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Invasive and non-invasive neuromodulation in refractory cluster headache: a systematic review

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Introduction
Refractory cluster headache (rCH) is a highly disabling subtype of trigeminal autonomic cephalalgia, characterized by persistent attacks despite optimized preventive therapy. Up to 15% of patients with chronic cluster headache do not respond adequately to at least three guideline-recommended preventive treatments, thereby meeting criteria for a refractory phenotype. Neuromodulation has emerged as a mechanistically targeted approach designed to modulate trigeminal–autonomic reflex pathways and correct hypothalamic dysfunction.

Objective
To compare the efficacy, safety, and quality of evidence of invasive and non-invasive neuromodulation strategies in refractory cluster headache.

Methods
PubMed/MEDLINE, SciELO, and LILACS were systematically searched for studies, published between January 2016 and April 2026 , investigating neuromodulation strategies in refractory cluster headache, in accordance with PRISMA 2020 criteria. Search terms included "refractory cluster headache," "neuromodulation," "vagus nerve stimulation," "occipital nerve stimulation," and "deep brain stimulation." Randomized controlled trials, as well as prospective and retrospective cohort studies, were considered eligible if they included adult patients with refractory or chronic cluster headache undergoing neuromodulation. Primary outcomes included reductions in attack frequency, pain intensity, and the proportion of patients achieving at least a 50% responder rate. Risk of bias was assessed using the Cochrane RoB 2.0 and ROBINS-I tools.

Results
From 312 records identified, 126 duplicates were removed; of the 186 records screened, eight studies met full inclusion criteria, totaling 1,240 patients. Non-invasive vagus nerve stimulation demonstrated an average reduction of 3.2–4.0 weekly attacks compared with standard care, with responder rates ranging from 30% to 40%. Occipital nerve stimulation was associated with a 40–50% reduction in attack frequency in chronic refractory cohorts, although device-related adverse events occurred in up to 20% of patients. Deep brain stimulation achieved reductions exceeding 50% in selected patients with extreme refractoriness, although the evidence relied primarily on small observational series.

Conclusion
Neuromodulation represents a clinically relevant therapeutic option for refractory cluster headache. Non-invasive vagus nerve stimulation provides the most favorable balance between efficacy and safety, while occipital nerve stimulation and deep brain stimulation may be considered for highly refractory cases managed by specialized centers. Standardized definitions of refractoriness and well-designed multicenter randomized trials are essential to strengthen the evidence base and refine treatment algorithms.

Keywords:
Refractory cluster headache
Neuromodulation
Vagus nerve stimulation
Occipital nerve stimulation
Deep brain stimulation

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