migraine in adults."** No cluster headache indication (TGA AusPAR PI, PDF). `[OFFICIAL/POLICY]`
- **PBS: items 12469G (continuing) and 12478R (initial), Authority Required (STREAMLINED), restriction number 14563, indication "Treatment-resistant migraine." DPMQ $523.36, patient charge $25.00** (PBS item 12469G); listed 1 June 2021 (PBS medicine status). `[OFFICIAL/POLICY]`
- **Bottom line: no PBS pathway for Emgality in cluster headache in Australia.** Off-label private supply would be at roughly the $523 DPMQ level per month, unsubsidised. (Note the 300 mg CH dose used in the US is 2.5× the 120 mg migraine dose, so real cost would be higher — see §2.3.)

gammaCore (non-invasive vagus nerve stimulator)

- **ARTG 355575.** The TGA advertising permission (dated 23 October 2023, last updated 10 September 2024) states: **"In Australia, GammaCore is indicated for the treatment and/or prevention of primary headache conditions (such as migraine and cluster headache) in adults"** and that it is **"available in Australia on authorisation by a registered healthcare professional"** (TGA advertising permission — Medistar/gammaCore). `[OFFICIAL/POLICY]`
- The Australian distributor (Medistar) requires an Authorisation and Consent Form from a healthcare professional; the device runs on refill cards that load days of therapy, and states the HCP provides initial and ongoing costs — **no prices are published** (Medistar — gammaCore for patients). `[OFFICIAL/POLICY]`
- **PBS/Medicare/Prostheses List subsidy for gammaCore in Australia: UNKNOWN — not verified.** It does not appear in the PBS medicine database (which covers medicines, not devices), and I found no MBS item or Prostheses List entry for it. **Australian price: UNKNOWN — not verified.** For scale, the NHS-facing price is £625 per 93 days ex-VAT (§4.4).

Australia summary table

Treatment	TGA-approved for CH?	PBS-subsidised for CH?	What you actually pay
High-flow oxygen	Not a PBS/TGA-listed medicine in Australia; supplied on prescription by gas companies	**No** — "oxygen" returns no results on the PBS	Full private cost (see §1.5 for community figures)
Sumatriptan tablets	Registered	Yes — but **restricted to "Migraine attack"**	~$20 DPMQ (general)
Sumatriptan injection (Clustran)	**Yes — CH is the labelled indication**	**No**	Private script, price not published
Sumatriptan nasal	**No supplier in Australia**	No	N/A
Zolmitriptan tablets	Registered	Yes (item 8266C)	$25.68 DPMQ
Zolmitriptan nasal	**Not available in Australia**	No	N/A
Verapamil	Registered (cardiac indications; CH use is off-label)	**Yes — unrestricted**	~$19–21 DPMQ
Galcanezumab (Emgality)	Migraine prophylaxis only	Only for **treatment-resistant migraine**	$25 co-pay if migraine criteria met; ~$523+/month private for CH
gammaCore	**Yes — CH named in the TGA-permitted indication**	Not found	Unknown; HCP-quoted

---

5.1.4 Who to see in Australia

- **The PBS/state rules mean the specialist you need for oxygen and the specialist you need for CH are different people.** A **neurologist or headache specialist** diagnoses and manages CH and writes the oxygen prescription for a private supplier; a **respiratory physician** is the only person who can access *government-funded* oxygen in SA — for a hypoxaemia indication you won't have (SA Health CPC). `[OFFICIAL/POLICY]`
- **Migraine & Headache Australia** (a division of the Brain Foundation) is the closest thing to a national headache patient body and has a CH page — but that page carries **no access, cost or oxygen-supply information** (Migraine & Headache Australia — Cluster Headache, Brain Foundation). `[OFFICIAL/POLICY]`
- **Is there an Australian equivalent of Clusterbusters or OUCH-UK?** After targeted searching: **no registered Australian CH-specific advocacy charity was found.** What exists is (a) **Migraine & Headache Australia**, (b) **Migraine Australia** (which does publish concrete access information — see Triptans and Discontinuations), (c) a patient-run site **Cluster Headaches Australia** (clusterheadaches.com.au), which is informational — it describes 100% oxygen via non-rebreather at "typically 12–15 litres per minute" and cites the 2023 European Academy of Neurology guideline, but it is not an advocacy organisation with an access-navigation service (Cluster Headaches Australia) `[COMMUNITY-REPORT]`, and (d) the **"Australia New Zealand Cluster Headache"** Facebook support group (see §1.5). A directory of world CH support groups lists exactly these two Australian entries and no advocacy charity (myclusters.nl — Patient support groups around the world). `[COMMUNITY-REPORT]`

5.1.5 Community knowledge on navigating access — Australia `[COMMUNITY-REPORT]`

Everything in this section is anecdotal patient report. None of it is verified policy. Some of it directly contradicts other reports, and I flag that where it happens.

The 2017 change.org petition (created 26 September 2017, 3,667 signatures) to the Minister for Health is the clearest documented statement of the Australian access problem from patients themselves: **"Proven front line abortives for this condition include Sumatriptan injections and 100% Medical grade oxygen. Both of which are not covered under the PBS Scheme and have**

high costs." It reports oxygen **"costing in excess of $300 a month"**, that **"medical grade oxygen requires a prescription… generally supplied by a neurologist"**, names **BOC and Supagas** as suppliers, and describes neurologist wait times of weeks to months at significant cost (change.org petition). `[COMMUNITY-REPORT]` — Note this petition's PBS claims **match** what I independently verified above, which raises its credibility on the cost figures.

Reddit r/ClusterHeadaches "Oxygen and Medicare" — an Australian thread (link) `[COMMUNITY-REPORT]`:

- **Explicit conflict:** the OP claimed **"Medicare covers the rental of medical oxygen cylinders for 36 months"**, while another commenter replied **"I am not aware of any Medicare rebate." My verification supports the sceptic**: there is no MBS/PBS oxygen item I could find, and the PBS returns no results for oxygen. Treat the "36 months" claim as **unverified and probably wrong** (it resembles the *US* Medicare DME 36-month oxygen rental rule, which does exist under US Medicare — see §2.1). `[COMMUNITY-REPORT]` + **INFERENCE**
- OP noted **"My Supagas paperwork lacks item numbers or claim details"** — consistent with there being nothing to claim.
- Costs reported: **~$15/month for a regulator**; **$188 for an E and D cylinder**; **Air Liquide $58.80 per E-size bottle** when self-collected; a Mega Medical **"Oxygen Demand Valve Resuscitator plus Regulator Series O" at roughly $800 for the pair**. An E cylinder was said to last about a week at CH usage rates.
- **QLD MASS supplies 4 E cylinders per month** and this was described as insufficient — which matches the official MASS Package 5 limit verified above (MASS packages).
- **Practical name worth knowing: "Kay Tebby at Supagas"** was described as having helped many Australians get supply set up, and as being active in the **"Australia New Zealand Cluster Headache" Facebook support group**. I could not independently verify this person's role — **UNKNOWN — not verified** — but it is the single most actionable lead in the Australian community material.

An Australian CH Facebook group post states that **"if you're in Australia and seeking medical oxygen for cluster… a doctor's prescription is required"** (Facebook group post). `[COMMUNITY-REPORT]` — I could not fetch the full post content (Facebook blocks retrieval), so treat the detail beyond that sentence as unverified.

Sydney anecdote on r/clusterheads describing local oxygen access (thread), and general community flow-rate consensus of **12–15 L/min, with 15–20 L/min described as ideal** (r/clusterheads oxygen thread, oxygen therapy thread). `[COMMUNITY-REPORT]` — note the community flow rate is **higher** than the 7–12 L/min in Australian Prescriber. That's a real, honest conflict between community practice and the Australian published guidance; the international literature and Clusterbusters both sit at 12–15 L/min.

Practical Australian checklist distilled from the above (community-derived, not official):

1. Get a **neurologist/headache specialist** diagnosis in writing — it's what suppliers and any funding conversation will hinge on.
2. Ask for the oxygen prescription to specify **100% oxygen, 12–15 L/min, via non-rebreather mask, 15–20 minutes per attack, as needed for cluster headache**, and to request **two large cylinders plus a portable** so you never run empty mid-bout.
3. **Check the regulator's maximum flow before accepting it** — many standard regulators cap at 15 L/min or lower, and a cap below 12 L/min makes the therapy fail.
4. **Do not accept a concentrator as a substitute** for CH abortive use (see §5).
5. Contact suppliers directly (BOC 1800 050 999 / referral form; Supagas; Air Liquide) and ask about **self-collection**, which community reports say is materially cheaper per refill.
6. Verapamil is unrestricted on the PBS — that part is cheap and your GP can handle it.
7. Ask your pharmacy for a **Clustran** price before you need it, and ask about a **compounded sumatriptan nasal spray** if injection cost is prohibitive (Migraine Australia).

5.2 United States

5.2.1 Oxygen — the big policy change of 2021

For decades US Medicare explicitly **did not cover** home oxygen for cluster headache under NCD 240.2.2.

On **2 July 2021** CMS issued a proposed decision memo (CAG-00296R2) to **remove NCD 240.2.2 (Home Oxygen Use to Treat Cluster Headache)** and modify NCD 240.2. Of 200 public comments, **188 were CH-related and all were supportive**; the request came from the **Alliance for Headache Disorders Advocacy** (CMS proposed decision memo CAG-00296R2). `[OFFICIAL/POLICY]`

The **final decision was published 27 September 2021**: CMS removed NCD 240.2.2 and revised NCD 240.2, so **coverage decisions for oxygen in these circumstances now sit with the Medicare Administrative Contractors (MACs)** rather than being nationally barred (Noridian DME MAC — Oxygen LCD L33797 update). `[OFFICIAL/POLICY]` The relevant LCD, **L33797 Oxygen and Oxygen Equipment**, confirms the September 27 2021 decision memo "Home use of Oxygen and Home Oxygen Use to Treat Cluster Headaches" in its history, is effective for services on or after 1 April 2023, and reimburses oxygen as a **bundled monthly rental payment** with a higher stationary-system allowance for flow rates above 4 L/min (CMS LCD L33797). `[OFFICIAL/POLICY]`

The earlier, superseded national non-coverage memo is at CMS NCA 244. `[OFFICIAL/POLICY]`

Important caveat, stated honestly: removing the national *non*-coverage rule is not the same as creating national *coverage*. **Whether any specific MAC now routinely pays for CH oxygen, and on what documentation: UNKNOWN — not verified.** The current CMS NCD 240.2 record page simply directs readers to their MAC (CMS NCD "Home Use of Oxygen"). `[OFFICIAL/POLICY]` In practice most US CH patients are under commercial insurance, not Medicare, and plan-by-plan variation is the norm.

5.2.2 Sumatriptan in the USA

- **FDA label for Imitrex injection: indicated for the acute treatment of migraine *and* of cluster headache** — the on-label status Australia lacks for the PBS but shares via Clustran (FDA Imitrex injection label, PDF). `[OFFICIAL/POLICY]`
- Cash pricing for generic sumatriptan subcutaneous 6 mg/0.5 mL is listed at **$14.19 per 0.5 mL unit; roughly $65.38–$69.95 for a 2-pack, or $44.75–$53.95 for a 5-pack** (USD; the aggregator does not date these) (Drugs.com price guide — sumatriptan). `[OFFICIAL/POLICY]` (commercial price aggregator — treat as indicative, not authoritative). This makes generic US injectable sumatriptan **dramatically cheaper than the Australian private route**, which is a genuine and unflattering comparison for Australia.

5.2.3 Galcanezumab (Emgality) in the USA

- **FDA-approved for both preventive treatment of migraine and treatment of episodic cluster headache** (FDA Emgality label, PDF). `[OFFICIAL/POLICY]` This is the crucial divergence: the US has an on-label CH indication that neither Australia nor the EU has.
- Cash cost is roughly **$700–$981 USD per month** depending on source, with the CH dose being **300 mg** versus 120 mg for migraine prevention (SingleCare, MedFinder). `[OFFICIAL/POLICY]` (commercial sources — indicative). Lilly's commercial-insurance savings card advertises **"as little as $35" for up to 12 months** (Emgality Savings Card). `[OFFICIAL/POLICY]` Prior-authorisation friction and denials are routinely reported (MedFinder). `[COMMUNITY-REPORT]`

5.2.4 gammaCore in the USA

FDA-cleared for episodic cluster headache (K211856), prescription required; reviewed for efficacy, safety and economic burden in episodic and chronic CH (AJMC review of nVNS/gammaCore). `[PEER-REVIEWED]` **US list price and insurance coverage: UNKNOWN — not verified.**

5.2.5 Verapamil in the USA

Generic, widely available, off-label for CH. **UNKNOWN — not verified** for specific US formulary tiers.

5.3 United Kingdom (the best-organised system of the four)

5.3.1 Oxygen — a dedicated CH pathway exists

NHS England's **"Good HOOF guide"** (4 November 2020) explicitly supports non-specialist primary care and out-of-hours teams ordering home oxygen for **palliative and cluster headache patients**, "normally following a consultant recommendation and not already under the care of a HOS-AR team" (NHS England — Good HOOF guide); the Home Oxygen Order Form (HOOF) documents are at NHS England — HOOF letters and guidance. `[OFFICIAL/POLICY]`

OUCH(UK) — the UK CH charity — documents the patient-side mechanics: in England and Wales **your GP can prescribe**; you can download a part-completed HOOF from OUCH's downloads; the GP completes the Home Oxygen Consent (HOC) and Initial Home Oxygen Risk Mitigation (IHORM) forms and submits the HOOF through the oxygen company portal; and **"it is specifically laid down in the Home Oxygen Assessment Service (HOAS) specification that GPs can prescribe oxygen for CH sufferers for pain relief."** OUCH puts response to oxygen at around **80%** and distinguishes **standard high-flow (SBOT)** from **demand valve** systems (OUCH(UK) — Oxygen for CH 2023, PDF). `[COMMUNITY-REPORT]` (patient charity guidance, corroborated by NHS documents)

Local implementation is concrete. Nottinghamshire APC's **Home Oxygen Pathway for Cluster Headaches v2.1** (reviewed November 2025) requires newly diagnosed patients to have neurologist confirmation; the neurologist completes the IHORM, HOCF and HOOF and sends them **direct to BOC via www.bochop.co.uk**; existing users need a GP referral to the Home Oxygen Service for a home safety assessment (Nottinghamshire APC pathway, PDF). `[OFFICIAL/POLICY]` There is also dedicated London cluster headache guidance for GPs and neurologists (Sept 2021). `[OFFICIAL/POLICY]`

Cost to the UK patient: home oxygen is supplied through the NHS home oxygen service at no charge to the patient. I did not find a single NHS page stating that in one sentence, so: the *absence* of a patient charge is implied by the HOOF/contracted-supplier model rather than explicitly verified — **INFERENCE**.

5.3.2 Drugs in the UK

- **Sumatriptan injection is licensed in the UK with cluster headache in its indication** (UK SmPC — sumatriptan injection). `[OFFICIAL/POLICY]`
- NHS prescriptions in England cost **£9.90 per item**, charged per item not per prescription; a **Prescription Prepayment Certificate (PPC)** is cheaper for people needing many items (NHS — prescription charges). `[OFFICIAL/POLICY]` (Prescriptions are free in Scotland, Wales and Northern Ireland — **UNKNOWN — not verified** from a primary source in this pass.)
- **Verapamil, zolmitriptan:** available on NHS prescription at the standard charge. **Specific NICE guidance on verapamil dosing for CH: UNKNOWN — not verified** in this pass (NICE CKS covers CH but was not fetched).
- **Galcanezumab for CH:** not licensed in the EU/UK for CH (see §4.2); **UK-specific NICE appraisal for CH: UNKNOWN — not verified**.

5.3.3 gammaCore — the UK is the only country with a positive HTA

NICE published **HTG533 "gammaCore for cluster headache" on 3 December 2019**, replacing MIB162 and MTG46, concluding **"Evidence supports the case for adopting gammaCore to treat cluster headache in the NHS"** and that **"gammaCore should be offered in addition to standard care."** Costs: **free of charge for the first 3 months (93 days), then £625 per 93 days excluding VAT**; modelling estimates a **£450 per person saving in the first year**, largely from reduced subcutaneous sumatriptan use. NICE also records the funding reality: **"It has been difficult for clinical services to get funding for gammaCore… the experts explained that they get it through individual patient funding requests to commissioners"** (NICE HTG533, PDF). `[OFFICIAL/POLICY]`

5.4 European Union / Germany

5.4.1 Germany has the strongest oxygen position of any country reviewed

Germany is the only country found where **oxygen is formally licensed as a medicine for cluster headache and the hardware is catalogued for that indication**:

- **BfArM approved "Sauerstoff, 100% Gas zur medizinischen Anwendung, druckverdichtet (Druckgasflaschen)" for the treatment of cluster headache on 14 December 2007, approval number 69557.00.00** (DMKG — Sauerstoffbehandlung bei Cluster-Kopfschmerz, PDF). `[OFFICIAL/POLICY]`
- In the statutory health insurers' **Hilfsmittelverzeichnis**, the **pressure regulator is listed under 14.24.05.0000 specifically for the indication cluster headache**, and the **oxygen cylinders themselves are consumables under 14.99.99.1** (DMKG — Empfehlungen Sauerstoff). `[OFFICIAL/POLICY]`
- **"Die Kosten für die Sauerstoffbehandlung werden von den gesetzlichen Krankenkassen übernommen, dazu ist eine ärztliche Verordnung erforderlich"** — the statutory health funds cover the cost of oxygen treatment; a medical prescription is required (DMKG PDF). `[OFFICIAL/POLICY]`
- The prescribing mechanics: for statutory-insured patients the doctor writes a **Hilfsmittelrezept** noting the required flow (**7–15 L/min, approx. 15–20 min per attack**) and the diagnosis; the patient takes it to a **Sanitätshaus**, which handles cost approval with the fund; in urgent cases contacting the fund directly saves time; **"Nur noch in Ausnahmefällen kommt es in den letzten Jahren zu Rückfragen des Medizinischen Dienstes"** (queries from the medical review service are now rare) (DMKG). `[OFFICIAL/POLICY]`
- DMKG's **model prescription** is worth copying almost verbatim in any country: **1 × pressure regulator with a 0–15 L/min range (Hilfsmittel position 14.24.05.0), 2 × 10-litre 200 bar medical oxygen cylinders (14.99.99.1), 2 × non-rebreather masks**, plus for mobile use an additional regulator and 2-litre cylinders (DMKG PDF). `[OFFICIAL/POLICY]`
- Two pointed pieces of German advice: **"Nicht sinnvoll ist ein Attest eines Lungenfacharztes"** — a certificate from a lung specialist is *not* useful — because **"Diagnose und Therapie des Clusterkopfschmerzens gehört als primäres Kopfschmerzsyndrom in das neurologische Fachgebiet"** (CH belongs to neurology, not respiratory medicine) (DMKG). `[OFFICIAL/POLICY]` **This is the exact opposite of the South Australian gatekeeping model**, where only respiratory physicians can access funded oxygen.
- German patient wiki guidance also warns that oxygen-conserving systems and concentrators, while appropriate for long-term oxygen therapy, are **explicitly not appropriate for cluster headache** (ck-wissen — Sauerstoff im Hilfsmittelverzeichnis). `[COMMUNITY-REPORT]`
- German patient co-payment amounts (the usual GKV Zuzahlung) for oxygen supply: **UNKNOWN — not verified**.

The German/DGN-DMKG guideline background confirms the clinical basis: oxygen inhalation efficacy proven in a placebo-controlled trial; **subcutaneous sumatriptan 6 mg and nasal zolmitriptan 5–10 mg** are the parenteral agents with the best acute efficacy (AWMF S1 guideline, Clusterkopfschmerz und trigeminoautonome Kopfschmerzen, PDF). `[PEER-REVIEWED]` (note: this version is marked expired/abgelaufen — a newer DMKG guideline exists at dmkg.de)

5.4.2 Galcanezumab was REFUSED for cluster headache in the EU

The EMA's CHMP **refused the extension of the Emgality marketing authorisation to episodic cluster headache on 28 February 2020** (procedure EMEA/H/C/004648/X/0004), on the grounds that **"superiority of galcanezumab compared with placebo in reducing the number of headache attacks within a cluster bout was not convincingly demonstrated"** (EMA Q&A on refusal, PDF; European Commission community register; Emgality EPAR). `[OFFICIAL/POLICY]` German coverage of the refusal: Schmerzklinik Kiel. `[PEER-REVIEWED]` (clinician-authored)

So: Emgality is on-label for episodic CH in the USA, refused for CH in the EU, and migraine-only in Australia. That is a genuine international regulatory conflict, and it is the honest answer to "why can't I get Emgality for my clusters here."

5.4.3 Other German/EU drug access

- **Sumatriptan 6 mg subcutaneous** is licensed and reimbursed in Germany; **nasal zolmitriptan (5–10 mg) is available in Europe** and is recommended in the German guideline (AWMF S1 guideline, PDF). `[PEER-REVIEWED]` **This is a formulation Australians simply cannot obtain** (Australian Prescriber).
- **Verapamil for CH in Germany is off-label**, as everywhere; **specific German Off-Label-Use reimbursement approval status: UNKNOWN — not verified**.
- A German home-care supplier publishes a CH oxygen prescription template citing DMKG first-line status at **8–12 L/min of 100% oxygen via mask** (OxyCare — Verordnung Cluster-Kopfschmerz, PDF). `[OFFICIAL/POLICY]` (supplier document)
- **gammaCore reimbursement in Germany/EU: UNKNOWN — not verified.**

5.5 Cross-Cutting Community Knowledge `[COMMUNITY-REPORT]`

Clusterbusters (US) publishes the most detailed practical oxygen guidance in the CH world:

- The prescription should read **“12–15 lpm with a nonrebreather mask”**, **“as needed for cluster headaches”** (Clusterbusters — Oxygen therapy for cluster headaches).
- **44% of oxygen users had to suggest oxygen to their doctors themselves** — self-advocacy is the norm, not the exception (same source). `[CITIZEN-SCIENCE]` (patient-org survey figure)
- **Concentrators are “essentially useless”** for aborting CH attacks, because they cannot deliver the required flow of 100% oxygen (same source). Corroborated independently by German patient guidance (ck-wissen).
- Ask for **two or more large tanks plus a small portable**; bring published studies to the appointment; consider changing doctors if refused (same source).
- **Minimum 12–15 LPM, and most suppliers’ standard regulators cap at 15 LPM** (Clusterbusters — oxygen resource).
- A **demand valve delivery system costs around $350 or more**; regulators rated to 15 lpm and above are sold by Linde Healthcare, Mada Medical and Flotec, and many patients buy them on eBay or Amazon (Clusterbusters knowledgebase). The same page notes some patients resort to **welding oxygen** because of insurance problems — recorded here as a documented community practice, **not** a recommendation.
- Clusterbusters also publishes a how-to guide to help providers successfully prescribe oxygen and a patient resources hub — both usable in Australia as documents to hand a reluctant GP.

Where the communities live: r/clusterheads and r/ClusterHeadaches on Reddit, the Clusterbuds and Clusterheads Discord servers, and country groups; for Australia specifically, the **“Australia New Zealand Cluster Headache” Facebook group** (myclusters.nl directory).

5.6 Side-by-Side Summary

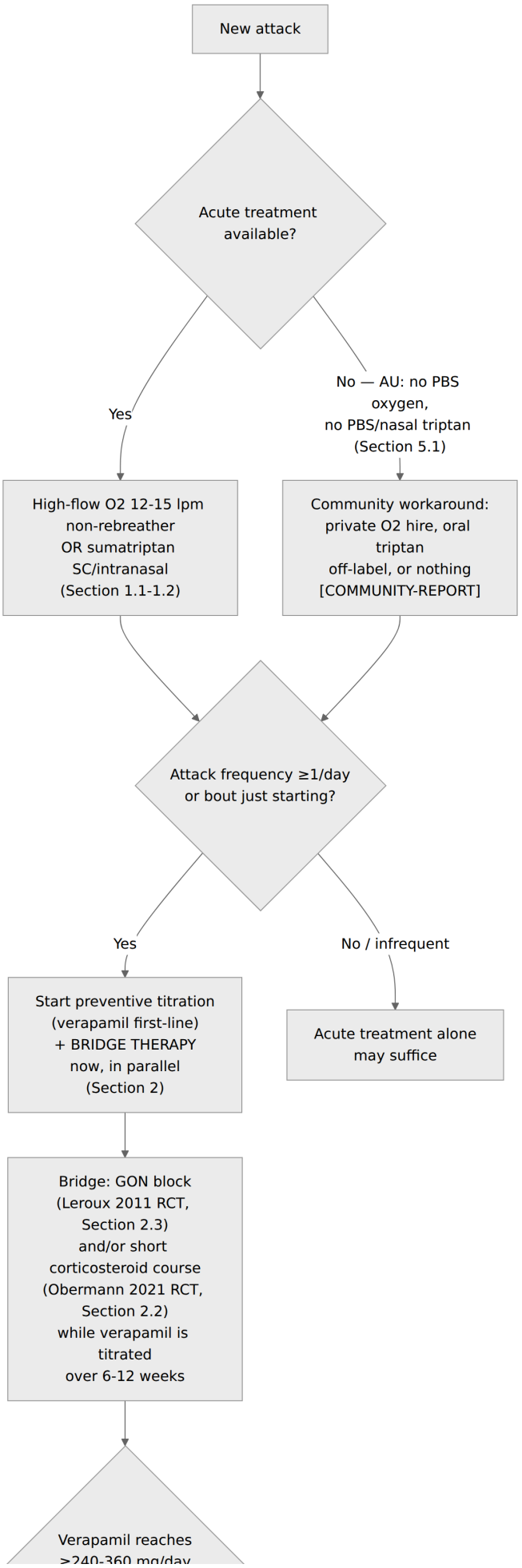
	Australia (SA)	USA	UK	Germany/EU
Oxygen licensed/listed for CH	No — not on PBS at all	N/A (device benefit, not a drug listing)	N/A (HOOF system)	**Yes — BfArM 69557.00.00 since 2007**
Who prescribes CH oxygen	Any doctor for a *private* supply; respiratory physician for *funded* supply (which CH doesn't qualify for)	Physician; MAC decides coverage	**GP can prescribe** (HOAS specification), usually after consultant recommendation	Neurologist; **explicitly not a lung specialist**
Who pays	**You do**	Medicare MAC discretion since Sept 2021; otherwise insurer	NHS	**Statutory health funds (GKV)**
Sumatriptan injection	TGA-approved for CH (Clustran) but **not on PBS**	On-label for CH; generic ~$65 USD/2-pack cash	Licensed for CH; £9.90 per item	Licensed and reimbursed
Nasal triptan for CH	**None available in Australia**	Available	Available	**Nasal zolmitriptan available and guideline-recommended**
Verapamil	**PBS unrestricted (~$20)**	Generic	NHS charge	Reimbursed (off-label)
Galcanezumab for CH	Migraine-only on PBS/TGA	**FDA-approved for episodic CH**	Not licensed for CH	**EMA refused, Feb 2020**
gammaCore	TGA-approved incl. CH; no subsidy found; price unpublished	FDA-cleared for episodic CH	**NICE HTG533 supports adoption**; £625/93 days after free 93 days	Unknown

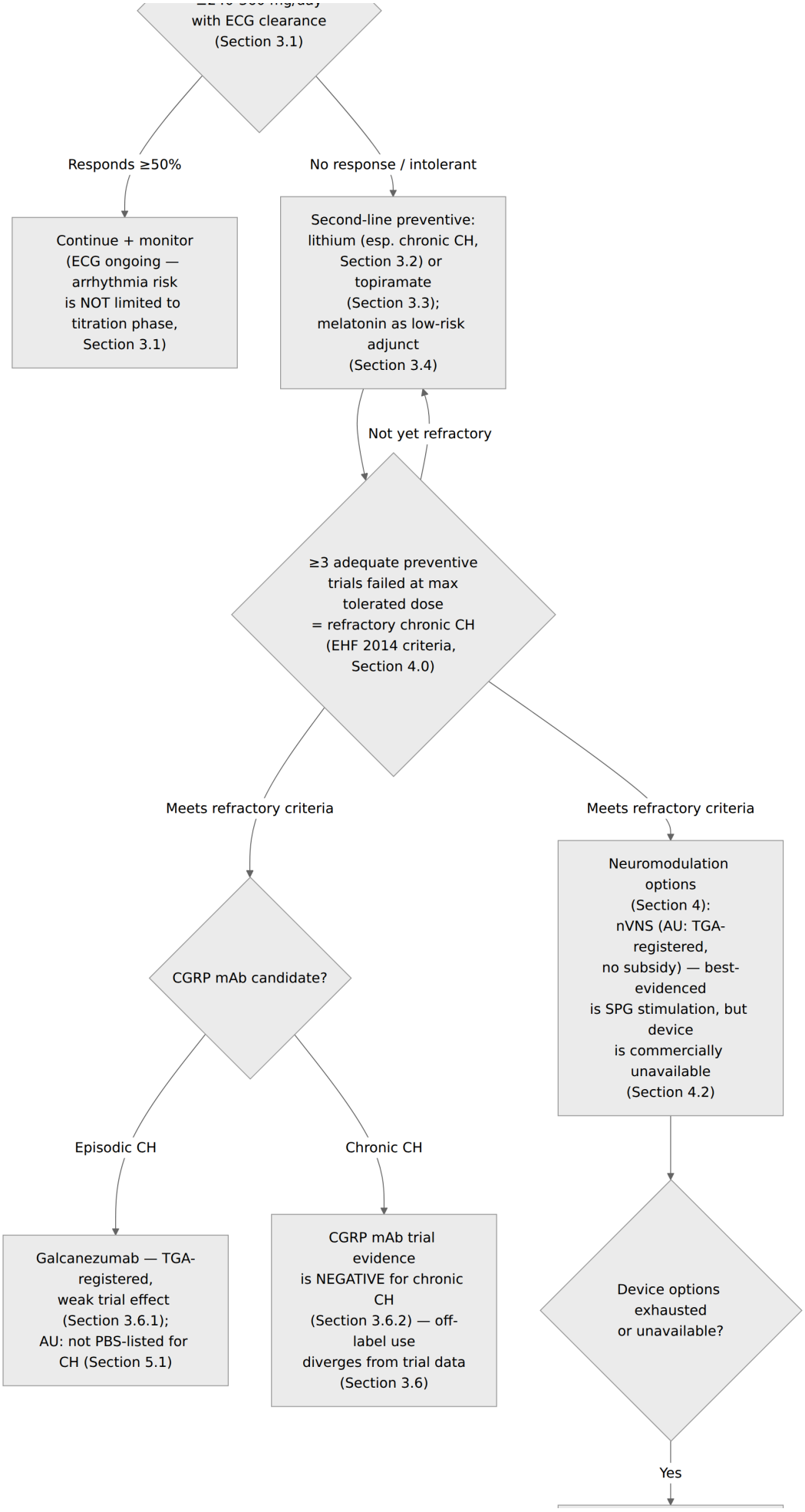
The single most important honest finding for an Australian reader: Australia has the *worst verified access position* of the four jurisdictions for the two most effective acute CH treatments. Oxygen has no subsidy pathway at all, and the injectable triptan that is TGA-approved *specifically for cluster headache* is not on the PBS, while the nasal formulations have left the market entirely.

---

6. Treatment Decision Tree

The diagram below is a synthesis of the pathway implied by the guidance and trial designs cited in Sections 1–3 above (Australian Prescriber 2022, EAN 2023, and the EHF refractory-CH consensus), not a new clinical recommendation. It shows how acute, bridge, and preventive treatment are meant to interlock, and marks where Australian access rules (Section 5.1) create a gap between the "textbook" pathway and what is actually obtainable.


New attack
Acute treatment available?
Yes
No — AU: no PBS oxygen, no PBS/nasal triptan (Section 5.1)
High-flow O2 12-15 lpm non-rebreather OR sumatriptan SC/intranasal (Section 1.1-1.2)
Community workaround: private O2 hire, oral triptan off-label, or nothing [COMMUNITY-REPORT]
Attack frequency ≥1/day or bout just starting?
Yes
No / infrequent
Start preventive titration (verapamil first-line) + BRIDGE THERAPY now, in parallel (Section 2)
Acute treatment alone may suffice
Bridge: GON block (Leroux 2011 RCT, Section 2.3) and/or short corticosteroid course (Obermann 2021 RCT, Section 2.2) while verapamil is titrated over 6-12 weeks
Verapamil reaches


with ECG clearance
(Section 3.1)
Responds ≥50%
No response / intolerant
Continue + monitor
(ECG ongoing —
arrhythmia risk
is NOT limited to
titration phase,
Section 3.1)
Second-line preventive:
lithium (esp. chronic CH,
Section 3.2) or
topiramate
(Section 3.3);
melatonin as low-risk
adjunct
(Section 3.4)
Not yet refractory
≥3 adequate preventive
trials failed at max
tolerated dose
= refractory chronic CH
(EHF 2014 criteria,
Section 4.0)
Meets refractory criteria
Meets refractory criteria
CGRP mAb candidate?
Neuromodulation
options
(Section 4):
nVNS (AU: TGA-
registered,
no subsidy) — best-
evidenced
is SPG stimulation, but
device
is commercially
unavailable
(Section 4.2)
Episodic CH
Chronic CH
Galcanezumab — TGA-
registered,
weak trial effect
(Section 3.6.1);
AU: not PBS-listed for
CH (Section 5.1)
CGRP mAb trial
evidence
is NEGATIVE for chronic
CH
(Section 3.6.2) — off-
label use
diverges from trial data
(Section 3.6)
Device options
exhausted
or unavailable?
Yes

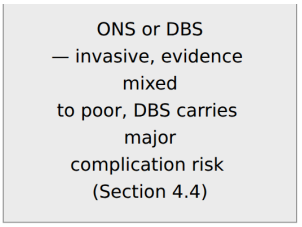


Diagram 3

Reading the diagram against Australian reality: the biggest divergence between the textbook pathway and what is actually available sits at the very first box. Oxygen — the acute treatment with the strongest and longest-standing evidence base — has no PBS pathway in Australia and is not subsidised as a home medical device for CH (Section 5.1). Nasal and injectable triptan formulations used internationally for fast abortive treatment are largely unavailable or unsubsidised here too. That means many Australian chronic sufferers enter the "bridge → preventive" arm of the tree without the acute-treatment layer functioning as designed elsewhere, which in turn raises the practical stakes of getting bridge and preventive therapy right quickly.

---

7. Cross-Cutting Observations, Oddities and Divergences

These are patterns that only become visible when the acute, bridge, preventive, neuromodulation and access material are read side by side. Individual items are also flagged within their own sections; they are gathered here because several of them recur across every treatment category and are easy to miss if the chapter is read section-by-section rather than as a whole.

7.1 The episodic/chronic split is the dominant axis of this entire chapter

`[PEER-REVIEWED]` `[CITIZEN-SCIENCE]` Wherever a treatment's trial or survey data is broken down by CH subtype, chronic patients do worse — sometimes dramatically so. Zolmitriptan 10 mg intranasal: 80% response episodic vs **36% chronic** (Cittadini 2006). GON block complete response 67.2% vs **50%**, pain-free duration 33.6 vs **14.3 days** (Gaul 2017); Merli complete response 47.8% vs **33.3%** (Merli 2022). A survey meta-analysis found oxygen and triptans both significantly less effective in chronic CH (Rusanen 2022). Verapamil: 94% vs 55% complete relief in one comparison (Blau & Engel), 44% vs 34% real-world response in a Danish survey. Melatonin: 50% responders episodic vs 0/2 chronic. Topiramate: 26% vs 10%. Galcanezumab: positive episodic trial, negative chronic trial. Eptinezumab: failed even in episodic. **Almost every drug and procedure in this chapter works less well, more slowly, or not at all in chronic disease than the headline figure you will most often be quoted implies — and the headline figure is almost always the episodic one.** Lithium is the notable partial exception: it has the strongest open-label data specifically in chronic CH, and is also the one major preventive whose use in chronic CH has never been put through a randomised trial (Section 3.2).

7.2 The citizen-science ranking largely validates clinical evidence — with one major exception

`[CITIZEN-SCIENCE]` Rusanen et al.'s hierarchical clustering of 8 patient surveys (5,419 respondents combined) places corticosteroids and verapamil in the high-efficacy prophylactic clade, and melatonin, valproic acid, gabapentin, amitriptyline and propranolol in the low-efficacy clade — concluding the "reported order of efficacy is generally in agreement with clinical studies" with "no results disagreeing with the current knowledge" (PMC9436841). The exception: **serotonergic psychedelics (LSD, psilocybin, ergoline alkaloids such as LSA) rank highest of all self-reported prophylactics, at roughly 75% efficacy — above verapamil and above corticosteroids** — despite essentially no randomised evidence at the time of that review. This sits outside the scope of a chapter organised around conventional pharmacology and procedures, but it is the single largest gap between community-reported efficacy and formal trial evidence identified anywhere in this research pass, and is flagged here so it is not lost. The reviewers themselves caution that support-group samples may be systematically less satisfied with conventional treatment (deflating verapamil/steroid rankings) and that some patient communities openly endorse tryptamines and ergolines (inflating that ranking) — both biases point the same direction, so the true effect size is more uncertain than the survey ranking alone suggests, but the pattern itself is unlikely to be pure artefact.

7.3 Cardiac monitoring failure on verapamil is real and documented from two independent directions, and the danger window is wider than commonly advised

`[PEER-REVIEWED]` `[COMMUNITY-REPORT]` 41% of 217 patients on a mean 512 mg/day of verapamil had never had an ECG in one peer-reviewed case series (Section 3.1); r/clusterheads users independently and repeatedly report never being offered ECG monitoring despite reporting cardiac symptoms. This matters because arrhythmia risk is not confined to the titration period — in a French series roughly 75% of serious arrhythmias appeared more than two years into treatment and were not clearly dose-dependent (Section 3.1). The common patient-facing advice to relax monitoring once a stable dose is reached is not well supported by that data.

7.4 Access, not efficacy, is frequently the binding constraint — and this cuts across every treatment category, not just oxygen

`[PEER-REVIEWED]` `[COMMUNITY-REPORT]` Oxygen has one of the best benefit-to-harm ratios of any CH treatment and no meaningful daily-use ceiling, and it is simultaneously the treatment patients are most likely to be unable to obtain through their health system. US Medicare patients report paying over $5,000/year out of pocket (Section 5.2); UK smokers and their housemates can be excluded from home oxygen supply outright under some local policies (Section 5.3); Australians have no PBS pathway for oxygen at all and pay privately (Section 5.1); Germany and Japan, by contrast, have oxygen specifically licensed and reimbursed for CH (Section 5.4). The same pattern repeats for CGRP mAbs (PBS-listed for migraine but not cluster headache in Australia; EMA-rejected in Europe) and for gammaCore (TGA-registered in Australia but with no subsidy attached). **In this disease, whether a treatment reaches a patient is often decided by which country's reimbursement paperwork they are filed under, independent of how good the evidence for that treatment actually is.**

7.5 Language bias in the literature is measurable, not hypothetical, and non-English sourcing changed several conclusions in this chapter

`[PEER-REVIEWED]` Some systematic reviews explicitly exclude non-English sources (one review excluded 19 non-English articles outright; another searched English-language terms only). Material that surfaced only in non-English sources during this research and materially affected specific sections: Japan's 7 L/min oxygen flow guideline and 2018 home-oxygen reimbursement criteria (Section 1.1 / 5.5); Germany's 2007 BfArM licensing of oxygen specifically for cluster headache, including a model prescription with cylinder sizing (Section 5.4); Danish real-world survey data on verapamil response rates that conflict with the pivotal RCT (Section 3.1); and German clinic dosing protocols for verapamil that contradict the dominant English-language community view on immediate-release vs sustained-release formulation (Section 3.1). Roughly a third of the practically useful detail in this chapter's preventive and access sections came from non-Anglophone sources, and the chapter is very likely still missing relevant Scandinavian, Italian, Japanese and Chinese clinical literature that a fully multilingual search would surface.

7.6 Community practice on hardware/technique frequently outruns formal guidance; community explanations of mechanism frequently lag behind or diverge from it

`[COMMUNITY-REPORT]` `[PEER-REVIEWED]` The community's insistence on non-rebreather masks, reservoir bags, blocking side vents, high flow rates and demand valves for oxygen delivery is grounded in real gas-delivery physics and is supported by FiO_2 measurement data. Its explanatory folk-physiology account of hypothalamic "false alarms" and dilating blood vessels is not established mechanism. Similarly, community reports of hair loss on galcanezumab (reported independently across at least three separate r/clusterheads threads) and of tachyphylaxis developing 6–24 months into CGRP mAb treatment (Section 3.6) are not captured in any labelled adverse-event list or published trial — not because they are false, but because nobody has formally studied either. **Take the accumulated technique seriously; treat the folk mechanism and the unstudied side-effect reports as flagged-but-unverified, not as established fact.**

7.7 The field has been strikingly static for 20–25 years, with a partial exception in neuromodulation

`[PEER-REVIEWED]` The pivotal verapamil trial is from 2000. The lithium-vs-verapamil comparison is from 1990. The one positive melatonin trial is from 1996. The capsaicin trial is from 1993. The clonidine pilot is from 1995. The baclofen pilot is from 2001. The warfarin trial (Section 3.5), with the single best NNT in the entire chapter (2.6), is from 2011 and has never been replicated in fifteen years. The one genuinely new pharmacological mechanism of the last decade — CGRP blockade — has now failed to show benefit in chronic CH across one adequately powered RCT and, per the 2026 meta-analyses that agree on this point even while disagreeing on episodic CH, the chronic-CH null result looks robust (Section 3.6). Neuromodulation is the partial exception: SPG stimulation and posterior-hypothalamic DBS are genuinely newer developments with their own trial bases, though the best-evidenced device (SPG stimulation) is no longer commercially available because its manufacturer dissolved (Section 4.2) — itself a striking failure mode, where the *evidence* problem in a treatment has been solved but the *access* problem has gotten worse, not better.

7.8 The disease's severity is independently documented, not a matter of patient self-report alone

`[PEER-REVIEWED]` Suicidal ideation is reported in 55% of CH patients in peer-reviewed data (Brandt et al. 2020). Japan's national headache society guideline states plainly that in severe cases self-harm to the head and suicide attempts have been reported, and describes the pain as characterised as stronger than labour pain. Australian Prescriber notes the colloquial name "suicide headache" and a diagnostic delay of up to eight years. This is documented in mainstream peer-reviewed and guideline literature, independently of the patient-forum record — it is a recognised clinical feature of the disease, not an exaggeration of it.

References (Part V)

1. JAMA 2009; PMID 19996400
2. 10.1001/jama.2009.1855
3. Guo et al., Med Gas Res 2019, PMC7802413
4. JHS CQ1
5. PMC8720466
6. 10.1002/14651858.CD005219.pub3
7. PMC6755552
8. 10.1186/s10194-018-0917-4
9. EAN 2023
10. Cephalalgia PDF
11. 10.1111/pme.12055
12. 10.1177/0333102415616878
13. King's College London research portal
14. Ray, Stark, Hutton, Aust Prescr 2022;45:15–20
15. 10.18773/austprescr.2022.004
16. OUCH-UK, Oxygen for CH 2023
17. PMC9163947
18. 10.3988/jcn.2022.18.3.271
19. DMKG "Sauerstoffbehandlung bei Cluster-Kopfschmerz"
20. Exeter Headache Clinic 2021/2023
21. OUCH Belgium oxygen leaflet
22. OUCH-UK forum, oxygen use
23. Clusterbusters CMS coverage page
24. Clusterbusters oxygen knowledgebase
25. clusterinfo.org oxygen guide

26. Clusterbusters provider guide
27. r/clusterheads thread
28. PMID 30221765
29. 10.1111/head.13405
30. PMID 30632614
31. PMC9436841
32. 10.1007/s11916-022-01063-5
33. OUCH-UK GP/neurologist information
34. NHS England London
35. CMS decision memo
36. CMS public comments
37. Alliance for Patient Access
38. US Pain Foundation, “The Never-Ending Battle for Oxygen Coverage”
39. DMKG 2016 cluster guideline
40. DGN guideline
41. MHLW documentation
42. Japanese Neurology Society 2021 headache guideline
43. Sundhed.dk patient handbook, klyngehovedpine
44. Ugeskrift for Læger review
45. DHOS Referenceprogram 2010
46. PMID 1647496
47. 10.1056/NEJM199108013250505
48. PMC4170909
49. 10.1002/14651858.CD008042.pub2
50. Leone & Proietti Cecchini 2016, PMC4731683
51. PMID 12601104
52. 10.1212/01.WNL.0000046589.45855.30
53. PMID 16966497
54. 10.1001/archneur.63.11.nct60002
55. PMID 17724283
56. 10.1212/01.wnl.0000267886.85210.37
57. NHS, sumatriptan dosing
58. WHO EML application
59. Aust Prescr 2022
60. 10.1212/WNL.0000000000002117
61. PMID 11062845
62. PMC7018790
63. 10.1007/s40263-019-00696-2
64. PMID 7737866
65. 10.1111/j.1526-4610.1995.hed3502083.x
66. reviewed at BestBETs
67. PMID 30098024
68. PMC3359256
69. DHE narrative review, PMC7003832
70. PMID 3520384
71. 10.1212/wnl.36.7.995
72. Nagy et al., Neurology
73. PMC7200221
74. PMID 15455406

75. 10.1002/ana.20210
76. PMID 33245858
77. [10.1016/S1474-4422(20)30363-X](https://doi.org/10.1016/S1474-4422(20)
78. Leroux & Ducros, Curr Pain Headache Rep 2013;17:325
79. Ambrosini et al., Pain 2005
80. 10.1016/j.pain.2005.07.015
81. PMID 21903477
82. [10.1016/S1474-4422(11)70186-7](https://doi.org/10.1016/S1474-4422(11)
83. PMID 21903478
84. 10.1177/0333102416654886
85. PMC3620288
86. 10.1186/1129-2377-14-S1-P60
87. PMC8940833
88. 10.1007/s00415-021-10884-0
89. Drug Treatment of Cluster Headache, PMC8748342
90. Robbins MS, Starling AJ, Pringsheim TM, Becker WJ, Schwedt TJ. *Headache* 2016;56(7):1093–1106, DOI 10.1111/head.12866, PMID 27432623
91. Schmerzklinik Kiel, German-language
92. WHO 25th EML Expert Committee review
93. 10.1212/WNL.54.6.1382
94. 10.1111/j.1526-4610.1990.hed3007411.x
95. Spanish-hosted review of lithium literature, SciELO
96. European Academy of Neurology guidelines on cluster headache, 2023, DOI 10.1111/ene.15956
97. BASH verapamil regime
98. Koppen H, et al. *Cephalalgia* 2016, DOI 10.1177/0333102416631968
99. PMC3072493
100. thread
101. thread
102. thread
103. *Neurologie pro praxi* 2025;26(1):54–60
104. PMC10476341
105. 9350389
106. e.g. Peres & Rozen case 1’s history of failed lithium 900 mg
107. 10.1046/j.1468-2982.2003.00665.x
108. 10.1097/WNF.0000000000000678
109. 41805259
110. Nilsson Remahl AIM, Laudon Meyer E, Cordonnier C, Goadsby PJ. *Placebo Response in Cluster Headache Trials: A Review*, Cephalalgia 2003
111. 10.1212/WNL.0000000000207240
112. PMC10259280
113. Gooriah R, Buture A, Ahmed F. *Ther Clin Risk Manag* 2015;11:1687–1696, DOI 10.2147/TCRM.S94193, PMC4646474
114. 8933994
115. 10.1046/j.1468-2982.1996.1607494.x
116. 10.1046/j.1526-4610.2002.02181.x
117. 12390642
118. 21395575
119. 12056936
120. 10.1046/j.1468-2982.1993.1302114.x
121. 8495452

122. 12047460
123. 20055254
124. r/clusterheads NHS thread
125. 10.1007/s11916-001-0014-1
126. 11252142
127. 10.1046/j.1468-2982.1995.1505430.x
128. 8536305
129. systematic review and meta-analysis, *Headache Medicine*
130. PMC4853809
131. 10.1056/NEJMoa1813440
132. 10.1177/0333102420905321
133. 32050782
134. 32266593
135. PMC7419360
136. 10.1001/jamaneurol.2025.1317
137. Lundbeck newsroom, 2024
138. [10.1016/S1474-4422(25)00065-1](https://doi.org/10.1016/S1474-4422(25)
139. 40252664
140. Thieme
141. 10.1007/s10072-026-09078-1
142. 42118310
143. 10.1177/03331024261434209
144. 41961550
145. 10.1177/03331024231226181
146. 38501892
147. Emgality for chronic CH thread
148. How long for Emgality to kick in
149. PBS galcanezumab listing
150. Australian Government Department of Health announcement on expanded Emgality PBS listing
151. Migraine Australia
152. Headache Australia
153. Mitsikostas DD, Edvinsson L, Jensen RH, Katsarava Z, Lampl C, Negro A, Osipova V, Paemeleire K, Siva A, Valade D, Martelletti P. *J Headache Pain* 2014;15(1):79. DOI 10.1186/1129-2377-15-79, PMID 25430992
154. Neurostimulation Treatment in Chronic Cluster Headache — a Narrative Review, *Neurol Ther* / PMC8665918, 2021
155. Medistar Australia — gammaCore for Patients
156. PMID 27593728
157. Goadsby 2018, DOI 10.1177/0333102417744362
158. PMID 31246132 / PMC6637721
159. PMID 28197844 / PMC5309191
160. PMID 37515405
161. NICE MTG46, evidence chapter
162. NICE HTG533 committee discussion
163. PMID 34322861 / PMC8611122
164. *Ont Health Technol Assess Ser* 2025;25(2):1-177, PMID 40496978 / PMC12148001
165. NeurologyLive
166. TGA advertising permissions — Medistar 2 Pty Ltd, gammaCore
167. Migraine Australia — Devices
168. Medistar — How to prescribe gammaCore in AU
169. electroCore investor release

170. ClusterBusters forum thread
171. r/ClusterHeadaches — vagus nerve stimulation
172. PMID 32109020
173. gammaCore reviews
174. Trigeminal Autonomic Cephalalgias: Beyond the Conventional Treatments, *Curr Pain Headache Rep* 2014;18(8):438 / PMC4119587
175. PMID 23314784 / PMC3724276
176. PMID 31701891
177. PMID 29349561 / PMC5773459
178. SAGE
179. PMC4961666
180. NHS England clinical commissioning policy document
181. UK Companies House, company 07239097
182. *Nature* — Abandoned
183. Neurotech Reports
184. BusinessWire, 18 August 2021
185. Realeve / Unity HA Breakthrough Device announcement
186. BusinessWire, 20 September 2023
187. Promex Industries, 8 May 2025
188. Realeve, January 2025
189. PMID 34146510
190. L-ICON, *eBioMedicine* 2023, DOI 10.1016/j.ebiom.2023.104895, PMC10755111
191. PMID 41803706 / PMC12980930
192. Falowski 2010
193. PMID 39607056
194. r/migraine — Experience with occipital nerve stimulation?
195. cited in Leone & Proietti Cecchini, *Cephalalgia* 2016, DOI 10.1177/0333102415607176
196. Karger systematic review
197. PMID 15689358
198. cited in Leone, IHS
199. PMID 11398301
200. cited in JNNP gamma knife trial
201. PMID 12707445
202. PMID 35112222
203. Sydney Headache Centre
204. PBS medicine search
205. SA Health — Home Oxygen Therapy
206. SA Health — Home Oxygen Adult Clinical Prioritisation Criteria
207. SA Health Home Oxygen Therapy Booklet, PDF
208. BOC Australia — Oxygen therapy
209. SA Health — Home Oxygen Therapy Rebate
210. Queensland Health MASS
211. SWEP Domiciliary Oxygen Prescriber Manual, PDF
212. EnableNSW respiratory
213. DVA DMOT
214. MASS oxygen packages and suppliers
215. PBS item 8144P
216. PBS item 1849H
217. TGA ARTG 209316

218. healthdirect — Clustran
219. Migraine Australia — Imigran discontinuations
220. Migraine Australia — Triptans
221. Pharmacy Online — Clustran
222. Chemist Warehouse — Clustran
223. PBS item 8266C
224. PBS verapamil items
225. TGA AusPAR PI, PDF
226. PBS item 12469G
227. PBS medicine status
228. Migraine & Headache Australia — Cluster Headache
229. Brain Foundation
230. Cluster Headaches Australia
231. myclusters.nl — Patient support groups around the world
232. change.org petition
233. link
234. Facebook group post
235. thread
236. r/clusterheads oxygen thread
237. oxygen therapy thread
238. CMS proposed decision memo CAG-00296R2
239. Noridian DME MAC — Oxygen LCD L33797 update
240. CMS LCD L33797
241. CMS NCD “Home Use of Oxygen”
242. FDA Imitrex injection label, PDF
243. Drugs.com price guide — sumatriptan
244. FDA Emgality label, PDF
245. SingleCare
246. MedFinder
247. Emgality Savings Card
248. AJMC review of nVNS/gammaCore
249. NHS England — Good HOOF guide
250. NHS England — HOOF letters and guidance
251. Nottinghamshire APC pathway, PDF
252. London cluster headache guidance for GPs and neurologists (Sept 2021)
253. UK SmPC — sumatriptan injection
254. NHS — prescription charges
255. NICE HTG533, PDF
256. DMKG — Empfehlungen Sauerstoff
257. ck-wissen — Sauerstoff im Hilfsmittelverzeichnis
258. AWMF S1 guideline, Clusterkopfschmerz und trigeminoautonome Kopfschmerzen, PDF
259. dmkg.de
260. EMA Q&A on refusal, PDF
261. European Commission community register
262. Emgality EPAR
263. Schmerzklinik Kiel
264. OxyCare — Verordnung Cluster-Kopfschmerz, PDF
265. Clusterbusters — Oxygen therapy for cluster headaches
266. Clusterbusters — oxygen resource

267. patient resources hub

Part VI — What Sufferers Have Worked Out: Citizen Science and Community Knowledge

Source: Chapter 4 in full (revised 13 August 2026 by its own follow-up research pass). Section numbering and the part's own reference list retained from the source chapter.

What the patient community has worked out for itself: the organised community, its data, the threads it identified before formal science did, and where community and clinic agree or diverge.

Revised 13 August 2026: a targeted follow-up research pass resolved several items flagged as open questions in the original version of this chapter — including the outcome of the vitamin D3 RCT, the current status of the Australian PEACE trial and the BOL-148/Ceruvia programme, a correction to the EPOCH trial's framing, and a language-by-language check of non-English patient-community citizen science. Updates are marked inline and summarised in the revised "Open Questions & Loose Threads" section at the end.

Cluster headache (CH) is a condition where the patient community has, in several documented instances, outrun formal medicine — not by accident, but through organised, semi-structured self-experimentation, data-sharing, and advocacy that pre-dated (and in the psychedelic case, directly caused) academic research programmes. This chapter treats that body of community knowledge as data, labelled honestly by evidentiary tier, alongside the peer-reviewed literature it has generated.

---

1. The Organised Community

Clusterbusters: origin and structure

Clusterbusters traces its origin to late 1998, when a man posting under the handle "Flash" on an internet bulletin board reported that LSD had interrupted his usual cluster cycles [PEER-REVIEWED/HISTORICAL][^1][^2]. Skepticism was the initial community response — sufferers had seen "a hundred scams" — but the claim had a plausible pharmacological basis: indole-ring hallucinogens bind serotonin receptors, and Albert Hofmann had originally investigated LSD partly as a headache/migraine treatment [HISTORICAL/CULTURAL][^1]. As reports of psilocybin use with similar results accumulated, a core group of self-described advisors and researchers built a website ("The Treatment of Vascular Headaches with Hallucinogenic Substances") and ran structured discussion and self-experimentation through 2000–2001 [COMMUNITY-REPORT][^1]. Concerns about the illegality of LSD and psilocybin for members in sensitive professions led the group to relocate and formalise; Clusterbusters, Inc. was founded in 2002 by Bob Wold, a long-time chronic CH patient, and registered as a US 501(c)(3) non-profit [HISTORICAL/CULTURAL][^3][^4][^5].

Clusterbusters now runs annual patient conferences in the US bringing together patients, caregivers, and headache specialists, and its directors are regularly invited to present at neurology and headache conferences [HISTORICAL/CULTURAL][^1][^5]. Its role has been documented in a full-length academic history — Joanna Kempner's book *Psychedelic Outlaws* — and in mainstream science press (*Nature*, 2006) as the origin point of what became a formal psilocybin research agenda at Harvard and Yale [HISTORICAL/CULTURAL][^2][^6][^7]. The organisation has since been involved, as a research partner (not merely a subject pool), in projects at Harvard, Yale, McGill, the University of West Georgia, and Hannover Medical School in Germany [HISTORICAL/CULTURAL][^3].

National and language-specific equivalents

OUCH(UK) — the Organisation for the Understanding of Cluster Headache — was founded independently of Clusterbusters, arising from UK patients meeting each other in NHS waiting rooms; it launched in 2001 and became a registered charity in 2002, with roughly 40 founding members and now a forum community exceeding 5,000 [HISTORICAL/CULTURAL][^8][^9][^10]. It is patronised by Professor Peter Goadsby and works with the Royal Free and King's College Hospitals in London [HISTORICAL/CULTURAL][^8]. On the clinical-research side rather than patient-advocacy side, the Danish Headache Center in

Copenhagen (Rigshospitalet) has run large patient-derived surveys such as the Danish Cluster Headache Survey, a “real-life treatment” study drawing on structured patient data from a tertiary clinic population [PEER-REVIEWED][^12]. A 2026 review in *Practical Neurology* traces the wider pattern: OUCH itself grew out of the same clusterheadaches.com message board that produced Clusterbusters, with Bob Wold’s 2002 non-profit and the UK charity as parallel, independently-arising responses to the same patient need [HISTORICAL/CULTURAL][^66].

Following up on this chapter’s original open question — how far does organised, data-collecting citizen science extend beyond the Anglophone world? — targeted research across German, Scandinavian, Italian, Japanese, Chinese, and Spanish sources found a sharp divide: one language community runs genuine patient-driven data collection with a peer-reviewed output; the rest have patient-founded advocacy and support bodies, but none currently publishes its own patient-collected dataset.

- **German — the strongest example of citizen science outside the Anglophone world.** Two distinct efforts exist. First, **Clusterkopfschmerz-Radar / CLUE** (“Clusterkopfschmerzen erforschen”), running on Germany’s national citizen-science platform mitforschen.org since November 2017, led by Jörg Scheidt at Hochschule Hof’s Institut für Informationssysteme, explicitly frames itself as patients researching their own disease (“die Betroffenen erforschen ihre Krankheit selbst”) and invites participants to submit their own hypotheses about triggers and treatment effectiveness [CITIZEN-SCIENCE][^67]. By September 2018 it had logged 113 active participants and 2,960 attacks [CITIZEN-SCIENCE][^68], and its patient-logged attack and medication data underpins a peer-reviewed paper: Drescher, Khouri, Amann, Gaul, Kropp & Scheidt, “Effectiveness of medication in cluster headache,” *BMC Neurology* 21:174 (2021), open access [CITIZEN-SCIENCE] [PEER-REVIEWED][^69]. Separately, the large German patient body **CSG e.V.** (clusterkopf.de, ~1,250 members in 2024) acts chiefly as a recruitment engine for academic surveys rather than an independent data publisher — it hosts links to clinician-run projects such as the Kiel “Cluster-Gender” study and a MigräneLiga/Frankfurt survey without posting results on its own site, and its transparency disclosures show €15,281.28 in health-insurer funding for a patient-situation survey [CITIZEN-SCIENCE][^70]. A CSG-recruited (but clinician-designed and -published) instrument, the Cluster Headache Scales (DRKS00016502, n=302), appeared in *Cephalalgia* in 2020 [PEER-REVIEWED][^71]. The Austrian site clusterkopfschmerzen.at has separately translated and disseminated the D3 loading protocol into German [COMMUNITY-REPORT][^11].
- **Scandinavian — organised, but no published patient-collected dataset.** Sweden’s Klusterhuvudvärksföreningen ran a 2016–2018 government-funded (Arvsfonden) project mapping, via its own members, where patients actually received CH care — a genuine patient-collected exercise, but one that produced a care-navigation guide rather than a public dataset or paper [COMMUNITY-REPORT][^72]. Sweden’s more systematic CH data instead sits in a clinician-run national quality register [PEER-REVIEWED][^73]. Denmark (Hovedpineforeningen, formed by a 2025 merger; Danmarks Patientforening for Hovedpineramte) and Norway (Hodepine Norge, ~6,500 members, active in 2026 health-policy advocacy) have well-organised patient associations but no identified patient-run CH datasets [COMMUNITY-REPORT][^74][^75].
- **Italian — patient-founded and patient-directed, but not data-collecting.** O.U.C.H. Italia (grappolaiuto.it) is explicitly patient-founded and patient-governed (“Non è un sito di medici”), confirmed independently by a Università Politecnica delle Marche report describing it as founded and directed by expert patients under president Luca Bonventre since 2002 — but it runs a support forum, not a survey or registry [COMMUNITY-REPORT][^76]. Published Italian CH survey data instead comes from institutional sources: a Censis survey of 129 patients and an earlier Al.Ce. access-to-care study [PEER-REVIEWED/institutional][^77].
- **Japanese and Chinese — no patient-run, data-collecting CH community located.** Native-language searching found no Japanese CH patient association or patient-run survey equivalent to the Tourette-syndrome patient group model that exists for other conditions in Japan; all located Japanese CH data is clinician- or insurer-generated (e.g. a 21,480-person DeSC claims-linked survey in the *Journal of Headache and Pain*, 2022) [PEER-REVIEWED][^78]. Chinese-language searching likewise found only clinical reference material and hospital case series, with no public patient organisation or dataset — though this is a weaker negative result than for Japanese, since much Chinese peer support activity likely occurs in non-indexable WeChat groups and Baidu Tieba forums that could not be assessed here [unverified/COMMUNITY-REPORT absent][^79].

- **Spanish — an organisation exists but does not publish its own dataset.** CRAES/ACRA (Asociación Cefaleas en Racimo y Primarias España, ~500 members since 2011) states research-promotion as a goal but hosts no named citizen-science project, survey instrument, or results on its own site; it has however participated as a recruitment partner in an international patient study (with Fundación del Cerebro) reporting 72.6% suicidal ideation and roughly 28% chronic CH among respondents [COMMUNITY-REPORT][^80].

The honest summary: outside the Anglophone Clusterbusters/OUCH model, only the German CLUE/mitforschen.org project has taken patient-logged data all the way to a peer-reviewed publication. Everywhere else checked, patient advocacy and support infrastructure exists, but the actual citizen-science step — collecting and publishing patient-generated data — has not yet happened, or happens invisibly in non-indexable channels this research could not verify.

Community survey research

The single most important artefact of Clusterbusters-driven citizen science is the **Clusterbusters Medication Use Survey**, first collected and eventually published as peer-reviewed research in 2015 [CITIZEN-SCIENCE][PEER-REVIEWED][^13][^14]. Recruited from CH websites and headache clinics, it captured 496 respondents' self-reported effectiveness of conventional and alternative treatments, and became the evidentiary basis for at least three further peer-reviewed secondary analyses: one on oxygen versus sumatriptan effectiveness [PEER-REVIEWED][^15][^16], one a mixed-methods qualitative analysis of free-text patient comments (memorably titled "You will eat shoe polish if you think it would help") [PEER-REVIEWED][^17], and the underlying dataset for the psychedelics analysis discussed below [PEER-REVIEWED][^13]. Separately, Clusterbusters helped fund and publicise the International Cluster Headache Questionnaire, with over 3,000 participants, published in the journal *Headache* in November 2021 [CITIZEN-SCIENCE][PEER-REVIEWED][^18].

Key findings from these citizen-science-originated surveys:

Finding	Evidence tier	Source
High-flow oxygen (>10 L/min) and injectable sumatriptan show comparable efficacy (~81–82% response)	PEER-REVIEWED (secondary analysis of citizen survey)	[^15][^16]
"Nothing worked" reported by 24.7% of respondents in free-text comments; illicit substances mentioned by 35.5%; vitamins/supplements by 12.2%; coffee by 5.3%; exercise by 4.7%	PEER-REVIEWED (qualitative analysis of citizen survey)	[^17]
Indoleamine hallucinogens rated comparable to or better than most conventional medications for aborting attacks and inducing remission	PEER-REVIEWED (citizen survey)	[^13]

2. The Vitamin D3 Regimen ("Batch Protocol")

History and originator

The regimen is attributed to Pete Batcheller, a retired US Navy fighter pilot and call-sign "Batch," a chronic CH sufferer who began the protocol around 2011–2015 and shared it within the community [COMMUNITY-REPORT][^19]. It is a daily anti-inflammatory supplement stack centred on high-dose vitamin D3 (cholecalciferol), typically alongside omega-3 fish oil and other cofactors, targeting a serum 25-hydroxyvitamin D (25(OH)D) concentration around 80 ng/mL, well above standard "sufficiency" reference ranges [CITIZEN-SCIENCE][^20][^21].

Loading protocols

Two accelerated loading schedules are documented on Clusterbusters' own resource page: a two-week schedule (50,000 IU/day in week 1, tapering to 10,000 IU/day maintenance) and a four-week schedule (20,000 IU/day plus weekly 50,000 IU boosters, tapering to 15,000 IU/day then to 10,000 IU/day maintenance) [CITIZEN-SCIENCE][^20]. Dose adjustments by BMI are also specified: subtract 100,000 IU total loading dose if BMI <18.5; add 100,000 IU if BMI >25 [CITIZEN-SCIENCE][^20]. These same protocols have been translated into German by the Austrian patient site clusterkopfschmerzen.at, indicating cross-language community uptake [COMMUNITY-REPORT][^11].

The published survey evidence

A conference abstract (Neurology, 2014) reported results from a structured survey of 110 CH sufferers using the daily anti-inflammatory D3 regimen [CITIZEN-SCIENCE][^21]:

- 80% reported significant reductions in frequency, severity, and duration of CH
- 60% reported remaining substantially pain-free
- Average starting 25(OH)D was 23.4 ng/mL; average response level after ≥30 days was 76 ng/mL
- Efficacy was slightly higher in episodic (85%) than chronic (70%) CH
- A "stress test" of D3 reserves after 13 months pain-free led to a return of CH within 8 days of stopping supplementation
- 33% reported comorbidities; no major adverse events were reported [CITIZEN-SCIENCE][^21]

This was a **conference abstract, not a full peer-reviewed journal article** — it is labelled here as [CITIZEN-SCIENCE] rather than [PEER-REVIEWED] because it did not undergo full journal peer review and has not, as far as located sources show, been followed by a full published paper. It is frequently cited in review articles (e.g., a 2021 systematic review on vitamin D and primary headache) as the sole cluster-specific data point on this regimen, categorised there as a "prospective" report [PEER-REVIEWED, citing CITIZEN-SCIENCE][^22].

Formal trial activity

A registered clinical trial, "High Dose Vitamin D Plus Multivitamin in the Prevention of Cluster Headache" (ClinicalTrials.gov NCT04570475, Houston, Texas, PI Dr Mark J. Burish, UTHealth), was designed as a double-blind, placebo-controlled study of high-dose D3 plus multivitamin against placebo plus multivitamin, using change in weekly attack frequency as its primary outcome [PREPRINT/TRIAL][^23][^22]. **Update (checked August 2026):** the trial's ClinicalTrials.gov record now shows status **TERMINATED**, with the stated reason "Low number met criteria to randomize" [PREPRINT/TRIAL][^23]. It had actually started 15 September 2021, reached actual completion 13 May 2024, and randomised only 27 participants; the record shows no posted results and no linked publication [PREPRINT/TRIAL][^23]. No abstract, preprint, or journal article reporting outcome data from this trial could be located. This is a notable and somewhat ironic outcome: the trial meant to formally test the community's D3 protocol seems to have failed on recruitment at least partly *because* so many CH patients already self-supplement with high-dose D3 outside the trial, making it hard to find enough D3-naïve, protocol-eligible candidates to randomise — a citizen-science practice arguably undermining its own formal validation. This inference about the recruitment mechanism is not stated in the registry record itself and should be read as this document's own reasoning, not a sourced fact.

Separately, vitamin D3 supplementation has been tested in randomised controlled trials for migraine (not cluster headache specifically): a 2018 trial found D3 (100 µg/day) superior to placebo in reducing migraine days over 24 weeks [PEER-REVIEWED][^24], and a 2020 Iranian trial of 2000 IU/day for 12 weeks in episodic migraine found improved headache characteristics and reduced some inflammatory markers (iNOS, borderline IL-6), though not others (IL-10, Cox-2) [PEER-REVIEWED][^25]. These findings are suggestive by analogy but are **not cluster headache data** and should not be read as confirming the Batch protocol's specific claims.

Proposed mechanism and evidence quality assessment

The proposed mechanism is anti-inflammatory: vitamin D is theorised to modulate cytokine and neuro-inflammatory pathways implicated in trigeminal-autonomic activation, with the migraine trial data offering partial (inconsistent) support for reduced inflammatory markers [PEER-REVIEWED][^25]. However, the flagship cluster-specific evidence (the 110-person survey) is: uncontrolled, unblinded, self-selected (participants had to find and enrol via patient community channels), and reported only as a conference abstract [CITIZEN-SCIENCE][^21]. This is a highly promising, well-organised, and rigorously described piece of citizen science — but it falls well short of the double-blind, placebo-controlled standard needed to establish causation, and the one registered RCT that attempted to resolve this (NCT04570475) was terminated on recruitment grounds in 2024 without reporting results [PREPRINT/TRIAL][^23]. Honest assessment: **plausible, patient-organised, promising, but now formally untested and unlikely to be resolved by the one trial designed to test it** — a rarer and more discouraging outcome than "pending," and worth flagging clearly rather than letting the original "awaiting results" framing stand uncorrected.

---

3. Psychedelics — The Community Origin of a Research Agenda

This is the best-documented case of community-led citizen science directly generating a formal academic research programme in headache medicine.

From bulletin board to Harvard: Sewell, Halpern & Pope (2006)

Building directly on the online reports described in Section 1, R. Andrew Sewell, John H. Halpern, and Harrison G. Pope Jr. of McLean Hospital/Harvard Medical School conducted a retrospective interview survey of 53 CH patients who had self-administered psilocybin or LSD outside clinical settings, verifying diagnoses against medical records [PEER-REVIEWED][^26][^27]. Published in *Neurology* in 2006, the results were striking: 22 of 26 psilocybin users reported the drug aborted attacks; 25 of 48 psilocybin users and 7 of 8 LSD users reported cluster period termination; 18 of 19 psilocybin users and 4 of 5 LSD users reported remission period extension [PEER-REVIEWED][^26][^6]. Notably, this was the first paper to document that sub-hallucinogenic ("sub-perceptual") doses could be effective, a detail directly derived from patient self-report protocols rather than any prior pharmacological theory [PEER-REVIEWED][^28][^29]. *Nature*'s contemporaneous news coverage highlighted that 85% of psilocybin users reported aborted attacks, versus 52% for oxygen in the same surveyed population — though this cross-treatment comparison came from self-report, not a head-to-head trial [PEER-REVIEWED, reported via HISTORICAL/CULTURAL][^6].

The 2015 Clusterbusters Medication Use Survey (Schindler et al.)

A second, larger analysis — again built on the community-collected Clusterbusters Medication Use Survey (496 respondents) — found indoleamine hallucinogens (psilocybin, LSD, and lysergic acid amide/morning glory seeds) rated comparable to or more effective than most conventional medications, both for aborting attacks and inducing remission of chronic CH, and again found infrequent, non-hallucinogenic doses reported as efficacious [PEER-REVIEWED][^13][^30][^28].

Yale/VA controlled trials (Schindler et al.)

Emmanuelle Schindler at Yale/VA Connecticut ran the first controlled investigations of psilocybin in CH:

- A 2022 randomised, double-blind, placebo-controlled pilot trial (14 patients, low-dose "pulse" regimen of ~10.6 mg psilocybin per session, 3–7 days apart) found a mean reduction of 3.2 attacks/week versus placebo's 0.03 increase over three weeks — not statistically significant overall (moderate effect size d=0.69), but a large effect size (d=1.25) in the chronic CH subgroup versus a small effect (d=0.35) in episodic CH [PEER-REVIEWED][^31][^32]. No serious adverse events occurred; symptom relief was not correlated with the intensity of the psychedelic experience itself [PEER-REVIEWED][^31][^32].
- A 2024 blinded extension of that trial (10 participants, second round of dosing ≥6 months later) found attack frequency dropped from a baseline of 18.4/week to 9.8/week (~50% reduction) in the three weeks following the first dose of the second round, regardless of whether the participant had responded during round one [PEER-REVIEWED][^33][^34][^35].

- An open-label study, EPOCH (NCT04280055), in chronic CH was designed to test the same low-dose psilocybin pulse regimen for a 30% attack-frequency reduction (P=.008) [PEER-REVIEWED][^36]. **Correction (checked August 2026):** the ClinicalTrials.gov record for NCT04280055 shows this study was actually **TERMINATED**, with the stated reason "Not possible to achieve the anticipated no. of patients due to Covid-19 pandemic"; actual enrolment reached only 10 participants against a larger target, with completion recorded in June 2022 [PREPRINT/TRIAL][^36]. A partial-data publication exists (PMID 38238974), but this should be understood as a curtailed, underpowered study rather than a completed trial that hit its pre-specified target — the earlier framing in this chapter overstated its completeness [PEER-REVIEWED][^36].

The consistent, cross-study finding that therapeutic benefit is dissociated from the intensity of the acute psychedelic experience is an important and somewhat unexpected result — it undercuts the intuitive assumption that a "full trip" is necessary, and directly validates what community members had reported for two decades about sub-hallucinogenic dosing [PEER-REVIEWED][^32] [^29].

Update (checked August 2026): no new completed CH-specific trial results from the Schindler/Yale group were located beyond the above. The most chapter-relevant new item is a direct extension of the citizen-science pattern this chapter documents: Schindler, Lenaburg, and Clusterbusters founder **Bob Wold** co-authored a 2026 conference abstract, "DMT use in Cluster Headache: Interim Analysis of an International Survey," presented at the American Academy of Neurology and indexed in *Neurology* [CITIZEN-SCIENCE][PEER-REVIEWED][^81] — a formal academic researcher and the community's own founding advocate co-running a new survey on a psychedelic (DMT) that has not yet appeared elsewhere in the formal literature on CH. This is presently only an interim conference abstract; full results are pending. Separately, a 2026 case series (Leighton et al.) and a registered Phase 2 LSD trial in chronic CH (NCT05477459) extend the pipeline but were not located in enough detail to summarise responsibly here [PEER-REVIEWED][^82].

BOL-148: turning a psychedelic into a non-hallucinogenic drug candidate

BOL-148 (2-bromo-LSD) is structurally related to LSD but lacks (or greatly attenuates) hallucinogenic activity at typical study doses, while retaining serotonin receptor activity relevant to CH [PEER-REVIEWED][^37][^38]. A German-American collaboration (Matthias Karst and Torsten Passie at Hannover Medical School, with John Halpern at Harvard) ran an open, non-randomised case series of five chronic, treatment-refractory CH patients given three doses of BOL-148 five days apart; the cluster cycle was interrupted in all five, with remissions lasting from months to years, and side effects were minimal to none [PEER-REVIEWED][^37][^39]. This is explicitly a Hannover (Germany)-originated, non-English-language-team result, though published in the English-language journal *Cephalalgia* [PEER-REVIEWED][^37]. The authors themselves caution these results are preliminary — unblinded and uncontrolled [PEER-REVIEWED][^37].

As of August 2026, Ceruvia Lifesciences has raised US$8 million (announced 3 August 2026, founder-backed by CEO Carey Turnbull) to complete an integrated Phase 1/2 trial of BOL-148 (also referenced under code names TD-0148A/NYPRG-101): Part 1 is a single-ascending-dose study in healthy adults, Part 2 a randomised, placebo-controlled Phase 2 proof-of-concept in CH patients [PREPRINT/TRIAL][^40][^41]. A Clinical Trial Application is planned for submission in Germany in September 2026, with first patient enrolment expected Q4 2026 and Phase 1 top-line data anticipated Q2 2027 [PREPRINT/TRIAL][^40]. **As of this update, no participant has yet been dosed under this new trial and no Phase 1 data exist** — this remains squarely trial-pipeline territory, not yet an approved treatment, and given that BOL-148/Ceruvia's timelines have slipped for well over a decade since the original 2010 Hannover case series, 2027 readouts should be treated as aspirational rather than assured [PREPRINT/TRIAL][^40].

A related but distinct compound, **BETR-001**, developed by a different company (BetterLife Pharma) and described as a 6R:9R stereoisomer in the same chemical family, remains at an earlier, **preclinical** stage as of a July 2026 investor presentation: an IND filing is expected Q1 2027, with Phase 1A/1B to start around the same time and safety/proof-of-concept data 12–18 months after that [PREPRINT/TRIAL][^83]. This should not be confused with Ceruvia's BOL-148 programme — the two are separate companies pursuing related but distinct molecules, and conflating them (as some secondary sources do) overstates how far either has actually progressed.

Legal status by jurisdiction, including Australia

Psilocybin and MDMA remain Schedule 9 (Prohibited) substances as raw materials in Australia, but from 1 July 2023 the Therapeutic Goods Administration rescheduled *final preparations* of psilocybin (Schedule 8) for use only in treatment-resistant depression, prescribable exclusively by TGA-Authorised Prescribers [PEER-REVIEWED/regulatory][^42][^43]. Cluster headache is **not** a TGA-approved indication for psilocybin prescribing in Australia; any CH-related use would need to occur within an approved clinical trial [regulatory fact][^42]. Notably, Australia is host to one of the world's first funded clinical trials specifically targeting CH: the PEACE pilot trial (Psilocybin Efficacy and Acceptability on Cluster Headache Episodes), led by Dr Faraidoon Haghdoost at The George Institute for Global Health and UNSW Sydney, funded through the Medical Research Future Fund (reported at AUD $800,000) and testing 10 mg psilocybin weekly for four weeks against placebo in a planned 40-patient randomised controlled design with 6-hour post-dose monitoring — described as the first newly approved CH treatment trial in Australia in at least two decades [PEER-REVIEWED/institutional][^44][^84].

Update (checked August 2026): the PEACE trial has not yet started recruiting. Dr Haghdoost's own September 2025 announcement stated recruitment "has not started yet — we expect this to begin in the second half of next year" (i.e. H2 2026) [PREPRINT/TRIAL][^85], and a March 2026 webinar advertised by his practice still described PEACE as an "upcoming" trial [PREPRINT/TRIAL][^86]. No ANZCTR or ClinicalTrials.gov registration number could be located for it in this research — a ClinicalTrials.gov search for cluster headache plus psilocybin plus Australia returned zero results, and ANZCTR's own search tool blocks automated access, so a definitive registration check would need to be done manually at anzctr.org.au [unverified][^85]. No interim or final results exist yet; treat this trial as **funded and designed, not yet running**, with any results at best a 2027 prospect once recruitment (H2 2026 earliest) and the trial itself conclude.

A directly relevant and newly published piece of citizen-science-adjacent research has emerged from the same Australian team: Haghdoost et al., "Patient perspectives on research gaps in cluster headache," *Headache* (2026), co-authored with Clusterbusters founder Bob Wold and recruited through patient advocacy channels [CITIZEN-SCIENCE][PEER-REVIEWED][^87]. Of 202 analysed respondents (mean age 46, 55% male, 72% with CH for more than 10 years), 35% rated their treatments as ineffective or only somewhat effective, and the most commonly cited challenges were treatment ineffectiveness (74%), side effects (54%), and cost (53%). 62% of respondents were interested in participating in future trials, and among those "very interested," psilocybin ranked as the top treatment of interest at 66% (ahead of anti-CGRP therapies at 66% combined-interest and devices at 71% combined-interest, with combination therapies highest overall at 84%) [CITIZEN-SCIENCE][PEER-REVIEWED][^87]. This survey is itself a small piece of the same community-informs-formal-research pattern this chapter documents throughout, now happening on Australian soil ahead of the PEACE trial it will presumably help justify and recruit for.

---

4. Other Community-Identified Threads

Energy drinks / caffeine aborts

Widely reported across patient forums: caffeine- and taurine-containing energy drinks (Red Bull, 5-Hour Energy, Rockstar) consumed quickly while cold, at the earliest sign of an attack or "shadow," are reported by many patients to abort or blunt attacks, with the taurine content specifically flagged by some as relevant [COMMUNITY-REPORT][^45][^46]. No controlled trial evidence for this specific intervention was located; the plausible mechanism proposed informally is vasoconstriction via caffeine [COMMUNITY-REPORT][^46]. **Confirmed still true as of August 2026:** a fresh check of PubMed and ClinicalTrials.gov found no registered trial or case series testing energy drinks or caffeine as a CH-specific abortive — the only PubMed hits for "energy drink AND cluster headache" are unrelated survey papers on oxygen/acute-treatment use and lifestyle factors, not intervention studies of the energy-drink abort itself [PEER-REVIEWED, absence confirmed][^88]. Of all the community-identified threads in this chapter, this is arguably the one with the **largest gap between how frequently it is reported and how little formal research interest it has attracted** — plausibly because, as one framing puts it, nobody can patent a can of Red Bull, removing the usual commercial incentive to fund a trial.

Physical exertion / exercise

This thread has moved partway from pure anecdote into small-scale formal research. A 2024 Korean cross-sectional survey of 167 registered CH patients (136 respondents) found 39.7% had tried exercise as an abortive; of those, 42.6% reported improvement and 29.6% reported ≥50% improvement, with running, squats, and stair-climbing most commonly cited and higher-intensity exercise somewhat more often effective (52.2%) than moderate intensity (43.5%) [PEER-REVIEWED][^47][^48]. A separate French case report similarly found moderate-intensity aerobic exercise (10–30 min) at attack onset reduced both severity and duration [PEER-REVIEWED][^49]. Community forum threads (r/clusterheads, r/ClusterHeadaches) show a striking split: many report vigorous exercise (sprinting, HIIT, rowing, push-ups) aborting attacks within minutes, apparently via adrenaline or vasoconstriction, while others report exercise and heat as reliable *triggers* during an active cluster bout — sometimes in the same person, depending on timing relative to attack onset [COMMUNITY-REPORT][^50][^51][^52]. This bidirectional, context-dependent relationship (helpful at onset, harmful mid-attack or as a trigger during a bout) is a genuinely unresolved and clinically interesting pattern that formal research (the Korean registry study) has only just begun to quantify [PEER-REVIEWED][^47].

Cold, heat, and breathing manoeuvres

Community reports describe applying ice, cold packs, or “slush” to the affected area, alongside deep breathing exercises, as adjunctive comfort measures during attacks [COMMUNITY-REPORT][^53]. Heat is much more frequently reported as a *trigger* than as a treatment, consistent with formal literature noting temperature and weather-pressure changes among recognised CH triggers [PEER-REVIEWED][^54][^55]. No controlled studies of cold application or breathing technique as CH-specific interventions were located; this remains squarely [COMMUNITY-REPORT] territory.

Kudzu

An interview-based case series of a cluster headache patient database found 16 of 235 patients had tried over-the-counter kudzu extract; of these, 69% reported decreased attack intensity, 56% decreased frequency, and 31% decreased duration, with minimal side effects [PEER-REVIEWED][^56]. The authors explicitly characterise this as anecdotal evidence warranting a randomised trial that, as far as this research could determine, has not since been conducted [PEER-REVIEWED][^56]. This is a rare example of a formally published paper that is itself transparently reporting [CITIZEN-SCIENCE]-tier community self-treatment data without pretending it is more than that. **Confirmed still true as of August 2026, seventeen years on:** a fresh PubMed search for “kudzu AND cluster headache” returns exactly this one 2009 case series and nothing else, and ClinicalTrials.gov’s kudzu/Pueraria listings (roughly 50 studies) cover alcohol use disorder, diabetes, menopause, lipids, and stroke — zero headache trials of any kind [PEER-REVIEWED, absence confirmed][^89]. Of the three community threads examined for follow-up in this update (D3, kudzu, energy drinks), kudzu is the one that at least received a single sympathetic peer-reviewed write-up calling for a trial; that trial has simply never materialised.

Capsaicin

Intranasal capsaicin has one of the more substantial formal-trial histories among “community-adjacent” CH treatments, including a 1993 double-blind placebo-controlled trial (13 patients) showing reduced headache severity by days 8–15 [PEER-REVIEWED][^57][^58], a larger open-label study (51 episodic + 19 chronic patients) finding ipsilateral (same-side) application far more effective than contralateral [PEER-REVIEWED][^59][^60], and a 2-year follow-up finding the effect reproducible in 65% of patients on repeat treatment, though transitory (lasting at most a month) in chronic patients [PEER-REVIEWED][^61]. Application is intensely irritating (burning, lacrimation, rhinorrhoea for ~20 minutes, decreasing after 5–8 applications), which has historically complicated blinding in these trials [PEER-REVIEWED][^62][^63]. A 2023 European Academy of Neurology guideline notes only modest confidence in this evidence and recommends restraint in clinical use [PEER-REVIEWED][^64].

Community observations on remission

Formal literature confirms cluster headache subtype can shift over time: in a 10-year follow-up of 189 patients, about 13% of episodic patients became chronic and about 30% of chronic patients reverted to episodic [PEER-REVIEWED][^55]. *(Editor’s note: fuller phenotype-transition data — the Danish interview cohorts and the contested chronic→episodic reversion rate — are in Part*

IV, §1; see also Unresolved Conflicts, item 4.) Community reports (r/clusterheads, forum threads) frequently describe remission or subtype shifts as coinciding with the psilocybin/LSD interventions above [COMMUNITY-REPORT][^26], with the D3 regimen [CITIZEN-SCIENCE][^21], or with no identifiable intervention at all, consistent with the known circannual and spontaneous remission patterns of the disease [PEER-REVIEWED][^54]. Disentangling genuine treatment effect from the disease's natural tendency to remit is a persistent methodological problem across almost all the citizen-science claims in this chapter, and is flagged explicitly wherever it applies.

Wearables and self-tracking

Structured self-tracking tools exist and are used within the CH and migraine community, notably the Curelator N1-Headache app, which logs daily factors against attack occurrence to generate a personalised "Personal Analytical Report" for sharing with clinicians [COMMUNITY-REPORT/product][^65]. No published, aggregated dataset specifically analysing pooled N1-Headache or similar app data for cluster headache (as opposed to migraine) was located in this research; this represents a **known gap** — a citizen-science-capable infrastructure exists, but publicly available aggregate analysis for CH specifically appears not to have been conducted or published.

5. Where Community and Clinic Disagree

Claim	Direction of disagreement	Current status
Sub-hallucinogenic doses of psilocybin/LSD can abort attacks and induce remission	Community reported this for years before trials confirmed dissociation of psychedelic intensity from therapeutic effect	Now substantially validated by controlled Yale trials [PEER-REVIEWED][^31][^32]
High-dose vitamin D3 (targeting 25(OH)D ~80 ng/mL) meaningfully reduces or resolves CH	Strongly held in community; the one formal RCT designed to test it (NCT04570475) was terminated in 2024 on recruitment failure, without reporting results	Contested / unresolved, and now unlikely to be resolved by the trial that was meant to settle it [CITIZEN-SCIENCE][PREPRINT/TRIAL][^21][^23]
Energy drinks/caffeine can abort attacks	Widely and consistently reported in community; no controlled trial has tested this specific intervention	Untested by formal science [COMMUNITY-REPORT][^45][^46]
Vigorous exercise at attack onset can abort attacks	Long-standing, extremely common community claim; science is only now beginning to test it, and results are more modest (about 30% of triers get ≥50% relief) and more context-dependent (helpful at onset, sometimes a trigger mid-bout) than the more emphatic anecdotal claims suggest	Science partially catching up, effect appears real but smaller/more conditional than community narrative implies [PEER-REVIEWED][^47]
Kudzu reduces attack intensity/frequency/duration	Community self-treatment claim, formally documented but never subjected to an RCT despite the original authors calling for one	Formally unstudied beyond the original case series [PEER-REVIEWED][^56]
Oxygen therapy is clearly superior to triptans, or vice versa	Long anecdotal disagreement in community about which is "better"	Citizen-science-derived secondary analysis found the two comparable in efficacy at adequate oxygen flow rates, resolving much of the debate
Intranasal capsaicin is a viable everyday preventative	Some community enthusiasm given easy access	Formal trials show effect is real but small, side-effect burden (intense burning) is high, and clinical guidelines urge caution/limited use

The single clearest case of “community ahead of science, science later validates” is psychedelics — a two-decade gap between message-board reports (1998) and a peer-reviewed controlled Yale trial (2022) [PEER-REVIEWED][^31]. The clearest case of “community belief science has not yet resolved” is the D3 regimen, where community-collected data are extensive and internally consistent but no completed double-blind trial result was located. The clearest case of “science partially deflating an emphatic community narrative” is exercise as an abortive — real, but with a much larger non-responder group and a confusing dual role as both trigger and treatment than forum enthusiasm alone would suggest [PEER-REVIEWED][^47][^51].

References (Part VI)

1. The History - Strange Beginnings - Clusterbusters - Historically, many cultures all over the world treated headaches with naturally occurring indole-rin…
2. Psychedelic Outlaws: Cluster Headaches, Citizen Science, and the Story of ClusterBusters - Listen to this podcast about cluster headaches, psychedelics, and ClusterBusters, with Joanna Kempne…
3. Bob Wold - AHDA
4. Featured Partner: Clusterbusters | American Migraine Foundation - Eileen Brewer and Andrew Cleminshaw of Clusterbusters discuss how their group helps speak out for th…
5. Clusterbusters, Inc. - Bob Wold founded Clusterbusters in 2002 with the goals of advancing research into cluster headache a…
6. Dropping acid may help headaches - Nature - the world’s best science and medicine on your desktop
7. Clusterbusters took treating cluster headache into their own hands - Psychedelic Outlaws documents the story of a patient group who experimented their way to an effectiv…
8. About OUCH(uk) | OUCH(UK) - The Cluster Headache Charity - OUCH (UK) was officially launched on Saturday June 9th 2001 and became a registered charity on May 8…
9. History of OUCH(UK) - Our patron - and chairman - Professor Peter Goadsby credits the NHS with the foundation of OUCH (UK)…
10. Top 10 charities - prd-ds-register-of-charities.charitycommission.gov.uk - Charity details for OUCH (UK) - Charity 1091919
11. Vitamin D3 Therapie – Ein Regimen für …
12. Real-life treatment of cluster headache in a tertiary headache center – results from the Danish Cluster Headache Survey - Anja Sofie Petersen, Nunu Lund, Rigmor Højland Jensen, Mads Barloese, 2021 - Background Pharmacological treatment of cluster headache constitutes the core of clinical management…
13. Indoleamine Hallucinogens in Cluster Headache - by EAD Schindler · 2015 · Cited by 151 — The Clusterbusters.org medication use survey sought to char…
14. A Quick Look at Some of Clusterbusters’ Historical Landmarks - A Quick Look at Some of Clusterbusters’ Historical Landmarks 1998-2002 Our community was built on a …
15. Survey Analysis of the Use, Effectiveness, and Patient-Reported Tolerability of Inhaled Oxygen Compared With Injectable Sumatriptan for the Acute Treatment of Cluster Headache - PubMed - Therapeutic response to inhaled oxygen at sufficiently high flow rates (>10 L/min) had comparable ef…

16. High-Flow Oxygen Therapy as Effective as Sumatriptan for Cluster Headaches - The effectiveness, tolerability, and use of inhaled oxygen compared with injectable sumatriptan was …
17. “You will eat shoe polish if you think it would help”-Familiar and lesser-known themes identified from mixed-methods analysis of a cluster headache survey - PubMed - This mixed-methods analysis identified challenges endured by cluster headache patients, as well as a…
18. Past Research - More than 3,000 people participated in the survey and results were published in the journal Headache…
19. Vitamin D3 Anti-Inflammatory Regimen for Cluster Headache - Created by Pete Batcheller, a retired Navy Fighter Pilot and chronic cluster headache sufferer, . Pr…
20. D3 Vitamin Therapy and Loading details - Explore D3 vitamin therapy and loading details. Using vitamin D3 has been proven to significantly re…
21. A Survey of Cluster Headache (CH) Sufferers Using Vitamin D3 as a CH Preventative (P1.256) | Neurology - OBJECTIVE: To present survey results of 110 CH sufferers (CH’ers) using a daily anti-inflammatory re…
22. The Vitamin D Role in Preventing Primary Headache in Adult and … - Headache is among the main neurological disorders with a great impact on both adults and children. T…
23. High Dose Vitamin D Plus Multivitamin in the Prevention of Cluster Headache
24. A randomized, double-blinded, placebo-controlled, parallel trial of … - D3-Vitamin was superior to placebo in reducing migraine days in migraine patients. Larger studies ar…
25. Vitamin D3 might improve headache characteristics and protect … - Based on the results of this study, we found that 2000 IU (50 μg)/day vitamin D3 supplementation for…
26. Response of cluster headache to psilocybin and LSD - PubMed - NIH - The authors interviewed 53 cluster headache patients who had used psilocybin or lysergic acid diethy…
27. [PDF] Response of cluster headache to psilocybin and LSD | Semantic Scholar - The authors interviewed 53 cluster headache patients who had used psilocybin or lysergic acid diethy…
28. Table 1. - Amid a lack of effective chronic pain treatments, psychedelics have gained attention as a potential …
29. Psilocybin and Cluster Headaches: Breaking the ’Suicide … - They call them suicide headaches — 10 attacks per day, each rated 10/10 pain, lasting up to 3 hours….
30. psilocybin for the treatment of cluster headache, case report - Results of the Clusterbusters Medication Use Survey. J Psychoactive Drugs. 2015 Nov- Dec;47(5):372-8…
31. Promising Signs for Psychedelic Use in Cluster Headache - A small study finds that low-dose psilocybin was safe and had a moderate effect size, though results…
32. Emmanuelle A. D. Schindler - The Consciousness Library - Research by Emmanuelle A. D. Schindler: 18 papers on The Consciousness Library, with citations, co-a…
33. Psilocybin pulse regimen reduces cluster headache attack … - NCT02981173.
34. Emmanuelle Schindler, MD, PhD - Yale Medicine - Emmanuelle Schindler, MD, PhD, is a neurologist focused on the management of headache disorders, wit…
35. Psilocybin pulse regimen reduces cluster headache attack …

36. Headache Horizons: The Study and Use of Psychedelics in Clus - None

37. The non-hallucinogen 2-bromo-lysergic acid diethylamide as preventative treatment for cluster headache: An open, non-randomized case series - Matthias Karst, John H Halpern, Michael Bernateck, Torsten Passie, 2010

38. BOL-148 - Wikipedia

39. Non-hallucinogenic LSD Derivative for Treating Cluster Headache - Ascenion Takes an Equity Position in Entheogen

40. Ceruvia Raises $8 Million to Complete Integrated Phase 1/2 Trial of …

41. LSD Analog Without the Trip: A New Hope for 'Suicide Headache' Sufferers - BriefGlance.com - Ceruvia Lifesciences secures $8M for a non-hallucinogenic LSD analog to treat cluster headaches, off…

42. Regulation of MDMA and Psilocybine | Office of Drug Control (ODC) - Overview of Australian regulations for MDMA and psilocybin, including authorised prescribing, import…

43. The Australia story: Current status and future challenges … - PubMed - The past decade has seen a huge increase in clinical research with psychedelic drugs and 3,4-methyle…

44. Hope for cluster headache community as psilocybin trial funded - One of the world's first clinical trials into the potential for psychedelic compound psilocybin to p…

45. Cluster Headache Triggers and Treatment Hacks for Patients - 2: Red Bull, 5-Hour Energy, and other drinks that contain caffeine and taurine have an uncanny abili…

46. Using Energy Drinks - The Cluster Headache Support Group - Many clusterheadache patients have heard that drinking energy drinks can abort an attack just about …

47. Exercise as an abortive treatment for cluster headaches - PMC - This study aimed to evaluate the potential of exercise as an abortive treatment for patients with cl…

48. Exercise as an abortive treatment for cluster headaches: Insights from a large patient registry | Semantic Scholar - While evidence is limited, exercise may help alleviate headaches and could be considered an adjuncti…

49. ORIGINAL ARTICLE / ARTICLE ORIGINAL

50. Intense exercise at onset helps abort my cluster attacks, anyone else? - Intense exercise at onset helps abort my cluster attacks, anyone else?

51. Exercise as a trigger? - Exercise as a trigger?

52. Workout during a cluster - Workout during a cluster

53. Aborting shadows - Aborting shadows

54. Cluster Headache: Epidemiology, Pathophysiology, Clinical … - by DYT Wei · 2018 · Cited by 171 — The prognosis of cluster headache remains difficult to predict. P…

55. Cluster headache: Clinical features and management - AbstractCluster headache is a primary headache disorder characterized by attacks of severe-to-very s…

56. Response of cluster headache to kudzu - Anecdotal evidence suggests that a component in OTC products labeled as kudzu may prove useful in ma…

57. A double-blind placebo-controlled trial of intranasal capsaicin for … - It has been suggested that treatment of cluster headache (CH) patients with topical capsaicin may de…

58. Management of Cluster Headache - Cluster headache, an excruciating, unilateral headache usually accompanied by conjunctival injection…

59. Preventative effect of repeated nasal applications of capsaicin in … - Preliminary studies have shown that repeated nasal applications of capsaicin prevented the occurrenc…

60. Pharmacotherapy Options for the Management of Cluster Headache - Jared L. Pomeroy, Michael J. Marmura, 2013 - Cluster headache is a primary headache syndrome characterized by attacks of severe unilateral headac…

61. “Capsaicin-sensitive” sensory neurons in cluster headache - PubMed - Capsaicin, when repeatedly applied to the nasal mucosa of cluster headache patients, has been shown …

62. OHP-053 Intranasal Applications of Capsaicin to Treat Cluster Headache, a Case Report - Background Cluster headaches are one of the most severe types of head pain. Intranasal medicines for…

63. Cluster headache - PMC - The revised International Headache Society (IHS) criteria for cluster headache are: attacks of sever…

64. [PDF] European Academy of Neurology guidelines on the treatment of …

65. N1-Headache - Apps on Google Play - Track and understand your migraine and headaches. Take back control.

66. Cluster Headache Advocacy: The Role and Impact of Patient-Led Organizations - Practical Neurology, 8 August 2026 - traces OUCH(UK) and Clusterbusters to the same clusterheadaches.com message board origin.

67. Clusterkopfschmerzen erforschen (CLUE) - Germany’s national citizen-science platform mitforschen.org, project page for the CH patient self-research project led by Jörg Scheidt, Hochschule Hof.

68. Kopfschmerz-Radar project status PDF, September 2018 - Reports 113 active CH participants and 2,960 logged attacks.

69. Effectiveness of medication in cluster headache - Drescher, Khouri, Amann, Gaul, Kropp, Siebenhaar, Scheidt - BMC Neurology 21:174 (2021), open access, peer-reviewed output of the CLUE patient-logged dataset.

70. CSG e.V. — Aktuelle Studien und Umfragen and Transparenz über Förderungen - German patient body’s survey-recruitment page and funding transparency disclosure.

71. Cluster Headache Scales validation study, DRKS00016502 - Klan et al., Cephalalgia 2020, n=302, recruited via CSG e.V.

72. Vägen till Horton-vården - Klusterhuvudvärksföreningen (Sweden), Arvsfonden-funded 2016-2018 patient care-mapping project output.

73. Swedish national headache quality register annual report 2024 - Clinician-run register, not patient-collected.

74. Hodepine Norge — national CH patient pathway proposal, February 2026 - Norwegian patient association (~6,500 members) health-policy advocacy document.

75. Hovedpineforeningen merger coverage and Danmarks Patientforening for Hovedpineramte - Danish patient association landscape, 2025.

76. O.U.C.H. Italia / GRAPPOLAIUTO and CRISS/Università Politecnica delle Marche report on Italian CH patient associations - Confirms patient-founded, patient-governed status since 2002 under president Luca Bonventre.

77. Censis survey of Italian cluster headache patients - Institutional (not patient-run) Italian CH survey, n=129.

78. DeSC claims-linked cluster headache survey, Journal of Headache and Pain 2022;23:70 - Clinician/insurer-generated Japanese CH data, n=21,480.

79. Baidu Baike: - Representative Chinese-language reference material found; no patient-run organisation or dataset located.

80. ACRA/CRAES patient study on suicidal ideation in cluster headache - Spanish patient association (CRAES/ACRA) recruitment partnership with Fundación del Cerebro.

81. DMT use in Cluster Headache: Interim Analysis of an International Survey (S23.003) - Schindler E, Lenaburg K, Wold R. Neurology 2026;106, conference abstract co-authored with Clusterbusters founder Bob Wold.

82. Leighton et al. 2025 psychedelic case series and LSD Phase 2 trial in chronic cluster headache, NCT05477459 - Extension of the psychedelics pipeline beyond psilocybin/BOL-148.

83. BetterLife Pharma investor presentation, July 2026 - BETR-001 (6R:9R stereoisomer) preclinical status, IND expected Q1 2027.

84. Researchers to trial psilocybin as hope for “screwdriver behind the eye” cluster headaches - The George Institute, PEACE trial scale and AUD $800,000 funding detail.

85. Cluster headache trial got funded in Australia - Dr Faraidoon Haghdoost, 30 September 2025 - states recruitment had not yet started, expected H2 2026.

86. Dr Faraidoon Haghdoost LinkedIn post, 17 March 2026 - Advertises a webinar on the “upcoming” PEACE trial.

87. Patient perspectives on research gaps in cluster headache - Haghdoost et al., Headache 2026, DOI 10.1111/head.70031, co-authored with Bob Wold, n=202 patient survey.

88. Real-life treatment of cluster headache in a tertiary headache center – Danish Cluster Headache Survey and PubMed search confirming no CH-specific energy drink/caffeine intervention trials exist as of August 2026.

89. ClinicalTrials.gov kudzu/Pueraria listings - Confirms zero headache trials among ~50 registered kudzu/Pueraria studies as of August 2026.

Part VII — The Frontier: Current Research and Where This Is Heading

Source: Chapter 5 (deep-verification edition, 13 August 2026), sections 5.1–5.4. The chapter's Watchlist has been moved to the end of this document as its final content section, per the assembly brief.

Where the field is heading: the active trial landscape, the emerging science, the chronic-CH problem, and the structural funding picture.

Deep-verification edition, compiled 13 August 2026. This supersedes an earlier quick-pass version of this chapter. Four dedicated research passes (global trial-registry sweep, funding/advocacy audit, genetics/imaging/biomarker verification, and psychedelics/PACAP/orexin verification) were run and cross-checked against primary sources. The verification pass found and corrected seven factual errors in the earlier draft — wrong GWAS locus list, wrong odds ratio, an inverted cytokine-direction claim, a misattributed review, and a mislabelled clinical outcome. Corrections are flagged explicitly below rather than silently fixed, in keeping with this document's evidence standards.

5.1 Active Research: The Global Trial Landscape

Registries searched directly: ClinicalTrials.gov (API v2), EU CTIS and the legacy EU Clinical Trials Register/EudraCT, ANZCTR (Australia/NZ), Japan's jRCT, China's ChiCTR, and Korea's CRIS. Japan's UMIN-CTR could not be retrieved despite three attempts and is recorded as a genuine gap, not a zero. Unless flagged otherwise, every trial below carries the evidence tag **[PREPRINT/TRIAL]** (a registered but not-yet-peer-reviewed record); where a result has been published in a journal it is additionally tagged **[PEER-REVIEWED]**.

5.1.1 The CGRP story: one win, four losses

This is the best-established recent trial programme in CH, and its pattern is the single most important fact in this chapter for a chronic-CH patient.

Drug	Trial	Population	Result	Source
Galcanezumab	NCT02397473	Episodic CH (n=109)	**Positive.** Weekly attacks −8.69 vs −5.22 placebo; LS mean diff −3.47 (95% CI −6.72 to −0.23), **p=0.036**	ClinicalTrials.gov
Galcanezumab	NCT02438826	Chronic CH (n=240)	**Failed.** −5.38 vs −4.59; LS mean diff −0.80 (95% CI −2.77 to 1.17), p=0.334	ClinicalTrials.gov
Fremanezumab	NCT02945046	Episodic CH (n=169)	**Terminated for futility.** p=0.9093 and p=0.1345 across doses	ClinicalTrials.gov
Fremanezumab	NCT02964338	Chronic CH (n=259)	**Terminated for futility.** p=0.2741 and p=0.3047	ClinicalTrials.gov
Eptinezumab (ALLEVIATE)	NCT04688775	Episodic CH (n=231)	**Failed.** −4.0 vs −4.6; mean diff 0.7 (95% CI −1.3 to 2.6), p=0.5048	ClinicalTrials.gov
Eptinezumab (CHRONICLE)	NCT05064397	Chronic CH (n=131)	Primary endpoint was **safety**, not efficacy — not a failed efficacy trial, just not an efficacy trial at all	ClinicalTrials.gov
Erenumab (CHERUB01)	NCT04970355	Chronic CH (n=101)	**Failed** — no results posted on the registry; published in JAMA Network Open 2025 **[PEER-REVIEWED]**	ClinicalTrials.gov

Only galcanezumab works, and only in episodic CH. Every single chronic-CH CGRP antibody trial — across three different drugs — has failed or been abandoned for futility. This is widely discussed in headache-specialist circles as the field's central unsolved puzzle for chronic sufferers specifically (see §5.3). *(Editor's note: full trial detail, the 2026 meta-analyses and the community's divergent real-world experience are in Part V, §3.6.)*

5.1.2 What's genuinely new since the last pass (2024–2026 registrations)

Trial	Intervention	Population	Location	Status	Notes
NCT07714369	Zavegepant intranasal (gepant)	Episodic CH, acute	US (UTHealth Houston)	Not yet recruiting, est. start Oct 2026	First gepant tested as an *acute* CH abortive
CTIS 2025-521470-34-00 / 2025-521529-34-00	Candesartan (**CandClus2**), two Phase 3 trials	Episodic + chronic CH	Denmark, Norway	Authorised Nov 2025, not started	Largest new preventive-drug programme in CH; candesartan (an angiotensin-II blocker) was trialled once before, 2004
NCT06950281 / CTIS 2025-523293-17-00	Low-sodium oxybate (**SUNCET**, Xywav)	Chronic CH, nocturnal attacks	Netherlands (LUMC)	Authorised, not yet recruiting	Targets the *nocturnal* attack pattern directly — sleep-architecture, not clock-gene, mechanism
NCT05477459 / CTIS 2024-520305-39-00	LSD 25µg minidosing (**CHIT**)	Chronic CH (n=65)	Netherlands (Radboud UMC)	**Recruiting**	The live psychedelic CH trial right now; every-3-days dosing over 3 weeks
NCT06540651	Light therapy (Luminettes device)	Chronic CH (n=48)	France	**Recruiting**	The only interventional circadian-targeted CH trial found anywhere — see §5.1.5
NCT05264714	Rimegepant (gepant)	CH	US	Completed 31 Dec 2025	Results not yet posted
NCT07677137, NCT07113470	First-in-human neurostimulation devices (ONS; combined trigeminal+ONS "PRIMUS")	Chronic CH	Belgium, Netherlands	Recruiting	Safety-phase device studies
NCT06787677, NCT06882278, ChiCTR2500106938	Sphenopalatine ganglion pulsed-radiofrequency / carotid sheath block	Episodic + chronic CH	China	Recruiting	A substantial Chinese procedural-treatment programme that is essentially invisible in Western headache literature
NCT07292090, NCT07348783	Yoga-based movement (**YOURHEAD**)	CH and/or migraine	Sweden	Active/Recruiting	Non-pharmacological, behavioural
NCT06917144	Repetitive TMS	Refractory chronic CH (n=8)	Spain	Completed	Results not posted

5.1.3 The psychedelics pipeline, in detail

This is the most active single therapeutic track in CH research right now, and it has become more crowded and more interesting since the last pass.

- **Ceruvia Lifesciences — BOL-148/NYPRG-101. [PREPRINT/TRIAL]** Announced an **$8 million founder-backed investment** on 3 August 2026, described by CEO Carey Turnbull as fully funding "an integrated Phase 1/2 study" — a single-ascending-dose Phase 1 in healthy adults feeding directly into a randomised, placebo-controlled Phase 2 proof-of-concept in CH patients, within one protocol (BioSpace). A **German Clinical Trial Application is expected September 2026**, first patient enrolment **Q4 2026**, Phase 1 top-line data **Q2 2027**, feeding a planned US+EU Phase 3. As of this writing there is **no registry entry anywhere** for the trial — consistent with a CTA not yet filed. The programme's human precedent is a 2010 Hannover open-label case series in which three doses of BOL-148 over ten days broke cluster cycles or converted chronic to episodic disease in several patients, with remissions lasting months (Karst et al., *Cephalalgia* 2010 **[PEER-REVIEWED]**).
- **Correction to the record: BETR-001 is a different company's different molecule. [PREPRINT/TRIAL]** BETR-001 belongs to **BetterLife Pharma Inc.** (Vancouver), not Ceruvia — it is the patented (6R,9R) active stereoisomer of 2-bromo-LSD, explicitly **migraine-led**, with cluster headache framed only as an orphan-designated "de-risking beachhead." Its FDA pre-IND meeting is complete and a US IND is anticipated Q1 2027 (BetterLife release, 13 Jul 2026). **As of August 2026, two independent 2-bromo-LSD programmes are running in parallel** — Ceruvia (CH-first, EU-first) and BetterLife (migraine-first, US-first) — which is a materially richer picture than a single programme.
- **Yale/VA Connecticut (Dr Emmanuelle Schindler). [PREPRINT/TRIAL]** No new CH-specific efficacy trial has been registered since the original psilocybin study (NCT02981173, completed). The one new 2024–2026 Schindler-affiliated registration, NCT06464367 ("Mechanistic Studies of Psilocybin in Headache Disorders"), is in **migraine**, not CH — but it is worth knowing about because it is the first psilocybin study to prospectively instrument circadian rhythm (actigraphy) and sleep EEG as candidate mediators of the durable post-pulse benefit, i.e. it is explicitly testing a chronobiological mechanism for psychedelic efficacy in headache. The published follow-up to the original pulse-regimen extension paper (May 2024) has so far been in migraine, not CH (PubMed sweep).
- **Clusterbusters/Yale DMT citizen-science survey — interim results now exist. [CITIZEN-SCIENCE]** Launched 2 August 2025 on the Clusterbusters forum, explicitly "in the tradition of citizen science," in collaboration with Yale (Clusterbusters forum). An interim analysis — Schindler E, Lenaburg K, Wold R, "DMT use in Cluster Headache: Interim Analysis of an International Survey" — was published as a conference abstract in *Neurology* 2026;106, DOI 10.1212/wnl.0000000000215894 **[PREPRINT/TRIAL]** (online 10 June 2026, consistent with an AAN 2026 Annual Meeting presentation). No sample size or numerical results are publicly rendered on the abstract page. Notably, co-author Mr Lenaburg discloses being Clusterbusters' Policy Director and Mr Wold discloses being Clusterbusters' Executive Director — this is advocacy embedded directly in the authorship, not merely acknowledged.

5.1.4 PACAP: the strongest un-trialled target in headache medicine

[PEER-REVIEWED] The single most striking finding of this research pass is a hard negative with a strong positive biology sitting right next to it. As of 13 August 2026, **no PACAP-targeting drug has a cluster-headache trial registered, planned, or publicly discussed by any sponsor, anywhere** — this was checked directly against ClinicalTrials.gov, EU CTIS, Lundbeck's global pipeline page, Lundbeck's own AHS June 2026 investor deck (which calls bocunebart "phase 3 ready" and mentions only migraine), Eli Lilly's LY3451838 programme (which appears dormant, two completed non-CH trials only), and the newly-launched Slate Medicines ($130M Series A, February 2026, for SLTE-1009 — also migraine-framed).

Set against that: interictal plasma PACAP-38 is elevated **34.3% overall** in CH patients versus controls, and **49.8% in chronic CH specifically** — the largest elevation of any CH subgroup studied — in a 205-patient Danish case-control study, partly funded by Lundbeck itself (Søborg et al., *Eur J Neurol* 2025 **[PEER-REVIEWED]**). PACAP-38 infusion provokes cluster-like attacks in roughly 45% of CH patients in an active phase, without changes to CGRP, tryptase, or histamine — implying a genuinely distinct

mechanism from the CGRP pathway that has now failed four times in chronic CH. The genetic case is weaker: the original ADCYAP1R1 association (from a small 99-patient Italian cohort) did **not** replicate in a larger 542-patient Swedish cohort, and ADCYAP1R1 is not among the loci found in the large 2023 international GWAS (§5.2.1).

Bottom line for a chronic-CH patient: PACAP is arguably the best-evidenced next drug target for CH — better evidenced pharmacologically than CGRP ever was for chronic disease — but nothing is in the clinic for CH specifically, and the earliest a CH-specific trial could plausibly start is after Lundbeck's migraine Phase 3 programme reads out, with no announced timeline for that indication expansion.

5.1.5 Orexin antagonists and circadian-targeted drugs — the direct answer to a specific question

This chapter was originally asked to check specifically for orexin-pathway and circadian-system drugs. The direct answer:

- **Orexin: a clean negative. [PEER-REVIEWED]** Registry sweeps of every dual/selective orexin antagonist (filanapant/vornorexant, seltorexant, suvorexant, lemborexant, daridorexant) against every headache condition returned zero cluster-headache trials and zero headache-indicated trials of any kind. The only orexin-antagonist trial ever conducted in any headache condition is Merck's filorexant pilot in **migraine** (2015): 120 vs 115 patients, no significant benefit on monthly migraine days (difference −0.4, 95% CI −1.3 to 0.4), more somnolence on drug (13% vs 4%), and an explicitly negative conclusion (Chabi et al., *Cephalalgia* 2015). That trial is now 11 years old and nobody has re-tested the mechanism in CH, despite a genuinely plausible anatomical rationale (orexinergic neurons project to the periaqueductal grey, trigeminal dorsal horn, locus coeruleus, thalamus and spinal cord). The genetic signal for *HCRTR2* (the orexin-2 receptor gene) has been reported in some small studies and not others, is explicitly called "unclear" in the definitive 2024 review (Stanyer, Hoffmann & Holland, *Expert Rev Neurother* 2024 **[PEER-REVIEWED]**), and does **not** appear among the loci in the large 2023 GWAS at all. This is a genuine, unexploited gap in the field rather than a settled negative — the biology has never actually been tested in the right patients.
- **Circadian drugs: thin but not empty. [PREPRINT/TRIAL]** Two live trials genuinely target the circadian/nocturnal attack pattern: NCT06540651, a recruiting light-therapy trial in France explicitly framed around cluster headache being "a chronobiological disease" whose "aim is to re-adjust chronobiological rhythms," and NCT06950281 (SUNCET), a Phase 2 low-sodium-oxybate trial targeting nocturnal chronic-CH attacks specifically. Neither is a clock-gene drug — light therapy targets circadian entrainment behaviourally, and oxybate targets sleep architecture pharmacologically. **No melatonin trial and no clock-gene-modulating compound (REV-ERB agonist, CRY stabiliser, casein-kinase inhibitor, or similar) exists in any stage of headache drug development.** The melatonin evidence base for CH remains two small, contradictory pilots from 1996 (positive) and 2002 (negative), described in a 2025 review as "not validated in high-quality clinical trials" (Burish et al., *Cephalalgia* 2025 **[PEER-REVIEWED]**).

5.1.6 Regional registry coverage — a note relevant to an Australian patient

[PREPRINT/TRIAL] There are **zero cluster-headache-specific trials natively registered in ANZCTR** as of August 2026 — a broad health-condition search on "headache" returned 62 records and none was CH. The only CH trial physically running in Australia is the ClinicalTrials.gov-registered NCT05868044 PRIMUS device study (n=5, active, not recruiting). Australia's one genuinely new CH research initiative — the **MRFF-funded psilocybin pilot ("PEACE")** — is not yet in any registry either; recruitment had not started as of its September 2025 funding announcement (see §5.4.2 for the patient-advocacy chain that produced it).

Asian coverage: Japan's jRCT lists exactly one substantive CH trial (the Japanese arm of eptinezumab's ALLEVIATE trial); China's ChiCTR lists three records including two national CH registries and one interventional carotid-sheath-block trial; Korea's CRIS lists **zero** CH trials (confirmed as a real negative, not a broken search, because control searches on "headache" returned non-zero results).

Diagram: selected trial timeline

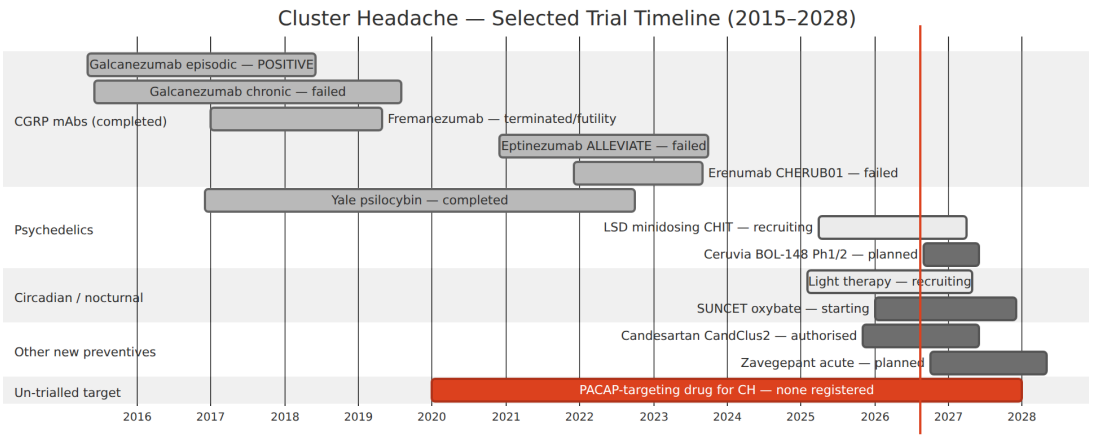


Diagram 4

5.2 Emerging Science: Genetics, Chronobiology, Imaging, Biomarkers (2023–2026)

Standing caveat that applies to this entire section: almost the whole modern CH evidence base rests on small-to-moderate samples (tens to a few hundred patients). Effect sizes are modest, replication across ancestries is patchy, and several headline findings below directly contradict one another. This is a map of active argument, not settled fact.

5.2.1 Genetics — the field's most solid ground, with corrections

[PEER-REVIEWED] The anchor finding is the 2023 International Consortium for Cluster Headache Genetics meta-analysis: 16 research groups across 13 countries (Norway, Netherlands, Sweden, Denmark, Germany, Greece, Spain, Italy, Taiwan, UK), 4,043 European cases and 21,729 controls (Ann Neurol 2023).

Correction: an earlier pass of this chapter listed the loci as MERTK, FHL5, SATB2-region, DUSP10, CAPN2, ADCYAP1R1, and MME. This is wrong. ADCYAP1R1 and MME come from an unrelated, much smaller 2016 Italian study and are **not** loci in the 2023 GWAS at all. The correct list, with three genuinely novel loci that the earlier pass omitted entirely:

Locus (gene)	Lead SNP	Odds ratio	p-value	Status
DUSP10	rs17011182	1.38	7.8×10^{-21}	known
MERTK	rs13399108	1.41	1.7×10^{-30}	known
FTCDNL1 (SATB2 region)	rs6714578	1.53	2.8×10^{-37}	known
FHL5	rs9486725	1.29	2.5×10^{-17}	known
WNT2	rs2402176	1.20	2.6×10^{-8}	**novel**
PLCE1	rs57866767	1.18	4.5×10^{-9}	**novel**
LRP1	rs11172113	1.18	5.2×10^{-9}	**novel**
CAPN2	rs10916600	—	1.3×10^{-13}	trans-ancestry only (driven by the Taiwanese cohort)

SNP heritability is 14.5% (SE 1.74%). Mendelian randomisation implicates **smoking as causal** for CH (IVW β=1.11, p=6.3×10^{-6}), though with significant heterogeneity (Cochran's Q p=0.03) that should temper confidence. Three loci — FHL5, PLCE1, LRP1 — are shared with migraine but have a **larger** effect in CH; migraine shares CH's genetic correlations with pain and ADHD/depression but notably **not** with smoking or risk-taking.

[PEER-REVIEWED] A parallel Taiwanese GWAS (734 patients) found the single largest locus effect reported in any ancestry — CAPN2, OR 1.59 — alongside MERTK, genuinely shared with the European cohorts (J Headache Pain 2022). Chinese registry data (816 patients) found a family-history rate of only 6.99%, markedly lower than European series — worth bearing in mind when interpreting heritability figures built almost entirely on European cohorts (*Cephalalgia* 2024).

[PEER-REVIEWED] A 2026 Swedish functional-validation study proposed that CH risk genes converge on **NLRP3-inflammasome regulation** — a possible link between genetics and inflammation (§5.2.4) (J Headache Pain 2026). **Correction:** the earlier pass reported the protective MERTK odds ratio as 0.69; the correct figure is **0.67** (95% CI 0.57–0.80), and the effect showed substantial heterogeneity (I^2=65.7%) — in the replication cohort alone, MERTK was **not significant**. This inflammasome argument is built on gene-expression annotation, not on measured inflammasome activity in patients, and should be read as a hypothesis, not a finding.

5.2.2 Chronobiology — real phenotype, unsupported genotype

[PEER-REVIEWED] Correction: the earlier pass attributed the current chronobiology synthesis to "Brandt & Fronczek." The correct authors are **Ran, Spulber and Belin (Karolinska Institutet, Sweden)** — "Chronobiology and cluster headache: insights into a hypothalamic disorder," *Curr Opin Neurol*, February 2026 (PMID 41709685). Brandt and Fronczek (Netherlands) wrote a separate, unrelated editorial the same season.

The most important sentence in the whole chronobiology literature comes from a critical 2025 review with authors from the US, Korea, and Sweden: **"Multiple small genetic studies have shown core circadian gene variants to be cluster headache susceptibility genes, whereas larger genetic studies have not shown core circadian gene variants"** (Burish et al., *Cephalalgia* 2025 **[PEER-REVIEWED]**). None of the eight loci in the 2023 international GWAS is a core clock gene. **The clock hypothesis currently survives on phenotype and physiology, not on genetics.** The same review's pooled figures: circadian rhythmicity is reported in ~70% of patients (16 studies, 4,953 individuals), the peak attack window is 2–3am, and autumn is the most common bout-onset season (31% of 3,709 patients).

[PEER-REVIEWED] Countering that partly, a April 2026 study using 707 CH cases and 682 controls genotyped clock genes not covered by standard GWAS panels (*BMAL1*, *NPAS2*, *CLOCK*, *CRY1-2*, *PER1-3*) and reported 258 of 897 marker combinations significantly associated with CH risk, concluding "molecular clock dysfunction [plays] a central role in the manifestation of cluster headache" (*Cephalalgia* 2026). This directly complicates the Burish et al. "large studies find nothing" conclusion — it depends heavily on which genes a study actually looks at. **No therapeutic intervention has been tested on the strength of either finding.**

[PEER-REVIEWED] A Portuguese/UK team found that CH patients' CLOCK gene expression fluctuates significantly *less* across the seasons than in healthy controls — a blunted circannual amplitude, unrelated to whether the patient was currently in or out of bout (*Cephalalgia* 2024). A Swedish/US rat study mapped melatonin receptors (MT1/MT2) directly onto the trigeminal and sphenopalatine ganglia, providing a *peripheral* anatomical rationale for melatonin in CH rather than the usual central/pineal one — animal data only, but mechanistically interesting (*J Headache Pain* 2025).

5.2.3 Imaging — an open, unresolved contradiction

This is a case where sources genuinely conflict and the conflict is presented explicitly rather than smoothed over, per this chapter's standards.

[PEER-REVIEWED] Positive finding (China): the largest CH imaging cohort ever assembled — 69 episodic CH patients vs 63 controls at 7T — found increased hypothalamic volume on the headache side (right anterior-inferior hypothalamus, p=0.019; right posterior hypothalamus, p=0.017) plus widespread functional changes across hippocampal and amygdalar subregions (*J Headache*

Pain 2025). A caveat worth noting: patient-group standard deviations on the volume measures were 4–5x those of controls, suggesting a handful of extreme values may be driving the result, and the patient and control groups were badly sex-mismatched.

[PEER-REVIEWED] Negative finding (Italy) — a direct contradiction, same question: a cleaner, tighter volumetric study — 26 in-bout episodic CH vs 20 matched controls, five hypothalamic subunits plus total volume, adjusted for age, sex and intracranial volume — found **no significant difference on any measure and no correlation with clinical features**, concluding CH is not a macrostructural hypothalamic disease (*Radiol Med* 2025). A second Italian multimodal study similarly found **no subcortical volume differences at all**, with the actual differentiating features being cortical (frontal cortical thinning) (*J Headache Pain* 2026). A larger Chinese 7T study directly comparing CH to migraine also found the headline differentiating features were cortical, cerebellar and brainstem — **not hypothalamic** (*J Headache Pain* 2026).

The honest reading: hypothalamic *macro*structure in CH is unproven and contested across three independent groups; the more consistent signals across studies are **functional and microstructural** rather than volumetric — reduced hypothalamic fractional anisotropy, increased mean diffusivity, altered network connectivity. But even here, a 2025 Italian study explicitly found **no correlation** between hypothalamic microstructural change and cortical-network connectivity change in the same patients — undercutting a simple "the hypothalamus drives the cortex" story (*J Headache Pain* 2025).

5.2.4 Biomarkers and inflammation — a corrected and genuinely contested picture

[PEER-REVIEWED] Correction: the earlier pass claimed IL-1β was elevated specifically in chronic CH. This is **wrong, and the direction is actually inverted** in the primary source. The largest CH cytokine study to date — the Danish Headache Center's plasma biobank, 412 participants across chronic CH, episodic-in-bout, episodic-remission and controls, 45 cytokines measured (*Ann Neurol* 2025) — found IL-1β was **decreased** in episodic-CH-in-bout plasma, not elevated in chronic CH. The genuinely correct and directly relevant finding for a chronic-CH patient is the study's broader pattern: **episodic CH in bout looks broadly anti-inflammatory (suppressed cytokines); chronic CH looks broadly pro-inflammatory (elevated IL-6, CCL7, CXCL9, HGF, MMP12, TGFα).** Oncostatin M is elevated across all three disease states.

[PEER-REVIEWED] A separate Swedish study measuring both CSF and serum in the same patients found CSF cytokines elevated in CH **both in bout and in remission** (arguing for a persistent, trait-like neuroinflammatory state rather than a bout-limited one) — but serum cytokines from the *same patients* moved in the **opposite direction**, decreasing during attacks (*J Headache Pain* 2024). This means peripheral blood is not a reliable proxy for what is happening in the central nervous system in CH, and any inflammation claim based on blood alone should be read cautiously.

[PEER-REVIEWED] As noted in §5.1.4, PACAP-38 is elevated across all CH states and most strongly in chronic CH (+49.8%) — currently the single most consistent circulating biomarker finding that specifically distinguishes chronic from episodic disease.

A blunt critical voice worth including directly, per this chapter's mandate to surface dissent: a Chinese (Chengdu, traditional-medicine-affiliated) review states the CH-inflammation relationship "remains an inference based on changes in inflammatory mediators and neuropeptides in clinical studies; it is not established by direct causal evidence" (*Front Neurol* 2025 **[PEER-REVIEWED]**).

5.2.5 Competing hypotheses — the field's live arguments

- **Against a single hypothalamic generator:** Coppola, Abagnale, Sebastianelli and Goadsby (Italy/UK) argue for a distributed network model in which the posterior hypothalamus is better understood as a "crossroads" than a generator, and propose instead an inherited misalignment between the suprachiasmatic nucleus and peripheral clocks that lowers the threshold for a bout (*Cephalalgia* 2024 **[PEER-REVIEWED]**).
- **The "epiphenomenon" question**, posed explicitly over a decade ago, remains unresolved: is the hypothalamus causal, or just along for the ride (PMID 21864072 **[PEER-REVIEWED]**)?
- **The Japanese Headache Society's consensus position** (published in Japanese) presents **four parallel mechanisms** rather than a single one: hypothalamic generator, neuropeptide/NO signalling, a peripheral origin near the internal carotid/cavernous sinus, and trigeminal hyperexcitability driving the sphenopalatine ganglion (Japanese Journal of

Headache 2026 **[PEER-REVIEWED]**, non-Anglophone source).

Diagram: competing pathophysiology models

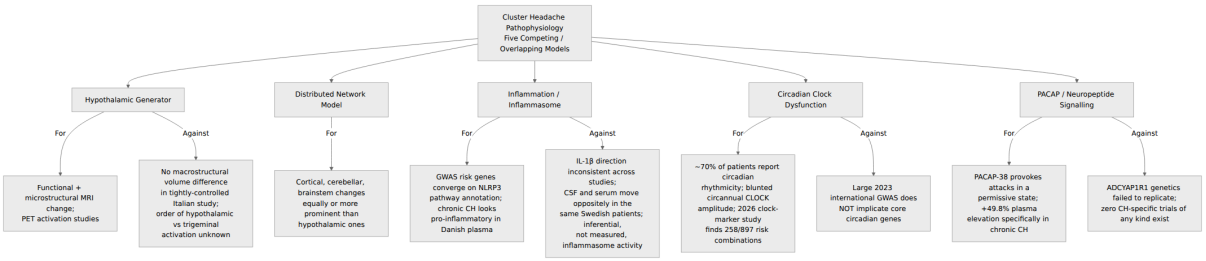


Diagram 5

5.3 The Chronic-CH Problem

Chronic CH — attacks continuing for more than a year without a remission of at least three months — is the harder-to-treat, more research-neglected form of the disease, and this pass found consistent, multi-source evidence for why.

The trial-failure pattern is stark and repeats across every drug class tried. Galcanezumab worked in episodic CH and failed in chronic CH. Fremanezumab failed in both, but the effect estimates were directionally worse in chronic. Eptinezumab failed its efficacy trial in episodic CH and never ran a dedicated chronic-CH efficacy trial at all — CHRONICLE's primary endpoint was safety. Erenumab, tested only in chronic CH, failed outright. **No CGRP-pathway drug has ever succeeded in chronic CH.** The authors of the erenumab trial explicitly recommended that future research "revisit the role of CGRP in chronic CH" — a striking admission from within the field that the leading drug mechanism of the last decade may simply be the wrong mechanism for this specific patient population.

Why chronic CH might be biologically distinct, based on this pass's findings: - **[PEER-REVIEWED]** The Danish cytokine biobank study is the one dataset that specifically separates chronic from episodic-in-bout biology, and it places chronic CH on the pro-inflammatory side of the ledger (elevated IL-6, CCL7, CXCL9, HGF, MMP12, TGFα) while episodic-in-bout looks broadly anti-inflammatory (*Ann Neurol* 2025). - **[PEER-REVIEWED]** PACAP-38 elevation is largest in chronic CH (+49.8%) of any subgroup measured, larger than episodic in-bout (+39.5%) or in remission (+34.1%) (*Eur J Neurol* 2025). - **[PEER-REVIEWED]** Chronic CH shows a different circadian phenotype — an "ultradian pattern with multiple less-predictable peaks" — compared to episodic CH's single early-morning peak (*Cephalalgia* 2025). - A 2025 *Cephalalgia* paper argues chronic CH should itself be treated as a **rare disease** for research and regulatory purposes (PMID 40836704 **[PEER-REVIEWED]**) — a framing that matters because rare-disease designation carries specific funding and regulatory levers (orphan drug incentives, smaller-trial statistical allowances) that chronic CH is not currently leveraging in most jurisdictions.

What is specifically in the pipeline for refractory/chronic patients right now: - **[PREPRINT/TRIAL]** BASIC — botulinum toxin A blockade of the sphenopalatine ganglion, Phase 3, treatment-refractory chronic CH, multi-country (Germany, Italy, Norway, Spain, UK), recruiting since 2019. - **[PREPRINT/TRIAL]** KETALGIA — ketamine + magnesium sulfate, refractory chronic CH, France, now **completed** (23 December 2025), results pending. - **[PREPRINT/TRIAL]** SUNCET oxybate specifically targets nocturnal chronic-CH attacks (§5.1.5). - **[PREPRINT/TRIAL]** Multiple neuromodulation device trials specifically enrol drug-resistant/refractory chronic patients: occipital nerve stimulation, combined trigeminal+occipital stimulation, and (suspended) bilateral occipital nerve field stimulation. - **[PEER-REVIEWED]** A 2025 systematic review of hypothalamic/ventral-tegmental deep brain stimulation in refractory CH is available, and is notable because DBS's delayed onset of benefit and its mixed sham-controlled trial history have themselves been used as an *argument against* pure hypothalamic causality, not just as a treatment option (PMC12382023).

The honest summary: chronic CH is failing drug trials at a higher rate than episodic CH across every mechanism tested so far, there is now real biomarker evidence (cytokines, PACAP) that it may be mechanistically distinct rather than just "worse episodic," and the current refractory-CH research agenda is leaning heavily on procedural and device interventions (botox, neuromodulation, DBS) precisely because the pharmacological pipeline keeps failing this specific population.

5.4 Structural Future: Funding, Advocacy, and Realistic Timelines

5.4.1 The funding numbers, quantified

[PEER-REVIEWED] The updated, CH-specific funding-gap audit that the earlier pass could not find does exist: Parra-Hinojosa, Percy & Gómez-Emilsson, "The heavy tail of extreme pain exacerbates health inequality: evidence from cluster headache underinvestment," *Humanities and Social Sciences Communications*, November 2025 (Nature). Its central finding, independently re-verified in this research pass by querying the UKRI and NIHR APIs directly:

Funder (period searched)	Multiple sclerosis	Cluster headache
UKRI Gateway to Research (since 2006)	£137,445,421	**£0**
NIHR Funding & Awards (since 1996)	£62,635,273	**£0**
Wellcome Trust (since 2005)	£27,147,667	**£0**
Total	**≈£227 million**	**£0**
UK charity income, 2023	£29.95M (MS Society + MS Trust)	**£29,444 (OUCH UK)**

This is despite CH being **more globally prevalent than MS** (roughly 53/100,000 one-year prevalence for CH vs 37/100,000 for MS globally). The paper's methodological contribution is a new metric, **Days Lived with Extreme Suffering (DLES)**, proposed because conventional DALY accounting flattens CH's "heavy tail" of extreme but short-duration pain — CH patients rate their pain a mean 9.7/10 (72% rate it a full 10/10), higher than labour pain, kidney stones, gunshot wounds, or migraine. Globally, CH accounts for an estimated 3.13 million person-days per year at ≥9/10 pain intensity.

[PEER-REVIEWED] At the US federal level, there is still no official NIH accounting category for cluster headache specifically — NIH's own categorisation system tracks "Headaches" and "Migraine" but not CH. Reconstructing from grant-level data via NIH RePORTER, this research pass found **exactly two** CH-specific NIH grants active in FY2022–2026, both to the same two investigators (Burish and Yoo) at the same institution (UTHealth Houston):

Grant	Focus	Awarded to date	Full period value
R01NS136677	Trigeminal ganglion clock and headache pain	$1,422,467 (FY24–26)	~$2.4M over 5 years
R61NS144491	Multi-modal mouse model of CH	$392,223 (FY26)	(exploratory grant)

Set against NIH's "Headaches" funding pool ($50–59M/year FY2022–2025), this derivation puts CH at roughly **0% of NIH headache funding in FY2022–2023** and **~0.8–1.0% in FY2024–2025** — a *smaller* share than the ~1.8% found by a 2007-era audit, even though the absolute dollar figure has roughly doubled. (This percentage is this pass's own derivation from two differently-constructed datasets, not an official NIH statistic, and should be read as an approximation.)

Other identified funders, for context: the EU's only CH money is €2.5M in company innovation funding to a Dutch neuromodulation device firm (not investigator-led science); Australia's MRFF funded the first CH trial there in over 20 years (amount undisclosed); Sweden's dedicated CH research centre at Karolinska received roughly £23,000 in total stipend funding in its entire 2025 announcement, two-thirds of which was pharmaceutical-company-sponsored. The single largest CH-relevant funder

identified anywhere is **private philanthropy** — the Will Erwin Headache Research Foundation's $20 million, 10-year pledge to a Houston research centre (not CH-exclusive, but the source of the preliminary work behind the only major NIH CH grant in existence).

5.4.2 Patient advocacy: doing the work public funders are not

[PEER-REVIEWED] The clearest documented case of patient advocacy directly producing a clinical trial is Australian. Haghdoost, Wold (Clusterbusters' founder, as co-author), Schindler (Yale, as co-author) and colleagues ran an unfunded ("Study funding: None") national patient-priorities survey, February 2024–October 2025, n=202 (*Headache* 2026). Top-ranked research priorities: understanding underlying causes (90% "very important"), developing more effective medications (88%), educating doctors and the public (82%). Psilocybin drew the strongest interest of any intervention (66% "very interested," 82% combined interest; 64% of all respondents said they would join a psilocybin trial specifically). The survey's recruitment target was explicitly set from power calculations for a *future* trial — **and that future trial is the MRFF-funded PEACE psilocybin pilot** described in §5.1.3/5.1.6. This is a clean, documented, citable chain from patient survey to funded science.

[COMMUNITY-REPORT / CITIZEN-SCIENCE] Clusterbusters (US, founded 2002 by Bob Wold) runs on roughly $180,000/year in revenue (its total assets fell 85% between 2022 and 2023, from $221,569 to $34,340, per its IRS filings — worth flagging as a possible capacity constraint on future citizen-science work). Despite this small scale, it built what it describes as the world's largest CH patient registry, helped fill enrolment for the CGRP antibody trials that led to Emgality's FDA approval (the first drug ever specifically approved for CH), co-authored the Australian patient-priorities paper above, and runs the DMT citizen-science survey (§5.1.3).

[PEER-REVIEWED] OUCH UK — on an annual income of **£29,444** — funded, designed and conducted its own comparative-effectiveness study of standard versus ultra-high-flow "demand valve" oxygen delivery, purchasing 30 demand valves independently because it could not afford more, and finding a mean time-to-abort of 36 minutes on standard oxygen versus 11 minutes on the demand valve (*Cephalalgia Reports* 2025). The data was collected in 2013–2014 by a charity trustee and not published until 2025 — an eleven-year lag that is itself a symptom of how under-resourced this corner of medicine is.

[CITIZEN-SCIENCE] Germany's patient organisation (CSG e.V.) runs no grant programme of its own but actively recruits for and disseminates German academic studies, and supports **CLUE**, a formally registered citizen-science project ("Clusterkopfschmerzen erforschen") that has produced at least one peer-reviewed output on medication effectiveness in CH (*J Headache Pain* 2021 **[PEER-REVIEWED]**).

The pattern across every patient organisation checked — Clusterbusters, OUCH UK, CSG e.V., Norway's Hodepine Norge, and others — is identical: recruitment, registries, surveys, conferences and in-kind support, never grant-making. No CH patient organisation anywhere runs a competitive research-grant programme with published award amounts, and no James Lind Alliance priority-setting exercise has ever been run for CH (unlike several adjacent neurological conditions).

5.4.3 Realistic timelines — informed projection, explicitly labelled as such

What could plausibly reach patients or produce a definitive answer in 2–5 years *(projection, not fact)*: - BOL-148 Phase 1 top-line data (Q2 2027) and, if positive, initiation of Phase 2 in CH patients - CandClus2 candesartan Phase 3 readouts (episodic and chronic arms) - SUNCET oxybate and light-therapy trial readouts, giving the field its first real evidence on whether circadian/nocturnal-targeted interventions work at all - LSD minidosing (CHIT) Phase 2 completion (targeted April 2027) - Possible, but currently unannounced: a first PACAP-targeting drug trial specifically in CH, contingent on Lundbeck's or another sponsor's migraine programme succeeding and being extended

What more plausibly sits in the 10+ year horizon *(projection, not fact)*: - A completed, successful Phase 3 psychedelic programme for CH (BOL-148 or otherwise) reaching approval - Any orexin-antagonist trial being initiated in CH at all — nothing currently points toward this happening on any specific timeline - A purpose-built clock-gene-targeting compound for headache — none exists even preclinically for this indication - Structural funding parity with comparably-prevalent conditions (a

UKRI/NIHR/Wellcome-scale investment) — nothing in the current advocacy or policy landscape suggests this is imminent; the funding-gap literature itself (Parra-Hinojosa 2025) frames its own recommendations modestly, as “supporting the few advocacy groups working to raise awareness,” not as a call that any funder has signalled it will answer

---

Unresolved Conflicts

Cross-chapter contradictions found during assembly. Per the assembly brief, none of these have been resolved by the editor: both claims are preserved in place, and this section flags them for the owner to investigate against primary sources. (Contradictions within *a single chapter — the CGRP direction dispute, the sex-ratio narrowing, weather triggers, the ONS placebo results, and so on — were already flagged in place by the chapters themselves and are collected in the consolidated Open Questions section below.)*

1. **Kudrow 1981 oxygen response rate: 75% vs 82%.** Part I, §1.7 reports the landmark Kudrow oxygen trial (52 patients) as "75% got relief with a 7 L/min oxygen mask; 62% aborted their attack within 7 minutes." Part V, §1.1.1, citing Guo et al. 2019, reports the same 1981 trial as "7 L/min for 15 minutes aborted more than 7 of 10 attacks in **82%** of patients." The two chapters relied on different secondary sources; the primary paper (Kudrow L, *Headache* 1981;21:1–4) should be checked directly.

2. **Galcanezumab episodic trial (CGAL, NCT02397473) sample size: 106 vs 109.** Part V, §3.6.1 gives n=106 randomised (49 galcanezumab / 57 placebo), sourced to the NEJM 2019 publication. Part VII, §5.1.1 gives n=109, sourced to the ClinicalTrials.gov registry record. Same trial, two authoritative sources, two numbers.

3. **Diagnostic-delay figures attached to different countries.** Part III, §4.7 lists "Japan 7.3 ± 6.9 years" among country-level mean delays. Part IV, §3 attributes a near-identical figure — "7.3 ± 8 years" — to an *Italian* clinic series (Cefalea a Grappolo, n=100), and gives Japan 8.1 years (Imai et al.) and 3.6–9 years (Japanese Headache Society data). Similarly, Part III lists "Serbia 7.8 ± 8 years" while Part IV lists "7.8 ± 8.3 years" for the Valladolid (Spain) registry. The overlapping numbers attached to different countries suggest at least one chapter's attribution is off; both tables are preserved as found.

4. **The Manzoni natural-history cohort: which study do the transition rates come from?** Part IV, §1 describes a "ten-to-twenty-five-year natural-history follow-up (Manzoni et al.) of 123 episodic and 9 chronic patients" yielding 12.9% episodic→chronic and 32.6% chronic→episodic. Part VI, §4 describes "a 10-year follow-up of 189 patients" yielding "about 13%" and "about 30%" for the same two transitions. Part IV's own reference list includes "Cluster headache — course over ten years in 189 patients" (PMID 1742772). Whether these are one study inconsistently described or two related cohorts is not resolved by either chapter.

5. **What the Danish 48.3% smoking figure denotes.** Part III, §4.4 reports the Danish Cluster Headache Survey (Lund et al. 2019) as finding 48.3% *current* smokers (with 74.5% ever-smokers) vs 9.0% of controls. Part IV, §5 describes the same survey's figure as "current or past smoking prevalence of 48.3%." These descriptions are incompatible; the primary paper defines which is right.

6. **Lifetime single-bout course: 25% vs 17%.** Part I, §2.1 states "about 25% of episodic-CH patients experience only one cluster period in their entire life." Part IV, §1 cites a 60-patient follow-up in which remission after an assumed first cluster period occurred in "only 17%" after 3+ years. These may be measuring different constructs (lifetime course vs medium-term follow-up after a first bout), but the chapters do not reconcile them.

7. **PEACE trial funding amount: disclosed or not?** Part VI states the Australian PEACE psilocybin trial's MRFF funding was "reported at AUD $800,000." Part VII's funding audit states the amount is "genuinely undisclosed in both public announcements found." Directly contradictory sourcing about the same trial.

8. **The chronic share of Western CH cohorts.** Stated as "10–15%" (Part I, §2.1), "10–37% typically reported in Western cohorts" (Part I, §4.6), "10–20%" (Part IV, §3), with cohort-level scatter up to 27.1% (Part IV, §1). Each range traces to different underlying cohorts; no chapter reconciles them into one figure.

9. **Evidence-tier label for the 2026 DMT survey abstract.** Part VI tags the Schindler/Lenaburg/Wold interim abstract `[CITIZEN-SCIENCE][PEER-REVIEWED]`; Part VII tags the same abstract `[PREPRINT/TRIAL]` + `[CITIZEN-SCIENCE]`. Labels preserved as found — the owner may want to settle one convention for conference abstracts.

10. **The International Cluster Headache Questionnaire's headline n.** Part I cites the Burish 2021 pain-comparison analysis at n=1,604 respondents; Part VI states the questionnaire had "over 3,000 participants" when published in *Headache* in November 2021; Part V separately cites "Pearson et al. 2019, Cluster Headache Questionnaire, n≈3,251." These are plausibly different analyses or waves of one instrument, but none of the chapters says so explicitly.

Open Questions & Loose Threads (Consolidated)

Merged from all five chapters. Each chapter's list is preserved intact below, grouped by origin, because the questions are phrased against each chapter's own evidence and section numbers (§ references inside each group refer to sections within the corresponding part). Several themes recur across more than one chapter's list and are worth reading together:

- *the CGRP direction-of-change contradiction and the failure of CGRP drugs in chronic CH (Parts I–II, V, VII);*
- *the smoking paradox — genetically causal for developing CH, yet quitting doesn't help, and never-smokers respond worse to oxygen (Parts III, IV, V);*
- *suicidality prevalence and whether a population-level excess risk exists (Parts III, IV);*
- *the possible East Asian phenotype — lower chronic share, higher male predominance, restlessness "uncoupling" (Parts I, III, IV);*
- *chronic → episodic reversion rates (Part IV's own contested figures; echoed in Part VI);*
- *the REM-sleep association (Parts II, IV);*
- *psychedelics as the largest community-vs-trial evidence gap (Parts V, VI, VII);*
- *and the absence of any Southern-Hemisphere / Australian population data (Parts III, V, VII).*

From Parts I–III (history, nature, mechanism, epidemiology)

This section exists because the master brief for this document explicitly requires "unknown" and "contested" to be treated as valid final answers, not gaps to be papered over. The following are genuinely unresolved, contested, or under-researched points raised across the four research passes behind this chapter:

1. **Etymology of "suicide headache" is unverified.** Two competing origin claims exist (Horton's 1939 description vs. unnamed French authors) and neither is confirmed by a primary source located in this research pass.
2. **Priority for the first historical description of CH is unresolved** among historians, with credible claims for Tulp (1641), Willis (1672), de la Pryme (~1702), Suárez de Ribera (1726), and van Swieten (1745) all contested against each other.
3. **The "pure hypothalamic generator" model is now considered outdated**, but no single replacement model has been definitively established; the "central permissive network" framing (Coppola et al. 2024) is the current best guess, not a settled answer. Hypothalamic volume (VBM) findings are themselves contested — not consistently replicated across studies.
4. **CGRP's direction of change in CH is directly contradicted** between the classic literature (elevated) and a recent, well-powered Danish study (lowered) — unresolved, with real treatment-relevant consequences given CGRP-drug trial results.
5. **Orexin/hypocretin's role is unreplicated**, with directly contradictory CSF findings between the two key studies (Cevoli 2011 vs. Barloese 2015).
6. **Whether smoking is truly causal for CH is a live paradox**: strong genetic/Mendelian-randomisation evidence for causality in disease *development* sits alongside consistent clinical evidence that quitting essentially never improves *established* disease, and a 2025 meta-analysis found no significant smoking-CH association at all in its own pooled analysis — three lines of evidence that do not yet fit together into one coherent story.
7. **Whether the historical male:female sex ratio has genuinely narrowed over time, or whether this is a diagnostic-ascertainment artefact**, is contested — the single most population-representative source (Fischera et al. 2008) explicitly could not confirm the narrowing trend that nearly all clinic-cohort studies report.
8. **Why Asian clinic-based cohorts show consistently higher male predominance (4.3:1–10:1) than recent Northern European registries (1.47:1–2:1)** is not explained in the literature reviewed — genuine biological/cultural difference vs. diagnostic ascertainment difference remains an open question.
9. **Why chronic CH is so much less common in East Asian cohorts (2–7.5%) than Western cohorts (10–37%)** is likewise unexplained.
10. **Whether CH prevalence truly varies by latitude/region** is contested between Fischera et al. 2008 ("independent of region") and a dedicated 2024 latitude review (positive associations found).

11. **No population-based CH prevalence study exists anywhere in the Southern Hemisphere**, a gap explicitly identified in 2008 and, as of this 2026 research pass, still unaddressed. This includes Australia specifically — no dedicated Australian national or population-based CH prevalence, registry, or demographic study was located in any of the four research passes behind this chapter.
12. **Whether CH carries a true population-level excess suicide risk is unresolved**: the most recent CH-specific meta-analysis finds no significant excess outside specialised clinical samples, while a large Danish national registry study of headache broadly (including the TAC category containing CH) finds a robust, population-level excess risk. Neither source definitively supersedes the other.
13. **Whether female sex independently predicts longer diagnostic delay is contested against a persistent narrative**: rigorous primary studies find no significant delay-duration effect by sex, even though the same cohorts often find women are more frequently misdiagnosed at some point along the way — two distinct claims that popular and even some clinical accounts tend to conflate.
14. **The indomethacin-response rule distinguishing CH from paroxysmal hemicrania is not perfectly absolute** — four documented CH case reports responded to indomethacin, complicating a rule usually taught as a bright line.
15. **The restlessness/behaviour "uncoupling" reported in Japanese and Taiwanese cohorts** (feeling restless without displaying it) is a single, interesting, minority finding — not yet corroborated or contradicted by comparable studies in other populations.
16. **Full verbatim patient quotes from two qualitative studies** (Palacios-Ceña et al. 2016; Schindler et al. 2021's "shoe polish" survey) could not be recovered from accessible abstract-only pages during this research pass, and would need full-text institutional access to extract directly.
17. **No dedicated Swedish- or Chinese-language *historical* source**, and no dedicated Italian-language pathophysiology-specific primary research beyond a single 1998 melatonin study, were located — these may simply reflect gaps in this research pass rather than true absences in the literature.
18. **Some sources could not be fetched at all** due to publisher paywalls or site-level access blocks during this research (notably several SAGE/*Cephalalgia* full texts, one PMC patient-story compilation, and a Springer review on cluster-headache behaviour) — figures drawn from these are based on abstracts or secondary citations and should be re-verified against full text before being treated as final in any downstream use of this chapter.

From Part IV (types, diagnosis and differentials)

- **Chronic-to-episodic reversion rate is genuinely contested, not just imprecisely measured.** The Danish Headache Center's most recent interview-based cohort puts 5-year chronic→episodic reversion at 25%; Manzoni's long-term natural history data put it at 32.6%; the 2023 European Academy of Neurology guideline describes reversion as occurring "rarely." These are not compatible framings of the same fact, and no source in this pass reconciled them. Possible explanations (different cohort eras, treatment intensity, or definitions of "reversion") are not confirmed.
- **Episodic-to-chronic conversion rate estimates cluster around 12–20% in recent structured cohorts but range from 4% to 15% depending on follow-up length and country** — treat any single-number claim ("X% convert to chronic") with suspicion; the true figure is clearly time-dependent and rises with longer follow-up.
- **REM sleep association**: contested. Early studies strongly link nocturnal CH attacks to REM sleep, especially in episodic CH; more recent work finds no significant REM association at all, and chronic CH appears to lack the REM link altogether. Unresolved.
- **OSA and CH — causal or parallel?** The literature explicitly states this remains undetermined: OSA could trigger CH attacks via hypoxic/desaturation mechanisms, or both conditions could be independent downstream effects of hypothalamic dysfunction. No prospective interventional trial (e.g. CPAP vs no CPAP) resolving this was found.
- **Alcohol and population-level CH risk**: two peer-reviewed cohort studies produce directly opposing risk ratios for non-drinkers vs drinkers; a meta-analysis could not adjudicate. The in-bout vs out-of-bout attack-triggering effect is well established; the broader epidemiological relationship between alcohol use and CH susceptibility is not.

- **Weather/temperature as a CH trigger is now a genuine, sourced conflict rather than an unverified claim.** A large Taiwanese nationwide study found temperature specifically associated with new bout onset; a 2026 Spanish primary-care time-series study found no significant association between any of 14 climatic variables (including temperature and barometric pressure) and CH consultation frequency. Barometric pressure specifically has no CH-specific peer-reviewed confirmation as a trigger found in this pass — the common patient belief in "pressure drops trigger attacks" currently rests on migraine-literature extrapolation and community report rather than CH-specific primary data.
- **Altitude as a CH trigger**: now supported by at least one specific peer-reviewed case report (oxygen-responsive, sumatriptan-refractory attack at altitude), but this is n=1 evidence. No population-level or cohort data quantifying altitude-triggering frequency across the general CH population was found — treat "altitude triggers CH" as plausible and case-documented, not established at a population level.
- **Suicidality prevalence range**: estimates vary enormously by study design, from ~8% lifetime ideation (population-representative meta-analysis) to 55% (self-selected US patient survey) and 47% (case-control community-recruited sample). Whether this reflects sampling bias, definitional differences (ideation vs risk vs attempts), or genuine subpopulation differences is unresolved.
- **Smoking and CH severity/cessation**: strong association between smoking and more severe CH phenotype is established, but a causal or even correlational benefit from quitting is not — most patients report no change after cessation, and this itself is a striking, still poorly explained finding given smoking's causal role in most other diseases it is linked to.
- **SUNCT vs SUNA as one disorder or two**: increasingly treated as a spectrum/single entity by researchers, but ICHD-3 retains them as formally separate diagnoses pending further study — an active taxonomic tension.
- **Possible East Asian phenotype difference**: Japanese clinic cohorts report markedly lower chronic-CH prevalence (as low as 2.8% vs 10–20% in Western cohorts) and a distinctive "uncoupling" between subjective restlessness and observed restless behaviour during attacks. The source authors themselves frame this as a genuine ethnic/phenotypic difference rather than an artefact, but this remains a minority, under-replicated finding and has not been independently confirmed in large multi-ethnic comparative cohorts.
- **German national patient-registry data (CSG surveys)**: Germany's national CH patient association has run recent surveys on sex differences and psychological burden in CH, but this research did not retrieve full published results from these specific surveys — flagged for direct follow-up with clusterkopf.de rather than treated as sourced here.
- **Community self-diagnosis narrative**: widely repeated across patient forums that many people self-diagnose from internet research before a clinician confirms it. This is no longer purely anecdotal — the Dutch cohort study found a specific figure of 16% self-diagnosing from books/magazines — but broader, more recent quantification (e.g. specifically "internet search" as the self-diagnosis route, as commonly described in forums today) was not found and remains anecdotal at the more specific level.
- **Diagnostic delay figures are inconsistent even within the same country** (e.g. Spain: 4.9 years in one national report vs 7.8 years in a separate regional registry; Germany: 44 months in one source vs 9.6 years in another cohort). This likely reflects genuine differences between clinic-referred and population-representative samples, but no single study in this pass reconciled the within-country discrepancies directly.

From Part V (treatment)

Genuinely contested or unresolved in the literature itself

- **Oxygen flow rate: no consensus, and the one head-to-head trial points the wrong way.** Guidance ranges from Japan's 7 L/min to Clusterbusters' ≥15 to community protocols of 25–40 L/min, yet the only head-to-head trial (Dirkx 2018) found no advantage for 12 L/min over 7 L/min and hinted at the reverse, while EAN cites an odds ratio in the opposite direction with a confidence interval that crosses 1 (0.58–24.28). **Unresolved.** The 25–40 L/min figures used in parts of the community have never been formally trialled at all — plausible extrapolation from demand-valve physiology, not demonstrated fact (Section 1.1).

- **Hyperventilate on oxygen, or don't?** German (DMKG) guidance says no; some community sources say yes, as fast as possible. **Contested**, with a plausible but unverified reconciliation that it depends on whether the gas is genuinely undiluted (Section 1.1).
- **Oxygen concentrators: useless or adequate?** Depends entirely on target flow rate and is stated inconsistently across sources depending on which flow rate they assume (Section 1.1).
- **Melatonin in chronic CH:** one small positive trial in which both chronic participants failed, one small negative trial, and case reports of chronic patients becoming headache-free. **Genuinely unresolved**, not merely under-studied (Section 3.4).
- **Verapamil formulation (immediate-release vs sustained-release):** the dominant English-language community view and at least one German clinic protocol disagree on this directly. Not resolved by the evidence assembled here (Section 3.1).
- **CGRP mAbs in episodic CH:** the two 2026 meta-analyses agree there is no benefit in chronic CH, but reach different conclusions on episodic CH (OR 1.65, p=0.02 vs no significant effect) purely because of different endpoint choices and inclusion criteria. This is a methodological disagreement, not a data disagreement, and is presented as such rather than resolved in either direction (Section 3.6).
- **The smoking paradox:** never having smoked predicts a *worse* oxygen response in both a clinical study and a 493-person community survey, while smoking is simultaneously used as a supply-eligibility barrier for home oxygen in the UK. No mechanistic explanation exists. **Unknown.**

Documented but not formally studied — flagged as community signal, not established finding

- **Serotonergic psychedelics (LSD, psilocybin, ergoline alkaloids) rank highest of all self-reported prophylactics in citizen-science surveys (~75% efficacy), above verapamil and corticosteroids**, despite almost no randomised evidence existing at the time of that survey data. This is the single largest gap identified anywhere in this chapter between community-reported efficacy and formal trial evidence (Section 7.2). It falls outside the acute/bridge/preventive/neuromodulation/access scope this chapter was scoped to, but is flagged here so it is not lost, and belongs explicitly in any future chapter on non-conventional or emerging treatments.
- **Hair loss on galcanezumab**, reported independently across at least three separate r/clusterheads threads, does not appear in any labelled adverse-event list for the drug (Section 3.6 / 7.6).
- **Tachyphylaxis (loss of effect) 6–24 months into CGRP mAb treatment**, reported repeatedly by community members, has never been formally studied (Section 3.6 / 7.6).
- **Warfarin's NNT of 2.6 (95% CI 1.7–5.5)** — the single best number-needed-to-treat figure anywhere in this chapter — comes from one 2011 trial that has never been replicated in fifteen years. Flagged as an odd, isolated finding, not a treatment recommendation (Section 3.5 / 7.7).

Access and regulatory gaps specific to Australia that remain unverified or unresolved despite this research pass

- **gammaCore/nVNS reimbursement pathways in the EU/Germany:** UNKNOWN — not verified in this research pass (Section 5.4).
- **Current verified Australian dollar figures for medical oxygen cylinder hire, sumatriptan autoinjector PBS co-payment, and GON block MBS rebate** were not locatable from primary sources within this research session. Anyone relying on these should check directly with a supplier (BOC, Air Liquide, Coregas) and the current PBS/MBS schedules rather than treating any figure elsewhere in this chapter as current (Section 1 / 5.1).
- **US formulary tier placement** for several off-label preventives was not verified for specific insurers (Section 5.2).

Sourcing limitations disclosed by the research process itself

- **Two PubMed records could not be retrieved directly** during this research pass and were sourced second-hand instead: Pearson et al. 2019 (PMID 30632614, the large Clusterbusters/CHQ survey, quoted via Guo et al. 2019) and a GON block meta-analysis (PMID 32781922, not incorporated at all — there may be pooled GON-block data this chapter does not

reflect). A valproate RCT (PMID 12047460) was also blocked on direct fetch and is sourced via PMC8748342's reproduction of the trial data instead (Sections 1, 2, 3).

- **No systematic search of Chinese-language literature was performed** for any section of this chapter. Italian (SISC), Japanese (JHS), German (DMKG/AWMF) and Swiss guideline PDFs were located but not all individually extracted within the research session's budget — the non-English findings actually used in the body text came specifically from Schmerzklinik Kiel (German), a 2025 Czech review, a SciELO-hosted lithium review, and the Japanese Headache Society CQ1 guideline. This is stated explicitly so no reader assumes the full text of every located non-English guideline was read and incorporated.
- **This chapter's own thoroughness is uneven by design of the parallel research process that produced it**: the acute/bridge draft and the preventive draft were each produced independently and did not cross-reference each other's treatment categories, so some cross-cutting connections (e.g. between bridge corticosteroids and the broader steroid literature, or between GON blocks as bridge therapy and GON blocks as a chronic-CH refractoriness criterion in Section 4.0) may be less tightly integrated than a single continuous research pass would have produced. Section 7 above is this document's attempt to repair that after the fact, but it should not be assumed exhaustive.
- **Reddit thread dates and participant counts throughout this chapter are approximate**, derived from page content rather than platform metadata, where exact dates were not stated on the fetched page.

From Part VI (citizen science and community knowledge)

This section was revised in a follow-up research pass (August 2026) that specifically targeted the items below. Resolved or substantially updated items are marked accordingly; several turned out to resolve toward disappointing or null answers rather than positive ones — which is itself useful information.

- **RESOLVED (negatively): the Vitamin D3 RCT outcome is now known — the trial failed.** NCT04570475 was **terminated** in 2024 after randomising only 27 of its intended participants, citing "low number met criteria to randomize," and never posted results [PREPRINT/TRIAL][^23]. The Batch protocol's flagship formal test no longer exists as a pending question; it exists as a failed attempt. Whether a differently designed trial (e.g. one not requiring D3-naïve participants) could still succeed is a new open question this raises.
- **Still unresolved: no full peer-reviewed paper for the D3 survey.** The 110-patient D3 survey still exists only as the 2014 Neurology conference abstract; nothing new was found on this point.
- **Still unresolved: mechanism of psilocybin/LSD/BOL-148 efficacy in CH.** No mechanistic resolution was found. If anything, the newly identified Schindler/Wold 2026 DMT survey abstract [^81] suggests the community-and-clinic collaboration is now testing a third psychedelic class, which will add data without yet answering the underlying "why does intensity not predict benefit" question.
- **Still unresolved: BOL-148's non-hallucinogenic status is itself contested** (unchanged from original chapter; not specifically re-investigated in this update).
- **Still unresolved: exercise as trigger or treatment.** No mechanistic account distinguishing responder subgroups was found in this update.
- **Still unresolved: no aggregated CH-specific wearable/app dataset.** Not specifically re-investigated in this update; treat as unchanged.
- **RESOLVED (negatively, and now more strongly confirmed): kudzu has never been formally trialled**, seventeen years after the original 2009 case series explicitly called for an RCT. A fresh check found no registered kudzu headache trial anywhere [PEER-REVIEWED, absence confirmed][^89].
- **UPDATED: the Australian PEACE psilocybin trial has not started recruiting as of August 2026.** The trial's own lead investigator stated in September 2025 that recruitment was expected to begin in the second half of 2026; a March 2026 webinar still described it as "upcoming." No ANZCTR/ClinicalTrials.gov registration number could be located in this research, which is itself worth someone manually checking at anzctr.org.au [PREPRINT/TRIAL][^85][^86]. Results are now a 2027-or-later prospect, not a "pending" near-term one.

- **RESOLVED (negatively, and now more strongly confirmed): energy drink/caffeine aborts have never been formally tested**, and a fresh literature check found nothing that changes this [PEER-REVIEWED, absence confirmed][^88].
- **PARTIALLY RESOLVED: cross-cultural and non-English community data.** Targeted native-language research now shows a clear pattern rather than a blank: **Germany has genuine patient-driven citizen science with a peer-reviewed output** (Clusterkopfschmerz-Radar/CLUE, feeding into a 2021 *BMC Neurology* paper) [CITIZEN-SCIENCE][PEER-REVIEWED][^67][^69], while **Scandinavian, Italian, and Spanish communities have well-organised patient associations but no published patient-collected datasets of their own**, and **no Japanese or Chinese patient-run, data-collecting CH community could be located** in indexable sources — though the Chinese negative result is weaker, since much peer support plausibly happens in non-indexable WeChat/Baidu Tieba channels this research could not assess [COMMUNITY-REPORT / unverified][^70][^72][^74][^75][^76][^77][^78][^79][^80]. The open question narrows from "is there data out there we haven't found?" to "why has only the German community converted patient-logged data into a publication, and could the German CLUE/mitforschen.org model be replicated elsewhere?"
- **NEW: EPOCH (NCT04280055) is not the completed 30%-reduction success this chapter originally implied.** It was terminated early due to COVID-19 recruitment problems, reaching only 10 participants; the earlier framing should be treated as corrected here [PREPRINT/TRIAL][^36].
- **NEW: a DMT-in-cluster-headache survey (Schindler, Lenaburg, Wold, 2026) is underway** as an interim conference abstract, extending the psychedelics research agenda to a third compound class with direct community-founder co-authorship; full results are not yet available and should be watched for [CITIZEN-SCIENCE][PEER-REVIEWED][^81].
- **NEW: BOL-148/Ceruvia's German Phase 1/2 trial has still not dosed a single participant** as of this update (August 2026), despite a fresh $8M raise; do not treat the Q4 2026 enrolment / Q2 2027 data timeline as assured given this programme's decade-plus history of slipping schedules [PREPRINT/TRIAL][^40].

From Part VII (the frontier)

- **The hypothalamic-imaging contradiction is unresolved.** A 69-patient Chinese 7T study found increased hypothalamic volume; a tightly-controlled 26-patient Italian study found none at all on the same question. Both are recent, both are peer-reviewed, and they directly disagree. [Contested]
- **The direction of IL-1β in CH is inconsistent across the literature**, and the earlier draft of this chapter got it backwards. Even within the single largest cytokine study, the inflammasome hypothesis's own authors acknowledge the conflict openly. Whether chronic CH is genuinely pro-inflammatory (as the Danish plasma data suggest) remains unreplicated by an independent group. [Contested]
- **CSF and serum cytokines move in opposite directions in the same CH patients** (Swedish study). This means most published "CH is inflammatory" claims based on blood alone may not reflect what is happening in the central nervous system. [Unresolved methodological problem]
- **Whether the inflammasome hypothesis reflects real pathophysiology or is an artefact of gene-annotation inference** is genuinely open — no study has yet measured actual inflammasome (NLRP3/caspase-1) activity in CH patients.
- **Whether core circadian clock genes matter genetically is disputed within the last 12 months of literature itself**: a large critical review says no, a newer (April 2026) targeted-genotyping study says yes. Both are recent and neither has been independently replicated yet. [Contested]
- **PACAP has the strongest pharmacological rationale of any drug target in CH and precisely zero CH-specific trials.** Whether any sponsor will ever run one — rather than leaving CH patients to benefit only incidentally from migraine drug development — is unknown and worth actively monitoring.
- **Orexin has never actually been tested in cluster headache**, despite a real anatomical rationale, because the only headache trial ever run (in migraine, 2015) was negative and nobody has revisited the mechanism in the population where it might plausibly matter most. This is a genuine, unexploited research gap, not a settled negative.
- **Japan's UMIN-CTR registry could not be retrieved** during this research pass despite three attempts (direct fetch, content-fetch service, and browser rendering all failed). A Japanese CH trial invisible to jRCT cannot currently be ruled out, though the risk is judged low.

- **Three Chinese trial registrations (ChiCTR) could not be resolved to phase, dates, or endpoints** because ChiCTR's detail pages are keyed by an internal ID not exposed in search results.
- **The MRFF PEACE psilocybin trial's funding amount is genuinely undisclosed** in both public announcements found.
- **Whether Clusterbusters' 85% asset drawdown between 2022 and 2023 reflects a real capacity constraint** on the organisation's future citizen-science and advocacy work is unknown; FY2024/2025 financial filings were not yet available to check.
- **The claim that CH is globally more prevalent than MS rests on a CH prevalence estimate with a wide confidence interval** (one-year prevalence 53/100,000, 95% CI 26–95) — the comparison is directionally likely true but not as tightly bounded as a single point estimate implies.
- **There is still no official government audit of cluster-headache-specific research funding anywhere in the world.** The NIH figures in this chapter are this pass's own reconstruction from grant-level RePORTER data, not an official NIH statistic — precisely the gap that the field's own advocacy literature (Orr & Shapiro 2022, "The elephant in the room") has been pointing at for years without it being filled.
- **No James Lind Alliance–style formal priority-setting partnership has ever been run for cluster headache**, unlike several adjacent neurological conditions — the 2026 Australian patient survey is currently the closest thing the field has to one, and it was unfunded.

Editor’s Queries

Items noticed during assembly that look like research or transcription errors, or ambiguities, in the source chapters. Per the assembly brief they were left as found (with one disclosed exception) rather than fixed silently.

1. **Misspelt source domain in Part V.** One in-text citation (§1.2.6) and reference [59] use the URL `australianprescriban.tg.org.au` — presumably a typo for `australianprescriber.tg.org.au`. Left as found.
2. **Truncated links in Part V’s reference list.** References [77], [82] and [138] end mid-DOI (e.g. `10.1016/S1474-4422(20)`). The in-text citations carry the full DOIs; only the end-list entries are truncated.
3. **One duplicated sentence removed.** Part V’s preventive-treatment introduction contained the same framing sentence twice in a row (“Before the drug-by-drug detail, three structural facts…”). The duplicate was removed as pure smoothing — no wording of the surviving sentence was changed. Disclosed here for transparency.
4. **Part IV reference-list numbering irregularities.** The list uses entries 24b and 25b and jumps from 55 to 57 (there is no [^56]). Footnote markers of the form `[^n]` are used in the text against a plain numbered list, so they will not render as live footnotes in most Markdown renderers. Left as found.
5. **Citation/label mismatch in Part VI.** Reference [88] is labelled with the Danish Cluster Headache Survey URL but is used to support the “no energy-drink/caffeine trials exist” absence claim. The label and the claim do not obviously match.
6. **Suspect URL in Part V, §4.2.7.** The Realeve FDA Breakthrough-Device announcement is cited at a realeve.net URL whose slug reads “15-best-blogs-to-follow-about-web-design” — likely a mis-scraped link; the claim itself is corroborated by the surrounding BusinessWire citations.
7. **Internal cross-reference drift in Part V.** Some of the chapter’s internal pointers (“see §1.5”, “§1.6”, “§4.1”, “§6”) reflect an earlier numbering of its own sections (e.g. §5.1.2’s subsections are numbered 1.2.1–1.2.6). Renumbering was not attempted, to avoid introducing new errors; navigate by heading text.
8. **Ambiguous questionnaire n.** The differing participant counts for the International Cluster Headache Questionnaire (1,604 / >3,000 / ≈3,251) are logged as Unresolved Conflicts item 10; flagged here too because it may simply be an under-specified description in one or more chapters rather than a true contradiction.
9. **Part I colophon scope.** Part I–III’s closing colophon (“Compiled from PubMed/PMC…”) describes the four research memos behind the original Chapter 1 only; it does not cover Parts IV–VII, which disclose their own sourcing limitations inline (see especially Part V’s “Sourcing limitations” and Part VII’s registry-coverage notes).
10. **Diagram merges.** The assembly brief permitted regenerating diagrams that merge cleanly. None did — the Part I attack-mechanism diagram, Part IV’s classification/conversion Mermaid diagrams, Part V’s decision tree and Part VII’s Gantt/model diagrams cover different ground — so all were retained unchanged.

Watchlist

Carried over from Part VII (Chapter 5, §5.5) and placed here as this document's final content section. Links and dates as compiled 13 August 2026.

A living table — the seed for ongoing monitoring.

Item	Type	What to watch for	Roughly when	Link
Ceruvia BOL-148	Drug (psychedelic)	German CTA filing; first patient dosed	Sept–Q4 2026	Ceruvia
Ceruvia BOL-148 Phase 1	Drug (psychedelic)	Top-line safety/dose data	Q2 2027	BioSpace
BetterLife BETR-001	Drug (psychedelic, migraine-led)	US IND filing	Q1 2027	BetterLife
CHIT LSD minidosing	Trial (psychedelic)	Primary completion / results	April 2027	NCT05477459
DMT citizen-science survey	Citizen-science	Full peer-reviewed publication beyond the AAN abstract	Unknown	Neurology abstract
CandClus2 (candesartan)	Trial (preventive)	Recruitment start; interim/final results	2026–2028	CTIS 2025-521470-34-00
SUNCET (oxybate)	Trial (nocturnal/circadian)	Recruitment start; results	2026–2027	NCT06950281
Light therapy (Luminettes)	Trial (circadian)	Results — first real circadian-intervention data in CH	2027	NCT06540651
Zavegepant intranasal	Trial (acute)	Trial start; first gepant tested as CH abortive	Oct 2026 onward	NCT07714369
BASIC (botulinum toxin, SPG)	Trial (refractory chronic)	Completion / results	Was due Sept 2025; watch for delay/results	NCT03944876
KETALGIA (ketamine)	Trial (refractory chronic)	Results publication	Completed Dec 2025; watch for paper	NCT04814381
Lundbeck bocunebart (PACAP)	Drug programme	Any indication-expansion announcement to CH/TACs	Watch every AHS/IHC conference	Lundbeck pipeline
Slate Medicines SLTE-1009 (PACAP)	Drug programme	Phase 1 initiation; any CH mention	Mid-2026 onward	Business Wire
Any orexin-antagonist CH trial	Drug class	First-ever registration in this indication	Unknown — currently zero	—
Karolinska Centre for Cluster Headache	Lab	Follow-up to inflammasome hypothesis; clock-gene work	Ongoing	KI
Danish Headache Center	Lab	Follow-up cytokine/PACAP studies	Ongoing	Rigshospitalet
UTHealth Houston (Burish/Yoo)	Lab	R01/R61 outputs — clock/mouse-model findings	2026–2029	NIH RePORTER
MRFF PEACE psilocybin trial	Trial	Recruitment start (Australia)	Delayed from H2 2026 estimate	George Institute
Chinese SPG pulsed-radiofrequency programme	Trial (procedural)	Results — large-N Chinese data mostly invisible in Western reviews	2026–2030	NCT06787677
Parra-Hinojosa funding-gap paper	Advocacy/policy	Any funder response or policy citation	Ongoing	Nature

Item	Type	What to watch for	Roughly when	Link
Clusterbusters financial position	Advocacy	FY2024/2025 Form 990 — did the 2023 asset drawdown continue?	Watch ProPublica	ProPublica

---

Changelog

- **13 August 2026** — v1.0 — Initial assembly from five research chapters.