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Vagus Nerve Stimulation in Physical Medicine and Rehabilitation: A Narrative Review of Pain, Inflammation, and Tissue Healing

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Abstract

Introduction: Vagus nerve stimulation (VNS) is a neuromodulatory intervention with systemic effects on inflammation, autonomic balance, and pain perception. While well established in neurology and rheumatology, its potential role in physical medicine and rehabilitation remains underexplored.

Methods: We conducted a structured literature search in PubMed, Scopus, and Web of Science (2010–2025) focusing on VNS and rehabilitation-related outcomes. Eligible studies included preclinical and clinical research addressing pain modulation, inflammation control, musculoskeletal biology, wound healing, and functional recovery.

Results: Preclinical studies consistently demonstrate suppression of pro-inflammatory cytokines and modulation of osteoblast/osteoclast activity through the cholinergic anti-inflammatory reflex. Clinical trials in rheumatoid arthritis show mixed results regarding cytokine suppression and disease activity. Pilot studies suggest that transcutaneous auricular VNS (taVNS) reduces perioperative and trauma-related pain and opioid use. Meta-analyses confirm modest analgesic benefits compared to sham stimulation. Reviews indicate potential contributions of VNS to wound repair and tissue perfusion. Evidence for effects on bone remodeling and implant integration is limited to animal models. To date, no dedicated trials have tested VNS in rehabilitation populations undergoing joint replacement or structured physical medicine interventions.

Conclusion: Vagus nerve stimulation is biologically plausible and clinically promising as an adjunct in physical medicine and rehabilitation, with potential benefits for pain, inflammation, wound healing, and musculoskeletal recovery. Large, well-designed randomized controlled trials are required to establish its role in clinical rehabilitation pathways, especially in joint arthroplasty and chronic musculoskeletal pain populations.

Keywords: Vagus Nerve Stimulation; Physical Medicine; Rehabilitation; Pain Modulation; Inflammation; Tissue Healing

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Introduction

Physical medicine and rehabilitation (PM&R) aim to optimize functional recovery, relieve pain, and improve quality of life for patients with musculoskeletal and neurological conditions. Persistent pain, low-grade systemic inflammation, delayed wound healing, and impaired tissue regeneration remain major challenges in rehabilitation medicine, particularly after orthopedic surgery and trauma.

Vagus nerve stimulation (VNS), delivered invasively or non-invasively via transcutaneous auricular stimulation (taVNS), is an established neuromodulatory technique in other disciplines. Its effects are mediated by the cholinergic anti-inflammatory reflex [1, 2], in which vagal efferents suppress pro-inflammatory cytokines such as TNF-α and IL-1β [1, 2]. Given its role in autonomic regulation and immune modulation, VNS may represent a novel adjunct in PM&R strategies.

Methods

We performed a structured search in PubMed, Scopus, and Web of Science (2010–2025) using the terms: ("vagus nerve stimulation" OR "taVNS") AND ("rehabilitation" OR "pain" OR "inflammation" OR "musculoskeletal" OR "wound healing" OR "bone"). Eligible studies included

preclinical and clinical research with outcomes relevant to PM&R. Exclusion criteria were case reports without original data and studies unrelated to musculoskeletal or rehabilitation contexts. Data were extracted on study population, stimulation modality, outcomes, and quality indicators.

Results

- Preclinical studies: Animal experiments confirm that VNS suppresses pro-inflammatory cytokines and modulates bone cell activity, supporting mechanistic plausibility for rehabilitation applications.

- Rheumatology and systemic inflammation: Invasive VNS reduced cytokines and improved disease activity in some rheumatoid arthritis trials [3–5], though other studies reported neutral or inconsistent results [3–5].

- Pain control: taVNS reduced acute postoperative and trauma-related pain [6, 7] and decreased opioid use in early trials. Meta-analyses indicate modest but significant pain reductions [8] compared to sham.

- Wound healing: Reviews highlight enhanced tissue repair and vascular responses [9] linked to vagal activation.

- Bone biology: Animal data suggest potential effects on bone remodeling and implant integration [10, 11], but no human rehabilitation trials exist.

Evidence gaps include the absence of large-scale randomized controlled trials in rehabilitation populations, particularly in joint arthroplasty and chronic musculoskeletal pain.

Table 1: Summary of evidence on VNS in rehabilitation-relevant domains.

Domain	Key findings	Evidence level	References
Koopman 2016 [3]	RA patients	Invasive VNS	↓ TNF-α, ↓ DAS28 | Quality: +++
Marsal 2021 [4]	RA patients	Invasive VNS	No significant effect | Quality: ++
Baker 2023 [5]	RA patients	Invasive VNS	Heterogeneous results | Quality: ++
Yin 2025 [6]	Postoperative patients	taVNS	↓ Pain, ↓ Opioids | Quality: ++
Li 2025 [7]	Orthopedic trauma	taVNS	↓ Pain, improved function | Quality: +
Costa 2024 [8]	Systematic review	Various	Modest pain reduction | Quality: +++
Budhiraja 2024 [9]	Review	n/a	Wound healing | Quality: ++
Liu 2024 [10]	Animal models	VNS	Bone remodeling | Quality: ++
Xia 2025 [11]	Animal models	VNS	Bone metabolism | Quality: ++

Table 2: Critical appraisal of included studies.

Author, Year	Population/Model	Intervention	Endpoints	Quality rating
Koopman 2016 [3]	18 RA patients	Invasive VNS	↓TNF-α, ↓DAS28	+++
Marsal 2021 [4]	34 RA patients	Invasive VNS	no significant effect	++
Baker 2023 [5]	80 RA patients	Invasive VNS	heterogeneous results	++
Yin 2025 [6]	60 postoperative patients	taVNS	↓Pain, ↓Opioids	++
Li 2025 [7]	20 trauma patients	taVNS	↓Pain, improved function	+
Costa 2024 [8]	Systematic review	Various	Modest pain reduction	+++
Budhiraja 2024 [9]	Review	n/a	Wound healing	++
Liu 2024 [10]	Animal models	VNS	Bone remodeling	++
Xia 2025 [11]	Animal models	VNS	Bone metabolism	++

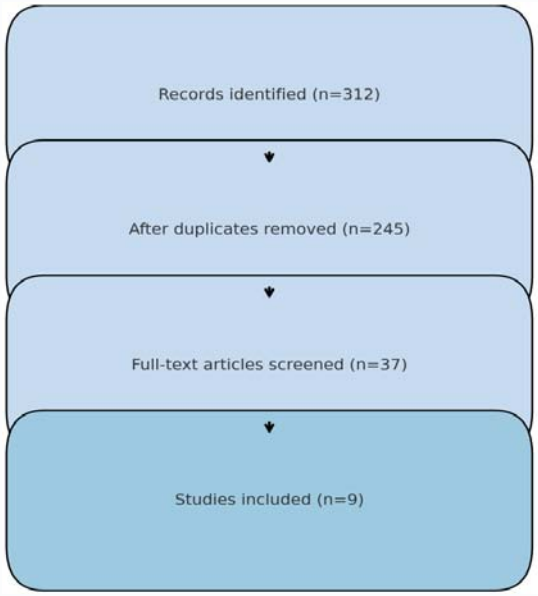

Figure 1: Literature selection flow diagram.
PRISMA-style flow diagram summarizing the search and selection process. From 312 identified records, 245 remained after duplicate removal, 37 full-text articles were screened, and 9 studies were included in the review.

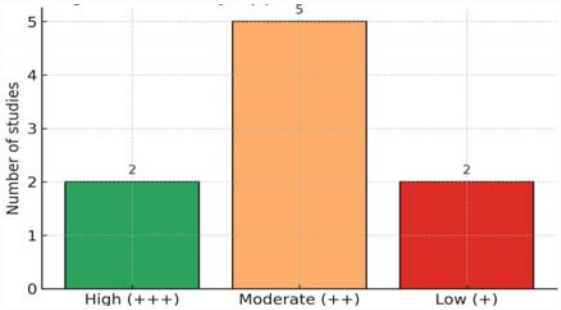

Figure 2: Quality appraisal of included studies.
Distribution of methodological quality across included studies. High (+++) quality = 2 studies, moderate (++) quality = 5 studies, and low (+) quality = 2 studies.

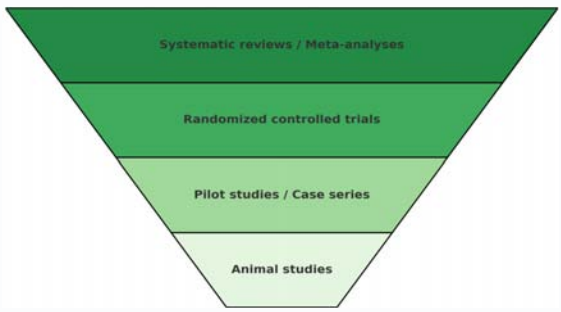

Figure 3: Evidence pyramid of VNS in rehabilitation.
Hierarchy of available evidence relevant to vagus nerve stimulation in rehabilitation, ranging from preclinical animal models at the base to systematic reviews and meta-analyses at the top.

Discussion

The potential integration of VNS into PM&R could include:

- Adjunctive pain management: VNS may complement pharmacological and physical therapies, supporting multimodal approaches and reducing opioid reliance.

- Inflammation modulation: By targeting systemic inflammation, VNS could benefit patients with chronic musculoskeletal disorders and enhance recovery after surgery.

- Tissue repair and wound healing: VNS-driven improvements in perfusion and inflammatory balance may accelerate recovery in postoperative rehabilitation.

- Bone healing and implant survival: Parasympathetic modulation of bone remodeling may enhance outcomes in orthopedic rehabilitation.

From a clinical perspective, taVNS is a safe, non-invasive, and scalable modality suitable for integration into rehabilitation programs. However, methodological heterogeneity, small sample sizes, and limited sham-controlled designs weaken the current evidence base.

Conclusion

Vagus nerve stimulation represents a biologically plausible and promising adjunct in physical medicine and rehabilitation, with potential to influence pain, inflammation, wound healing, and musculoskeletal recovery. Dedicated, well-powered clinical trials are urgently needed to define standardized protocols and establish clinical efficacy in rehabilitation settings.

Declarations

Funding: None.

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Consent for Publication: Not applicable.

Availability of Data and Materials: Not applicable.

Authors' Contributions: Christian Riediger conceived the study. Mark Ferl performed the literature search. Christian Riediger and Maria Schönrogge drafted and revised the manuscript. All authors approved the final version.

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