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Review Article

Treatment of Chronic Central-Origin Pain in Pediatric Patients with Vagal Neuromodulation

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Abstract

Chronic central-origin pain in pediatric patients requires a multidisciplinary approach addressing altered pain processing, autonomic dysregulation, and psychosocial factors. Vagal neuromodulation, particularly transcutaneous auricular vagus nerve stimulation, represents a promising noninvasive strategy for modulating pain related pathways. This article reviews its underlying mechanisms, potential clinical applications, and current limitations, alongside the possible role of neuroendocrine, neurotransmitter-related, and gut microbiota assessments. Although biologically plausible, clinical evidence in children remains limited. Further controlled trials, standardized stimulation protocols, and validated biomarkers are needed to establish its safety, efficacy, and role in individualized pediatric chronic pain management.

Keywords: *Chronic Central-Origin Pain; Pediatric Patients; Vagal Neuromodulation; Transcutaneous Vagus Nerve Stimulation (tVNS)*

Introduction

Chronic pain in children and adolescents is a complex clinical condition in which persistent nociceptive input, altered central nervous system processing, autonomic dysregulation and psychosocial factors may interact to maintain symptoms beyond the expected period of tissue healing. Chronic pain is generally defined as pain persisting or recurring for more than three months. Within this framework, the concept of central-origin pain encompasses conditions associated with dysfunction of central somatosensory pathways, central sensitization and altered descending pain modulation. These mechanisms should be distinguished from the formal diagnostic categories of chronic primary and chronic secondary pain, as defined by the International Association for the Study of Pain [1].

In pediatric patients, central sensitization may contribute to persistent pain, hypersensitivity to sensory stimuli, sleep disturbances, fatigue, reduced school attendance and functional impairment.

The clinical presentation reflects the interaction between developing neural networks, emotional regulation and environmental influences rather than a simple correspondence between pain intensity and peripheral tissue damage [2]. Early recognition is therefore essential to prevent disability and the consolidation of maladaptive pain-related behaviors. A neuroscience-informed, multidisciplinary approach provides the basis for integrating conventional treatment with emerging neuromodulation strategies.

Vagal neuromodulation: Mechanisms and clinical applications

The vagus nerve is a major component of the parasympathetic nervous system and participates in bidirectional communication between the brain, visceral organs and immune system. Vagal stimulation may influence pain processing through brainstem noradrenergic pathways, descending inhibitory circuits, autonomic regulation and the cholinergic anti-inflammatory pathway. These mechanisms provide a rationale for investigating vagal neuromodulation as an adjunctive intervention in chronic pain, although the magnitude and clinical relevance of these effects remain dependent on the underlying condition and stimulation protocol.

Vagus nerve stimulation can be divided into invasive and non-invasive approaches. Implantable cervical vagus nerve stimulation involves surgical placement of an electrode around the cervical vagus nerve and is established for selected neurological indications, but it is not a routine treatment for pediatric chronic pain. Non-invasive transcutaneous vagus nerve stimulation (tVNS) offers a less invasive alternative, particularly relevant to younger populations.

Two principal transcutaneous approaches are currently used. Cervical tVNS applies electrical stimulation over the cervical region, targeting accessible vagal structures. Transcutaneous auricular vagus nerve stimulation (taVNS) stimulates regions of the external ear innervated by the auricular branch of the vagus nerve, commonly the cymba conchae or tragus. Auricular stimulation is particularly attractive in pediatric practice because it avoids surgery and can be delivered using external electrodes. Nevertheless, differences in electrode placement, stimulation intensity, frequency and treatment duration limit comparability between studies.

A systematic review of pediatric tVNS studies highlighted substantial heterogeneity in treatment protocols and the absence of adequately justified, development-specific stimulation parameters [3].

Evidence from adult chronic pain studies is encouraging but cannot be directly extrapolated to children. Preliminary adolescent research on transcutaneous vagal neuromodulation in other clinical contexts also illustrates the growing interest in autonomic modulation, while underscoring the need for condition specific trials [4].

Accordingly, vagal neuromodulation should currently be considered an investigational or complementary strategy for pediatric chronic pain, selected on an individual basis and integrated with established pharmacological, physical and psychological interventions.

Laboratory assessment: Neuroendocrine function, neurotransmitters and the gut-brain axis

A comprehensive assessment may identify biological factors that influence pain persistence and treatment response. Laboratory investigations should, however, be guided by the clinical history and examination rather than used as a substitute for a structured pain assessment.

Salivary cortisol and hypothalamic pituitary-adrenal axis

Chronic pain frequently coexists with sleep disruption and altered stress regulation. Serial salivary cortisol sampling across the day can characterize the diurnal cortisol profile, including the awakening response and evening decline. Reference data demonstrate a marked daily rhythm in healthy school-aged children [5]. When clinically indicated, sampling at standardized times over a 24 hours period may provide exploratory information about hypothalamic-pituitary adrenal axis function. Interpretation requires consideration of age, sleep timing, acute stress, medication exposure and collection procedures. No specific cortisol profile has been validated as a diagnostic marker of central pain or as a predictor of response to vagal stimulation.

Dopaminergic and serotonergic pathways

Dopamine and serotonin participate in reward processing, affective regulation and descending pain modulation. Human neuroimaging research supports associations between dopaminergic and serotonergic receptor availability and experimental pain sensitivity [6]. Nevertheless, a peripheral dopamine/serotonin concentration ratio is not an established surrogate for central neurotransmission. Its measurement should therefore be considered exploratory, not a validated clinical test for selecting treatment.

Gut microbiota and the gut-brain axis

Bidirectional communication between the intestinal microbiota and central nervous system involves immune, endocrine, metabolic and neural pathways, including vagal afferents. Microbial metabolites and inflammatory signaling may influence nociceptive processing, providing a plausible link between dysbiosis and certain chronic pain phenotypes [7]. Microbiota assessment may be considered in selected patients with gastrointestinal symptoms or other clinical indications. However, commercial dysbiosis profiles lack validated thresholds for diagnosing central-origin pain, and evidence does not support routine microbiome testing as a prerequisite for neuromodulation.

From initial assessment to clinical treatment: Current state of the art

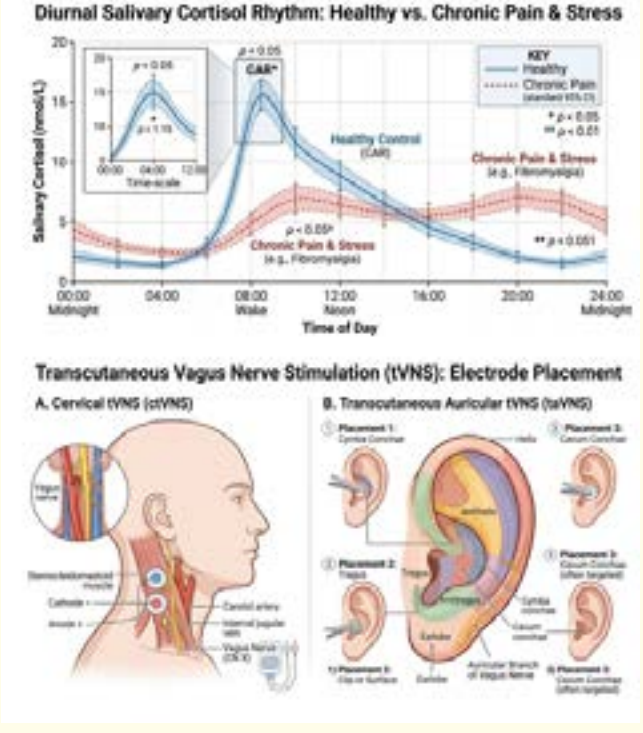
The first step in managing pediatric chronic pain is a comprehensive clinical evaluation, including pain history, neurological examination, functional impact, sleep, emotional well-being, school participation and family context.

Appropriate investigations should exclude identifiable underlying disease and address relevant differential diagnoses. Validated age-appropriate pain and disability measures provide a baseline against which treatment response can be assessed.

Treatment should then follow an individualized, multidisciplinary pathway combining pain education, graded physical rehabilitation, psychological interventions, sleep optimization and pharmacotherapy when indicated. Non-invasive vagal neuromodulation may be considered as an adjunct in carefully selected patients, preferably within a specialist service or clinical research protocol. Outcomes should include not only pain intensity but also daily functioning, quality of life, sleep, school attendance and treatment tolerability.

At present, the principal limitation is the gap between biological plausibility and robust pediatric clinical evidence.

Standardized stimulation protocols, age specific safety data, controlled trials and validated predictive biomarkers are still needed. Cortisol profiling, neurotransmitter-related investigations and microbiota analysis may contribute to hypothesis-driven research, but should not determine treatment independently.



Figure

Conclusion

In conclusion, chronic central-origin pain in childhood requires early recognition and a coordinated approach that addresses neurobiological, functional and psychosocial dimensions. Vagal neuromodulation represents a promising non-invasive avenue for investigation, rather than an established stand-alone treatment. Its future clinical role will depend on rigorous pediatric trials, reproducible treatment protocols and clinically meaningful outcomes. The most appropriate current strategy remains a personalized pathway from accurate diagnosis to multidisciplinary care, with neuromodulation introduced cautiously and evaluated against measurable functional goals.

Acknowledgement

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Bibliography

1. Nicholas M., *et al.* "The IASP classification of chronic pain for ICD-11: chronic primary pain". *Pain* 160.1 (2019): 28-37.
2. Lebel A and Schuster NM. "Pediatric Pain". *Continuum (Minneapolis, Minn.)* 30.5 (2024): 1517-1535.
3. Sigrist C., *et al.* "Transcutaneous auricular vagus nerve stimulation in pediatric patients: a systematic review of clinical treatment protocols and stimulation parameters". *Neuromodulation* 26.3 (2023): 507-517.
4. Castelletti M., *et al.* "Modulating the autonomic nervous system: transcutaneous vagal neuromodulation improves outcomes in adolescent post traumatic stress disorder — a double-blind trial". *EC Neurology* 18.1 (2026): 01-15.
5. Tzortzi C., *et al.* "Cortisol daily rhythm in saliva of healthy school children". *International Dental Journal* 59.1 (2009): 12-18.
6. Martikainen IK., *et al.* "Dopaminergic and serotonergic mechanisms in the modulation of pain: In vivo studies in human brain". *European Journal of Pharmacology* 834 (2018): 337-345.
7. Liu L., *et al.* "Gut microbiota in chronic pain: Novel insights into mechanisms and promising therapeutic strategies". *International Immunopharmacology* 115 (2023): 109685.

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