

Review Article

Occipital Nerve Stimulation in Medically Refractory Chronic Cluster Headache

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Abstract

Background: A meaningful minority of chronic cluster headache (CCH) patients become refractory to pharmacological prophylaxis. Occipital nerve stimulation (ONS) has been used off-label for over two decades in this population.

Objective: To synthesise published evidence on ONS for medically refractory CCH against other neuromodulation approaches.

Methods: Narrative review of case series, randomised sham/placebo-controlled trials, comparator, and complication/durability literature.

Findings: Early case series reported roughly 50% responder rates with continuous ONS. The dose-controlled ICON trial found high- and low-amplitude tonic ONS both reduced attack frequency by about 50% without separating from each other, with benefit sustained over a 2-8-year extension. A newer placebo-controlled trial of paresthesia-free burst ONS, however, did not outperform placebo. Sphenopalatine ganglion stimulation, vagus nerve stimulation and hypothalamic deep brain stimulation show efficacy signals with differing risk profiles. Lead migration and infection are the dominant device-related complications.

Conclusions: ONS is a reasonably well-supported, comparatively low-risk option for refractory CCH, though blinded evidence remains limited and stimulation-paradigm effects are unresolved.

Keywords: Cluster headache; Occipital nerve stimulation; Neuromodulation; Refractory headache; Deep brain stimulation

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Introduction

Cluster headache is a trigeminal autonomic cephalalgia characterised by strictly unilateral, excruciating orbital or temporal attacks lasting 15-180 minutes, accompanied by ipsilateral autonomic features and often restlessness [1]. A pooled meta-analysis of population-based studies estimated a lifetime prevalence near 1 in 1000 [2]. Roughly 10-15% of patients have the chronic subtype, in which

attacks recur for more than a year without remission of at least three months [1]. A meaningful minority of chronic cluster headache (CCH) patients fail an adequate trial of standard prophylactic agents (verapamil, lithium, corticosteroid bridging, topiramate) and acute therapies (oxygen, triptans); the European Headache Federation formalised criteria for this "refractory chronic cluster headache" (rCCH) to standardise selection for invasive treatment [3]. For these patients, neuromodulation has become the principal therapeutic avenue.

Occipital nerve stimulation (ONS) — subcutaneous electrodes placed over the greater and/or lesser occipital nerves and connected to an implantable pulse generator — has been trialled in rCCH since the mid-2000s. This narrative review synthesises the published case series, randomised controlled trials, comparator neuromodulation literature and complication/durability data on ONS for medically refractory CCH.

Chronic Cluster Headache and Treatment Refractoriness

CCH carries a substantial burden: near-daily, severely painful attacks erode sleep, employment and mental health, and many rCCH patients have failed multiple preventive drug classes at adequate doses and durations, along with acute therapies [3]. The European Headache Federation consensus defines refractoriness as failure (lack of efficacy or intolerable side effects) of at least three evidence-based prophylactic drugs used at adequate dose for an adequate trial period, in patients with an unequivocal CCH diagnosis and no significant psychiatric comorbidity confounding assessment [3]. This definition underpins eligibility criteria in essentially all modern ONS trials and case series, allowing comparison across otherwise heterogeneous cohorts.

Rationale and Mechanism of Occipital Nerve Stimulation



The rationale for ONS rests on convergence of trigeminal nociceptive afferents and upper cervical (C1-C3, including the greater and lesser occipital nerves) somatosensory afferents onto second-order neurons of the trigeminocervical complex in the caudal brainstem and upper cervical cord. Electrical stimulation of the occipital nerves was hypothesised to modulate this shared circuit and, secondarily, more rostral pain-processing structures. Positron emission tomography (PET) studies support this: in chronic migraine patients with suboccipital stimulators, ONS was associated with metabolic changes in the dorsal rostral pons, anterior cingulate cortex and other pain-modulatory regions [4]. In CCH specifically, an FDG-PET study of ten ONS-treated patients found evidence of a central modulatory effect, though hypothalamic activation persisted even in good responders, suggesting ONS acts as a symptomatic, network-level modulator rather than correcting a primary hypothalamic abnormality [5]. This distinguishes the proposed mechanism from that invoked for hypothalamic deep brain stimulation (DBS), discussed below.

Clinical Evidence

Early case series. The first prospective pilot study implanted eight patients with drug-resistant CCH; the majority reported at least 50% reduction in attack frequency or severity with continuous stimulation [6], with sustained benefit reported on longer follow-up of the same and expanded cohorts [7]. An independent series of eight patients with medically intractable CCH reported similarly favourable long-term outcomes [8], later extended to 14 patients [9]. The largest single-centre cohort to date, 51 patients followed a mean of over three years, found a 46.1% improvement in attack frequency across the group (49.5% in those with CCH alone) [10]. A French cohort with exceptionally long follow-up confirmed sustained efficacy of ONS in drug-resistant CCH even many years after implantation [11], and an

observational study using validated quality-of-life instruments found meaningful gains in medically intractable CCH beyond attack frequency alone [12]. The French national ONS registry, analysing long-term outcomes in a large multicentre cohort, likewise reported sustained efficacy for medically intractable CCH [13]. These series are uniformly open-label, unblinded and subject to placebo, regression-to-the-mean and selection effects, motivating controlled trials.

Table 1: Key case series and randomised trials of occipital nerve stimulation for medically refractory chronic cluster headache reviewed here [6,8,9,10,11,12,13,14,15,16]; N = 10 studies.					
Study (year)	Design	N	Stimulat ion	Follow-u p	Key outcome
Magis 2007	Open-lab el pilot	8	Tonic, co ntinuous	Mean ~15 mo	~63% had ≥50% improv ement
Burns 2007	Open-lab el	8	Tonic, co ntinuous	Long-ter m	Majority ≥50% improved
Burns 2009	Open-lab el	14	Tonic, co ntinuous	Extended cohort	~36% ≥50% improved
Miller 2017	Open-lab el cohort	51	Tonic, co ntinuous	Mean 39 mo	46.1% frequency im provement
Leone 2017	Open-lab el, long-t erm	15	Tonic, co ntinuous	Exceptio nal long-t erm	Sustained benefit confirmed
Fontaine 2017	Observati onal, pro spective	Not st ated	Tonic, co ntinuous	Prospecti ve	Improved quality of life
Leplus 2021	Registry, observati onal	Multi centr e (Fre nch r egistr y)	Tonic, co ntinuous	Long-ter m	Sustained long-term efficacy
Wilbrink 2021 (ICON)	RCT, dos e-control led	150	High- vs l ow-ampli tude tonic	12 weeks	~50% reduction, both arms; no between-arm difference
Brandt 2023	Open-lab el extension of ICON	Subse t of ICON	Tonic, co ntinuous	2-8 years	Benefit sustained or improved

Study (year)	Design	N	Stimulation	Follow-up	Key outcome
Fogh-Andersen 2026 (HortONS)	RCT, placebo-controlled	38 randomised	Burst vs placebo	12-week blinded + open-label	Burst did not beat placebo (blinded phase)

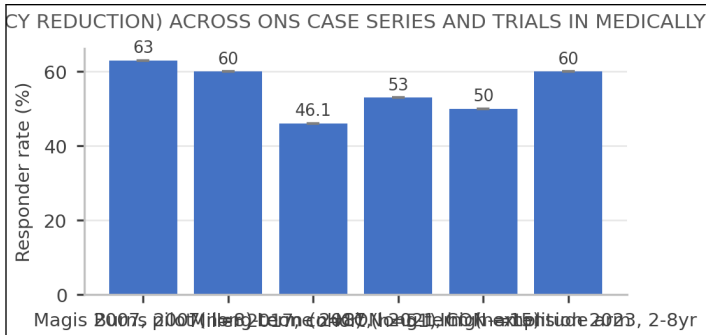


Figure 1: Responder rates ($\geq 50\%$ attack-frequency reduction) reported across open-label occipital nerve stimulation (ONS) series and the ICON trial in medically refractory chronic cluster headache [6,8,10,11,14,15].

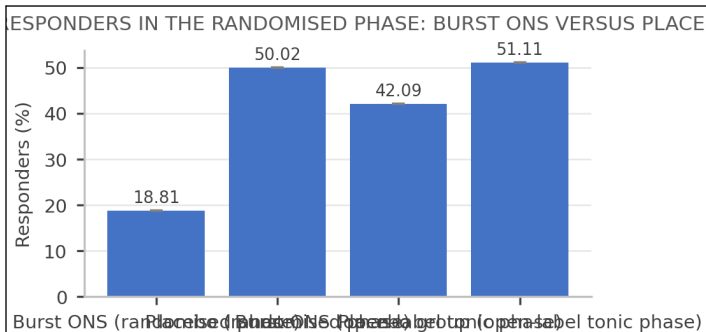


Figure 2: Proportion of $\geq 30\%$ responders with burst occipital nerve stimulation versus placebo in the randomised and open-label phases of the HortONS trial; burst stimulation did not separate from placebo in the blinded phase ($p=0.042$ favouring placebo) [16].

Randomised and sham/placebo-controlled trials. The ICON trial randomised medically intractable CCH patients to high-amplitude versus low-amplitude ("subtherapeutic") tonic ONS in an electrical dose-controlled, double-blind design, given the difficulty of blinding overt paresthesia-based stimulation against a true off condition; both arms saw roughly 50% reductions in weekly attack frequency without a significant between-group difference on the primary endpoint, though safety was favourable and over 90% of participants would recommend the therapy [14]. A prospective

open-label extension followed patients for two to eight years and found effect sizes were sustained or improved, with continued acceptable safety [15]. More recently, an investigator-initiated trial (HortONS) used paresthesia-free burst stimulation against a genuinely blinded, deactivated placebo condition; in the randomised phase, $\geq 30\%$ responder rates were numerically lower with burst ONS (18.8%) than placebo (50.0%), a difference favouring placebo ($p=0.042$), though both groups improved similarly once all participants received open-label tonic stimulation [16]. This is an important, sobering result: it suggests the efficacy demonstrated for tonic, paresthesia-inducing ONS may not generalise to paresthesia-free burst paradigms, and it underscores how difficult unconfounded blinding remains in ONS trials.

Comparison with Other Neuromodulation Approaches

Sphenopalatine ganglion (SPG) stimulation targets the parasympathetic outflow implicated in cluster autonomic features. The Pathway CH-1 trial, a randomised, sham-controlled study of an implantable SPG microstimulator, found substantially higher rates of pain relief with full versus sham stimulation for acute attacks, alongside a preventive effect in some patients [17]. Non-invasive vagus nerve stimulation (nVNS) has been evaluated in two sham-controlled trials for acute attack termination (ACT1, ACT2), with more consistent benefit in episodic than chronic cluster headache [18,19], and an open-label adjunctive prevention study (PREVA) suggested reduced attack frequency when nVNS was added to standard management in CCH [20]. Pharmacological neuromodulation of the CGRP pathway has also been tested: a phase 3 randomised trial of galcanezumab in CCH did not meet its primary endpoint over three months of double-blind treatment, illustrating how refractory this population remains even to newer

mechanisms and providing useful context for interpreting device trial effect sizes [21]. Hypothalamic DBS, first reported in a single intractable case [22], targets the posterior hypothalamic grey matter implicated in cluster attack generation; the only randomised, double-blind DBS trial found no significant difference between active and sham stimulation in its blinded phase, and electrode-location analyses have refined the anatomical target [23], while stimulation has documented cardiovascular effects requiring monitoring [24]. Relative to DBS, ONS is generally regarded as lower-risk given its extracranial location, though direct comparative trials are lacking; a 2021 narrative review situates ONS alongside these approaches as part of a broader neurostimulation armamentarium for CCH, noting comparable efficacy signals but substantially different invasiveness and complication profiles [25].

Table 2: Neuromodulation approaches for chronic cluster headache compared with occipital nerve stimulation [17,18,19,20,22,23,24].				
Approach	Target	Invasive-ness	Key controlled evidence	Notable risk
Occipital nerve stimulation	Occipital nerves / trigeminocervical complex	Subcutaneous, extracranial	ICON dose-controlled RCT [14]	Lead migration, infection
Sphenopalatine ganglion stimulation	Sphenopalatine ganglion	Intraoral microstimulator implant	Pathway CH-1 sham-controlled RCT [17]	Facial sensory disturbance
Non-invasive vagus nerve stimulation	Cervical vagus nerve	Non-invasive, external device	ACT1/ACT2 sham-controlled RCTs [18,19]	Limited efficacy in chronic subtype
Hypothalamic deep brain stimulation	Posterior hypothalamic grey matter	Stereotactic intracranial implant	Randomised double-blind DBS trial, negative blinded phase [23]	Intracranial haemorrhage, autonomic effects [24]

Complications and Device-Related Issues

ONS is generally well tolerated, but hardware-related complications are common relative to its modest invasiveness. Lead migration is the most frequently

reported problem, occurring in roughly 10-24% of implanted patients across series, often requiring surgical revision [10,26]. Infection, hardware fracture, battery/generator-site discomfort and loss of efficacy over time are also described [27]. A recent technical review analysing surgical approach in relation to outcome argued that variability in lead placement and anchoring technique contributes materially to both efficacy and revision rates, suggesting standardisation of surgical technique could reduce complication burden [27]. Burst (paresthesia-free) stimulation platforms have been explored partly to preserve blinding and comfort, with small open-label studies suggesting comparable efficacy to tonic stimulation for some patients [28], though the HortONS controlled data above tempers that optimism [16]. Overall, no ONS trial or large series has reported life-threatening complications, distinguishing its risk profile favourably from craniotomy-based hypothalamic DBS [24].

Long-Term Outcomes and Durability

Durability data are reassuring where available. The ICON open-label extension followed patients for two to eight years and found that benefit was maintained or improved beyond the initial randomised phase, with an acceptable long-term safety profile [15]. Independent long-term cohorts report sustained attack-frequency reductions and quality-of-life gains at three or more years of follow-up [10,11,12,13]. These findings are important because CCH is by definition a persistent disorder without spontaneous remission, so any effective device-based therapy must show durability rather than a transient effect. That said, most long-term data derive from open-label, non-randomised follow-up of trial or case-series cohorts, and attrition (through loss of efficacy, device removal or complications) is incompletely captured across studies, meaning true long-term "real-world" effectiveness may be somewhat lower than reported.

Conclusion

The published evidence supports ONS as a comparatively low-risk, moderately effective option for patients with medically refractory chronic cluster headache who have exhausted standard prophylaxis. Open-label series consistently report roughly 50% responder rates with tonic stimulation, corroborated by the electrical dose-controlled ICON trial and its long-term extension, while a more recent placebo-controlled trial of burst stimulation failed to demonstrate superiority over sham. Alongside SPG stimulation, vagus nerve stimulation and hypothalamic DBS, ONS occupies a favourable position on the invasiveness-efficacy spectrum, but device-related complications, particularly lead migration, remain a meaningful burden, and the field would benefit from further blinded trials directly comparing stimulation paradigms and from standardised surgical technique to improve durability.

References

1. Headache Classification Committee of the International Headache Society (IHS) (2018) The International Classification of Headache Disorders, 3rd edition. *Cephalalgia*, 38(1): 1-211.
2. Fischera, M., Marziniak, M., Gralow, I., Evers, S. (2008) The incidence and prevalence of cluster headache: a meta-analysis of population-based studies. *Cephalalgia*, 28(6): 614-618.
3. Mitsikostas, D.D., Edvinsson, L., Jensen, R.H., Katsarava, Z., Lampl, C., Negro, A., Osipova, V., Paemeleire, K., Siva, A., Valade, D., Martelletti, P. (2014) Refractory chronic cluster headache: a consensus statement on clinical definition from the European Headache Federation. *Journal of Headache and Pain*, 15: 79.
4. Matharu, M.S., Bartsch, T., Ward, N., Frackowiak, R.S.J., Weiner, R., Goadsby, P.J. (2004) Central neuromodulation in chronic migraine patients with suboccipital stimulators: a PET study. *Brain*, 127(1): 220-230.
5. Magis, D., Bruno, M.A., Fumal, A., Gerardy, P.Y., Hustinx, R., Laureys, S., Schoenen, J. (2011) Central modulation in cluster headache patients treated with occipital nerve stimulation: an FDG-PET study. *BMC Neurology*, 11: 25.
6. Magis, D., Allena, M., Bolla, M., De Pasqua, V., Remacle, J.M., Schoenen, J. (2007) Occipital nerve stimulation for drug-resistant chronic cluster headache: a prospective pilot study. *Lancet Neurology*, 6(4): 314-321.
7. Magis, D., Gerardy, P.Y., Remacle, J.M., Schoenen, J. (2011) Sustained effectiveness of occipital nerve stimulation in drug-resistant chronic cluster headache. *Headache*, 51(8): 1191-1201.
8. Burns, B., Watkins, L., Goadsby, P.J. (2007) Treatment of medically intractable cluster headache by occipital nerve stimulation: long-term follow-up of eight patients. *Lancet*, 369(9567): 1099-1106.
9. Burns, B., Watkins, L., Goadsby, P.J. (2009) Treatment of intractable chronic cluster headache by occipital nerve stimulation in 14 patients. *Neurology*, 72(4): 341-345.
10. Miller, S., Watkins, L., Matharu, M. (2017) Treatment of intractable chronic cluster headache by occipital nerve stimulation: a cohort of 51 patients. *European Journal of Neurology*, 24(2): 381-390.
11. Leone, M., Proietti Cecchini, A., Messina, G., Franzini, A. (2017) Long-term occipital nerve stimulation for drug-resistant chronic cluster headache. *Cephalalgia*, 37(8): 756-763.
12. Fontaine, D., Blond, S., Lucas, C., Regis, J., Donnet, A., Derrey, S., et al. (2017) Occipital nerve stimulation improves the quality of life in medically-intractable chronic cluster headache: results of an observational prospective study. *Cephalalgia*, 37(12): 1173-1179.
13. Leplus, A., Fontaine, D., Donnet, A., Regis, J., Lucas, C., Buisset, N., et al. (2021) Long-term efficacy of occipital nerve

- stimulation for medically intractable cluster headache. *Neurosurgery*, 88(2): 375-383.
14. Wilbrink, L.A., de Coö, I.F., Doesborg, P.G.G., Mulleners, W.M., Teernstra, O.P.M., Bartels, E.C., et al. (2021) 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 Neurology*, 20(7): 515-525.
 15. Brandt, R.B., Wilbrink, L.A., de Coö, I.F., Haan, J., Mulleners, W.M., Huygen, F.J.P.M., et al. (2023) 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*, 98: 104895.
 16. Fogh-Andersen, I.S., Sørensen, J.C.H., Petersen, A.S., Knudsen, A.L., Meier, K., et al. (2026) Safety and efficacy of occipital nerve stimulation as treatment of chronic cluster headache: an investigator-initiated, double-blind, randomized, placebo-controlled study. *Journal of Headache and Pain*, 27: 77.
 17. Schoenen, J., Jensen, R.H., Lanteri-Minet, M., Láinez, M.J., Gaul, C., Goodman, A.M., et al. (2013) Stimulation of the sphenopalatine ganglion (SPG) for cluster headache treatment. *Pathway CH-1: a randomized, sham-controlled study. Cephalalgia*, 33(10): 816-830.
 18. Silberstein, S.D., Mechtler, L.L., Kudrow, D.B., Calhoun, A.H., McClure, C., Saper, J.R., et al. (2016) Non-invasive vagus nerve stimulation for the acute treatment of cluster headache: findings from the randomized, double-blind, sham-controlled ACT1 study. *Headache*, 56(8): 1317-1332.
 19. Goadsby, P.J., de Coö, I.F., Silver, N., Tyagi, A., Ahmed, F., Gaul, C., et al. (2018) Non-invasive vagus nerve stimulation for the acute treatment of episodic and chronic cluster headache: a randomized, double-blind, sham-controlled ACT2 study. *Cephalalgia*, 38(5): 959-969.
 20. Gaul, C., Diener, H.C., Silver, N., Magis, D., Reuter, U., Andersson, A., et al. (2016) Non-invasive vagus nerve stimulation for PREvention and Acute treatment of chronic cluster headache (PREVA): a randomised controlled study. *Cephalalgia*, 36(6): 534-546.
 21. Dodick, D.W., Goadsby, P.J., Lucas, C., Jensen, R., Bardos, J.N., Martinez, J.M., et al. (2020) Phase 3 randomized, placebo-controlled study of galcanezumab in patients with chronic cluster headache: results from 3-month double-blind treatment. *Cephalalgia*, 40(9): 935-948.
 22. Leone, M., Franzini, A., Bussone, G. (2001) Stereotactic stimulation of posterior hypothalamic gray matter in a patient with intractable cluster headache. *New England Journal of Medicine*, 345(19): 1428-1429.
 23. Fontaine, D., Lanteri-Minet, M., Ouchchane, L., Lazorthes, Y., Mertens, P., Blond, S., et al. (2010) Anatomical location of effective deep brain stimulation electrodes in chronic cluster headache. *Brain*, 133(4): 1214-1223.
 24. Cortelli, P., Guaraldi, P., Leone, M., Pierangeli, G., Barletta, G., Grimaldi, D., et al. (2007) Effect of deep brain stimulation of the posterior hypothalamic area on the cardiovascular system in chronic cluster headache patients. *European Journal of Neurology*, 14(9): 1008-1015.
 25. Evers, S. (2021) Neurostimulation treatment in chronic cluster headache: a narrative review. *Current Pain and Headache Reports*, 25(12): 81.
 26. Vencio, R.C., et al. (2021) An unusual case of lead migration in occipital nerve stimulation: a case report and literature review. *Surgical Neurology International*, 12: 189.
 27. Kurt, E., Kollenburg, L., van Dongen, R., Volkers, R., Mulleners, W., Vinke, S. (2024) The untold story of occipital nerve stimulation in patients with cluster headache: surgical technique in relation to clinical efficacy. *Neuromodulation*, 27(1): 22-35.
 28. Garcia-Ortega, R., Edwards, T., Moir, L., Aziz, T.Z., Green, A.L.,

FitzGerald, J.J. (2019) Burst occipital nerve stimulation for chronic migraine and chronic cluster headache. Neuromodulation, 22(5): 638-644.