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Original article

Non-invasive auricular vagus nerve stimulation in fibromyalgia: Impacts on autonomic function, central sensitization and pain catastrophizing

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ABSTRACT

Introduction: Fibromyalgia is a complex chronic pain disorder frequently associated with autonomic dysregulation, central sensitization, and cognitive-emotional disturbances. Transcutaneous vagus nerve stimulation (tVNS) has recently emerged as a non-invasive neuromodulatory approach with potential to modulate autonomic function, pain perception, and affective processing. We aim to evaluate the short-term effects of a 28-day tVNS protocol on autonomic function, symptom severity, central sensitization, neuropathic-like pain features, and pain catastrophizing in patients with fibromyalgia.
Methods: Twenty-five female patients with fibromyalgia (mean age 48.6 ± 7.3 years; mean disease duration 68 ± 24 months) underwent twice-daily 30-minute tVNS sessions using the Nurosym™ device for 28 consecutive days. Outcome measures included: Composite Autonimic Symptom Score 31 (COMPASS-31), Revised Fibromyalgia Impact Questionnaire (FIQR), PainDETECT Questionnaire (PDQ), Central Sensitization Inventory (CSI-9), and Pain Catastrophizing Scale (PCS). Pre- and post-treatment scores were compared using paired statistical analyses.
Results: Significant improvements were observed in total COMPASS-31 scores ($P < 0.05$), particularly within the orthostatic ($P < 0.05$), vasomotor ($P < 0.05$), and pupillomotor ($P < 0.05$) subdomains. FIQR scores decreased from 69.12 ± 17.58 to 62.24 ± 19.19 ($P < 0.01$), indicating a moderate reduction in overall symptom burden. PDQ and CSI-9 scores also improved significantly ($P < 0.01$ and $P < 0.05$, respectively), suggesting a reduction in neuropathic-like symptoms and central sensitization. Although PCS scores showed a downward trend, the change was not statistically significant ($P = 0.070$).
Conclusions: This pilot study suggests that tVNS may be a safe, well-tolerated, and effective intervention for modulating autonomic and central mechanisms in fibromyalgia. The results support further controlled trials to define optimal protocols and assess long-term outcomes.

1. Introduction

Fibromyalgia is a chronic, multifactorial syndrome characterized by widespread musculoskeletal pain, fatigue, sleep disturbances, cognitive impairment, and emotional distress [1]. Although its etiopathogenesis remains incompletely understood, accumulating evidence implicates complex dysfunctions within the central nervous system (CNS) and autonomic nervous system (ANS), particularly involving central sensitization and autonomic imbalance [2,3].

Despite the availability of both pharmacological and non-pharmacological interventions, clinical management remains challenging. Pharmacologic agents such as duloxetine, venlafaxine, pregabalin, and gabapentin provide modest benefits for a subset of patients, though their utility is often constrained by side effects and poor long-term adherence. Non-pharmacological approaches, including physical exercise, cognitive-behavioural therapy (CBT),

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and pain neuroscience education (PNE), have shown variable efficacy, underscoring the urgent need for safe, accessible, and multimodal therapeutic alternatives [4–6].

Neuromodulation, particularly through non-invasive stimulation techniques, has recently gained attention as a novel strategy to modulate aberrant pain pathways.

Transcutaneous vagus nerve stimulation (tVNS) offers a non-invasive method of stimulating the auricular branch of the vagus nerve via the external ear [7]. This stimulation activates several key brainstem structures involved in pain modulation and autonomic regulation, most notably the nucleus tractus solitarii (NTS) and the locus coeruleus (LC) [8,9]. The LC is the principal site of noradrenergic neurons in the brain and plays a critical role in modulating arousal, stress responses, and descending pain inhibition. Through its widespread projections to both cortical and subcortical regions, the LC serves as a pivotal hub coordinating autonomic responses and central pain modulation [10].

tVNS is thought to influence the LC by enhancing its activity and modulating noradrenaline release, thereby facilitating the reactivation of descending inhibitory pain pathways that are frequently impaired in fibromyalgia [11,12]. Additionally, the LC contributes to restoring autonomic homeostasis by attenuating excessive sympathetic output, a hallmark of fibromyalgia pathophysiology. This neuromodulatory mechanism may help reduce central sensitization, a core feature underlying widespread pain in fibromyalgia [13]. Preclinical and early clinical research suggests that tVNS may exert analgesic, anxiolytic, and anti-inflammatory effects, partially mediated through its action on the LC and other brainstem nuclei [14,15]. These therapeutic effects are believed to arise from a reduction in sympathetic overactivity and an enhancement of vagally mediated parasympathetic tone. Notably, tVNS has demonstrated beneficial effects on heart rate variability (HRV), a reliable index of autonomic nervous system function that is frequently reduced in fibromyalgia patients, reflecting impaired vagal activity [16].

Sleep disturbances, traditionally considered a symptom of fibromyalgia, are increasingly recognized as playing a contributory role in the development of the disorder. Recent studies have revealed a bidirectional relationship between sleep disorders and widespread musculoskeletal pain. Insomnia, in particular, often precedes the onset of chronic pain and appears to be predictive of both the initiation and persistence of pain symptoms [17]. Experimental research in healthy individuals has further demonstrated that sleep deprivation can lead to hyperalgesia, increase the frequency of spontaneous pain, and provoke mood disturbances, particularly anxiety and depression [18]. These findings suggest that disrupted sleep may be a key factor in the emergence of both somatic and affective symptoms.

One valuable metric for assessing sleep continuity is the Cyclic Alternating Pattern (CAP), an electroencephalographic marker of sleep instability, consisting of recurring sequences of transient EEG events during non-REM sleep [19,20]. CAP consists of transient, phasic events recurring at intervals of less than one minute and is distinguishable from the background rhythm [21]. CAP abnormalities are highly prevalent in patients with fibromyalgia and have been linked to non-restorative sleep, increased pain severity, and greater disease burden [22].

This lead to consequent chain reactions: pain heightens sympathetic nervous system activity and disrupts sleep quality, leading to lighter sleep, increased CAP rate, more frequent arousals, a higher periodic limb movement index (PLMI), and more episodes of periodic breathing (PB). These changes contribute to impaired cardiovascular autonomic regulation and heightened sensitivity to pain [23].

tVNS has the potential to influence sleep microarchitecture. Through parasympathetic activation and sympathetic inhibition, tVNS may stabilize NREM sleep and reduce CAP A phases, which are associated with central hyperarousal. Consequently, this modulation may contribute to improved sleep quality and a reduction in fibromyalgia symptoms. This hypothesis is supported by studies highlighting the neurophysiological effects of tVNS on autonomic tone and central sensory processing [24,25]. These findings reinforce the importance of considering sleep dysregulation not merely as a symptom, but as a potential pathophysiological mechanism in fibromyalgia.

Studies by Kutlu et al. [26], Abdel-Baset et al. [27], and Paccione et al. [28] provide notable contributions to understanding tVNS efficacy and application in this matter. Kutlu et al. conducted a randomized controlled trial on 60 female patients with fibromyalgia, assessing the combined effect of auricular tVNS and home-based exercise for 20 sessions. The trial found that while both the treatment (exercise + tVNS) and control (exercise only) groups had significant improvement in pain, depression, anxiety, functionality, and quality of life, the addition of tVNS did not yield statistically significant additional benefits to exercise alone, except for certain subdomains of the SF-36 quality of life measure [26]. On the other hand, Abdel-Baset et al. performed a three-arm randomized controlled trial in 99 individuals comparing the impact of tVNS alone, pain neuroscience education (PNE) alone, and combined tVNS and PNE. They reported improvement in all groups but overall, most significant improvements for pain intensity, fibromyalgia impact, pain catastrophizing, and anxiety levels took place in the combined tVNS and PNE group [27]. Paccione et al. designed a protocol for a randomized controlled trial in a single-blind setting to examine the effects of tVNS and motivational nondirective resonance breathing (MNRB) on (HRV) and pain in fibromyalgia patients. While the trial was primarily attempting to establish the effectiveness of the interventions on autonomic function, it also wanted to establish their effectiveness on pain perception and quality of life [28].

Collectively, these studies are suggestive of the potential of tVNS as an adjunctive treatment for fibromyalgia.

The issue with the limited number of studies currently available lies in the heterogeneity of both the stimulation methods employed and the outcomes assessed. The only outcome that is consistently reported and compared across the three studies previously mentioned is the Visual Analogue Scale (VAS) of pain.

This study aims to investigate the clinical impact of tVNS on key physiological and psychological alterations of fibromyalgia in women, specifically focusing on autonomic function, central sensitization, and pain catastrophizing. The primary objective is to determine whether tVNS can modulate autonomic function. A secondary aim is to explore whether tVNS could determine improvements in central sensitization and pain catastrophizing, both of which are known to contribute significantly to the chronic pain experience in fibromyalgia. We hypothesize that the therapeutic effects of tVNS on autonomic function may extend to broader neural networks involved in pain modulation and emotional regulation. If effective, tVNS may help to disrupt the pathological feedback loops that sustain heightened pain sensitivity and maladaptive cognitive-emotional responses, ultimately reducing symptom severity and improving quality of life.

2. Methods

2.1. Study design and inclusion/exclusion criteria

This is a real-life observational study, as no randomization procedures were implemented and all interventions were conducted in an open-label manner.

Currently, treatment with tVNS—with the treatment protocol described below—is offered in routine clinical practice at our outpatient Clinic to patients diagnosed with fibromyalgia, according to the 2016 American College of Rheumatology criteria [29] for at least six months. Eligible patients are in a moderate stage of disease severity, defined by a revised Fibromyalgia Impact Questionnaire (FIQR) score > 40 [30], and have been receiving 'optimal' pharmacological treatment for at least three months.

The optimal pharmacological regimen consists of the combination of duloxetine and pregabalin at the highest tolerated doses. tVNS is also offered to patients not receiving pharmacological treatment, provided they are intolerant to one or both aforementioned medications. The tVNS is proposed to patients with sufficient competencies to ensure correct management of the device at home.

Patients with implanted pacemakers or other electronic devices, those with a history of ischemic or arrhythmic cardiovascular disease, individuals with severe neurological or psychiatric disorders, and those with poorly controlled chronic inflammatory joint diseases are excluded from treatment. Before starting of the treatment every patient underwent a resting electrocardiogram in order to rule out cardiac or arrhythmogenic subclinical comorbidities.

2.2. Ethical issues

This protocol and the template informed consent forms was reviewed and approved by the local Ethics Committee, named "Comitato Etico Territoriale (CET) della Regione Marche" with respect to scientific content and compliance with applicable research and human subjects' regulations. Each important modification to the protocol (e.g., changes to eligibility criteria, outcomes analyses) or to its relevant parties (e.g., investigators, HRECs, trial participants, trial registries, journals, regulators) would have been submitted to the CET Regione Marche. Each member of the study has obtained informed consent from every potential participant for appropriate consent procedures for persons with at age ≥ 18. Informed consent was required for the participation. Given the fact that the study is observational, no insurance was required for this study. Anonymization of gathered data was guaranteed to each subject and the study procedures were carried out in accordance with the principles of the Declaration of Helsinki.

2.3. Treatment protocol

Patients received 28 days (5 days a week for 4 weeks total) of treatment with tVNS using Nurosym™, consisting of two 30-minutes sessions split into a morning and an afternoon session every day. The device was delivered to all patients at our outpatient Clinic. At the time of delivery, patients received a detailed explanation from the staff regarding the device's operation and the treatment protocol, prior to the initiation of therapy. In this context, patients are invited to test the device, and the staff ensures that each patient is able to operate it correctly.

Nurosym™ produces non-invasive electrical stimulation via electrodes applied to the tragus of the left ear (Fig. 1). The device delivers a biphasic, asymmetrical waveform with a pulse duration of less than 250 microseconds and a frequency of 20 Hz. Stimulation intensity was individually adjusted during each treatment session based on the patient's sensory threshold.

2.4. Clinimetric assessment

Clinical assessments were performed at baseline (T0) and at the end of the 28-day treatment period (T1). The following validated instruments were used.

2.4.1. Composite Autonomic Symptom Score 31 (COMPASS-31)

It is a self-administered questionnaire that evaluates autonomic dysfunction across six specific domains (secretomotor, vasomotor, gastrointestinal, orthostatic, pupillomotor, and bladder function).

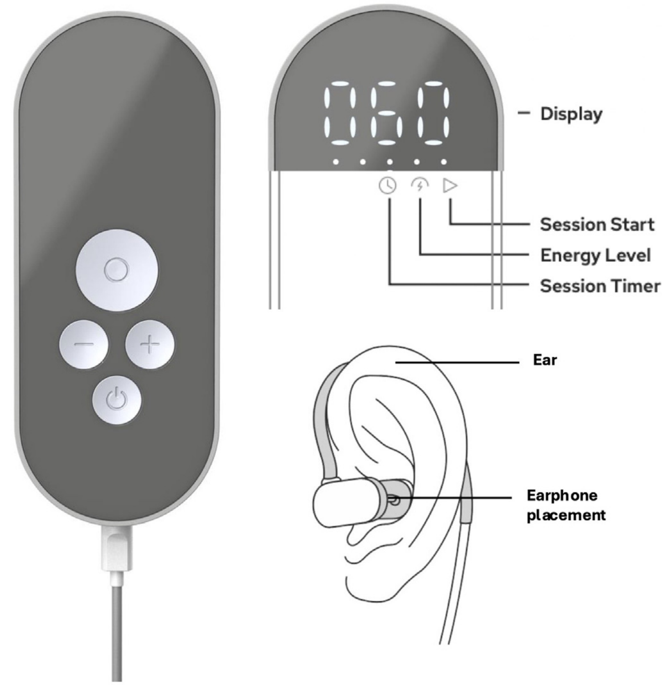

Fig. 1. © 2025. Representative image of the Nurosym® device and its application to the left tragus.

It provides a total score out of 100, with higher scores indicating greater autonomic dysfunction [31].

2.4.2. Revised Fibromyalgia Impact Questionnaire (FIQR)

The FIQR is the updated version of the FIQ [32], It consists of 21 items, 11-point numerical rating scales (0–10) that investigate three main domains in relation to the previous week: FM symptoms (10 items), physical function (9 items), and overall impact (2 items). The final score may range from 0 to 100 (higher scores indicate more severe disease) and is calculated as the algebraic sum of the symptom's domain divided by two, plus the physical function domain divided by three, plus the two items of the overall impact domain [32]. The severity states for FIQR were determined by combining the mean 75th and 25th percentiles of adjacent categories: 0–23 for remission, 24–40 for mild disease, 41–63 for moderate disease, 64–82 for severe disease, and > 83 for very severe disease [30,32].

2.4.3. PainDETECT (PDQ)

The PDQ is a wholly self-administered questionnaire that does not need to be evaluated objectively [33]. The PDQ contains four items in which the patient must describe the temporal pattern of pain (score −1 or +1 depending on the indicated temporal pattern), a manikin in which pain irradiation can be represented (irradiated pain +2 points), and seven 5-point scales in which the patient can report characteristic symptoms of neuropathic pain (sudden pain, allodynia, hyperalgesia, dysesthesia). The final score (which ranges from −1 to 38) should be evaluated in terms of the likelihood of neuropathic pain: below 12, above 19, and between 13 and 18 is considered equivocal [33].

2.4.4. Central Sensitization Inventory – short form (CSI-9)

CSI-9 is a shortened version of the original CSI and is used to assess symptoms associated with central sensitization syndromes [34]. CSI-9 adequately comprises all components of CSS (emotional distress, urological and general symptom, muscle symptom, headache/jaw symptoms and sleep disturbance). Overall, CSI-9

Table 1
Baseline demographic and clinical characteristics.

Variables	Mean ± SD or N (%)	Range
Age (years)	48.6 ± 7.3	32–62
Disease duration (months)	68 ± 24	36–120
BMI (kg/m^2)	24.9 ± 3.1	19.6–30.5

showed adequate psychometric properties for use in evaluating health symptoms related to CSS in patients with musculoskeletal pain disorders [34]. A score ≥ 20 suggests clinically relevant central sensitization [34].

2.4.5. Pain Catastrophizing Scale (PCS)

The PCS is a 13-item self-report questionnaire widely used to assess catastrophizing tendencies in chronic pain research and clinical settings [35]. The PCS directs respondents to consider how they tend to think and feel in the broad context of pain stimuli. A sample item from the PCS: "I become afraid that the pain will get worse". Respondents rate their endorsement of frequency for each item using a 0–4 Likert scale (0 = not at all; 4 = all the time). The total PCS score was computed, as well as the three subscores for pain magnification (items 6, 7, and 13), rumination (items 8 through 11), and helplessness (items 1 through 5 and 12). The total PCS score ranges from 0 to 52, and a score of 30 or greater has been established to indicate catastrophizing [35]. The successfully translated Italian version of the PCS-I, used in this study [28] has good psychometric properties replicating those of other versions [35]. The PCS-I was also satisfactorily sensitive to change: at a 95% confidence level, the Minimal Detectable Change (MDC) indicates that a change of more than 10 points after a given intervention would not be a measurement error.

2.5. Statistical analysis

Data normality was assessed with the Shapiro–Wilk test. Pre- and post-treatment differences were analyzed using paired *t*-tests, or Wilcoxon signed-rank tests in cases of non-normal distributions.

Effect sizes were calculated using Cohen's *d* for paired comparisons to quantify the magnitude of pre- to post-treatment changes. According to conventional benchmarks, Cohen's *d* values of 0.2, 0.5, and 0.8 are interpreted as small, medium, and large effect sizes, respectively.

Statistical analyses on original data were conducted using IBM SPSS Statistics 28.

3. Results

Between February and May 2025, a total of 25 female patients were treated with transcutaneous vagus nerve stimulation (tVNS) at our outpatient clinic. The mean age was 48.6 ± 7.3 years, and the average disease duration was 68 ± 24 months. The baseline FIQR score was 69.1 ± 17.5, indicating a moderate-to-severe level of disease severity. Table 1 summarizes the main demographic characteristics at baseline.

The 28-day tVNS protocol was well-tolerated: all 25 patients completed the treatment. Adverse effects were mild and transient. Three patients reported tinnitus during stimulation, which resolved after the treatment cycle. One patient experienced nausea, dizziness, and distress, which subsided by the end of the treatment. One patient reported a worsening of pain symptoms associated with insomnia.

3.1. Disease severity

The FIQR total score significantly decreased from mean of 69.1 ± 17.5 to 62.2 ± 19.1 ($P < 0.01$), indicating a moderate improvement in overall symptom burden following tVNS. This change is clinically relevant and reflects a potential benefit in terms of fibromyalgia severity (Table 2).

3.2. Autonomic function

As shown in Fig. 2, the COMPASS-31 total score significantly improved, decreasing from 49.4 ± 19.1 to 43.1 ± 16.6 ($P < 0.05$). Among the subdomains:

- orthostatic domain: from 21.6 ± 13.6 to 16.0 ± 11.6 ($P < 0.05$);
- vasomotor domain: from 1.96 ± 1.74 to 1.58 ± 1.55 ($P < 0.05$);
- pupillomotor domain: from 3.54 ± 1.10 to 3.19 ± 1.06 ($P < 0.05$);
- secretomotor domain: from 8.66 ± 2.88 to 8.42 ± 3.01 (NS);
- gastrointestinal domain: from 10.9 ± 4.39 to 10.8 ± 3.85 (NS);
- bladder function domain: from 2.81 ± 2.70 to 3.01 ± 2.27 (NS).

These findings highlight a selective improvement in orthostatic, vasomotor, and pupillomotor symptoms, suggesting a partial rebalancing of autonomic regulation through tVNS.

3.3. Neuropathic pain features and central sensitization

The PDQ score improved significantly, decreasing from a mean of 23.0 ± 5.33 to 21.2 ± 6.05 ($P < 0.01$), suggesting a reduction in neuropathic-like pain symptoms.

The CSI-9 also showed a statistically significant improvement, decreasing from a mean of 30.3 ± 3.35 to 29.1 ± 3.42 ($P < 0.05$), supporting a modest reduction in central sensitization features.

3.4. Pain Catastrophizing

The PCS total score showed a slight decrease from a mean of 32.6 ± 10.3 to 30.4 ± 10.0, but this change did not reach statistical significance ($P = 0.070$). Although there was a numerical trend toward improvement, no conclusions can be drawn regarding the impact of tVNS on the cognitive-emotional components of pain processing.

4. Discussion

This is the first study describing whether tVNS can modulate autonomic function and whether could determine improvements in central sensitization and pain catastrophizing in patients with fibromyalgia.

In our cohort, we observed improvements in three key domains affected in fibromyalgia: symptom severity, autonomic dysfunction, and sensory-cognitive processing. Statistically significant reductions were seen in FIQR, COMPASS-31, PDQ, and CSI-9 scores. In particular, the orthostatic, vasomotor, and pupillomotor subdomains of COMPASS-31 showed the greatest sensitivity to change, suggesting that tVNS may modulate autonomic tone by enhancing parasympathetic activity.

The decrease in CSI-9 scores may reflect reduced central sensitization, potentially via descending pain inhibition mechanisms originating from vagus-activated nuclei. This neurophysiological hypothesis is supported by parallel reductions in neuropathic-like symptoms, as captured by the PainDETECT scale. Moreover, although the decrease in PCS total scores did not reach statistical significance ($P = 0.070$), the trend may hint at a broader psychological benefit of vagal modulation, particularly in domains such as rumination and magnification. Given the known role of pain

Table 2
Clinical outcomes pre- and post- transcutaneous vagus nerve stimulation (tVNS).

Outcome Measure	Pre-tVNS (mean ± SD)	Post-tVNS (mean ± SD)	Pre-tVNS (median)	Post-tVNS (median)	Pre-tVNS 95% CI for the median	Post-tVNS 95% CI for the median	Pre-tVNS IQ range	Post-tVNS IQ range
COMPASS-31 total	49.4 ± 19.1	43.1 ± 16.6	51.2	41.8	40.0 to 60.1	29.3 to 52.4	33.9 to 65.5	28.0 to 53.8
Orthostatic	21.6 ± 13.6	16.0 ± 11.6	28.0	20.0	20.0 to 31.4	12.5 to 20	12.0 to 32.0	0.0 to 24.0
Vasomotor	1.96 ± 1.74	1.58 ± 1.55	2.49	1.67	0.00 to 3.34	0.00 to 3.00	0.00 to 3.34	0.00 to 3.00
Secretomotor	8.66 ± 2.88	8.42 ± 3.01	8.58	8.57	8.57 to 10.3	6.74 to 8.57	6.42 to 10.7	6.42 to 11.0
Gastrointestinal	10.9 ± 4.39	10.8 ± 3.85	10.71	10.71	8.03 to 11.4	9.84 to 12.3	8.03 to 3.61	8.02 to 13.3
Pupillomotor	3.54 ± 1.10	3.19 ± 1.06	3.67	3.00	3.34 to 4.28	3.00 to 4.00	3.00 to 4.34	3.00 to 4.00
Bladder function	2.81 ± 2.70	3.01 ± 2.27	2.23	3	1.11 to 4.45	1.14 to 4.00	0.00 to 4.72	1.00 to 4.00
PDQ	23.0 ± 5.33	21.2 ± 6.05	23.0	22.0	20.0 to 25.8	17.2 to 25.0	19.7 to 27.2	16.7 to 26.2
CSI-9	30.3 ± 3.35	29.1 ± 3.42	31.0	29.0	29.0 to 32.8	27.1 to 31.0	28.7 to 33.0	26.0 to 32.0
PCS total	32.6 ± 10.3	30.4 ± 10.0	35.0	32.0	26.1 to 38.8	24.2 to 36.7	22.7 to 39.5	22.0 to 38.0
FIQR total	69.1 ± 17.5	62.2 ± 19.1	77.0	62.0	58.4 to 79.0	52.2 to 76.4	55.0 to 81.0	50.7 to 77.2

COMPASS-31: The Composite Autonomic Symptom Score 31 item; PDQ: PainDETECT questionnaire; CSI-9: Central Sensitization Inventory – short form; PCS: Pain Catastrophizing Scale; FIQR: Fibromyalgia Impact Questionnaire Revised.
$P < 0.05$ for: COMPASS31 total, Orthostatic, Vasomotor, Pupillomotor, CSI-9. $P < 0.01$ for: PDQ. $P < 0.001$ for: FIQR total. Not significant for: PCS total, Secretomotor, Gastrointestinal, Bladder function.

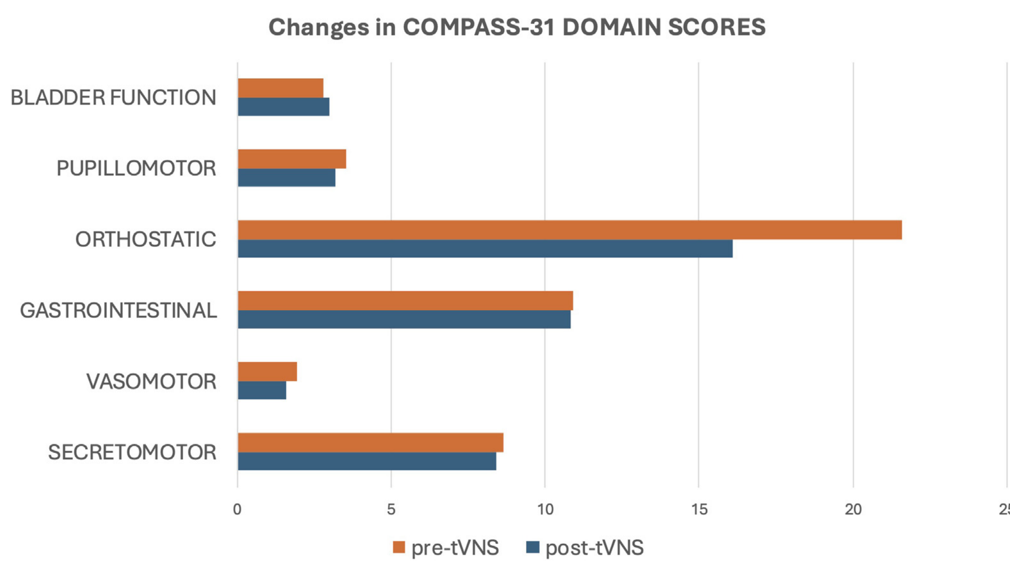

Fig. 2. Bar charts illustrating the improvement in individual domains of the Composite Autonomic Symptom Score 31 (COMPASS-31) following transcutaneous vagus nerve stimulation (tVNS).

catastrophizing in amplifying perceived pain and predicting poor outcomes [36–38], even minor changes could be clinically meaningful over longer periods or with enhanced protocols [39].

Accordingly, the role of the vagus nerve appears to be even more clearly defined, highlighting its central involvement in the regulation of chronic pain, the stress response, and inflammatory pathways—key physiological processes that are notably disrupted in fibromyalgia. As a major component of the parasympathetic nervous system, the vagus nerve exerts wide-ranging influence through both afferent (sensory) and efferent (motor) fibers. Afferent signals transmitted to the brainstem, particularly NTS and LC, serve to modulate the activity of higher-order brain regions including the amygdala, insula, and anterior cingulate cortex, which are all implicated in pain perception, emotional regulation, and autonomic control [8,9].

This integrative role places the vagus nerve at a critical intersection between peripheral physiological states and central nervous system processing. In fibromyalgia, which is characterized by central sensitization, a heightened sensitivity to pain, and an imbalance in autonomic tone (often with parasympathetic underactivity and sympathetic overdrive), the modulation of vagal tone represents a compelling therapeutic target. tVNS has emerged as a promising neuromodulatory intervention. Unlike pharmacological treatments, tVNS targets underlying neurobiological dysfunctions by influencing central pain circuits and neurotransmitter systems. It has been shown to modulate levels of key neuromodulators such as serotonin, gamma-aminobutyric acid (GABA), and norepinephrine often dysregulated in fibromyalgia and other chronic pain syndromes. Additionally, tVNS may suppress nociceptive transmission both at the spinal cord level and within supraspinal structures, thereby reducing pain perception and interrupting the chronic pain cycle [10–12]. Furthermore, growing evidence—including work by Shen et al. and others [13] demonstrates that vagal activation leads to a downregulation of pro-inflammatory cytokines and a shift toward an anti-inflammatory state, largely through the cholinergic anti-inflammatory pathway. This anti-inflammatory action, coupled with pain inhibition and autonomic rebalancing, makes vagal nerve stimulation particularly well-suited to addressing the multidimensional nature of fibromyalgia. Altogether, these findings support the potential of tVNS as a safe, non-invasive, and mechanism-based intervention that targets both peripheral and central components of this complex disorder.

The anatomical accessibility of the auricular branch of the vagus nerve (Arnold's nerve), especially at the left tragus and cymba

Table 3
Randomized controlled trials regarding transcutaneous vagus nerve stimulation (tVNS) in fibromyalgia.

Study	Design	Sample size	Intervention	Outcomes	Main Findings	VAS pain reduction (in the tVNS arm)	Cohed *d*	Effect size
Kutlu et al. (2020) [26,38]	Randomized controlled trial	$n = 60$ (52 completed)	Exercise vs. exercise + auricular tVNS (20 sessions) Electrodes on both ears	VAS pain, FIQ, SF-36, Beck Anxiety & Depression scales	Both groups improved; tVNS group showed better SF-36 subdomains (physical, social, pain), but no significant added benefit overall	2.22	1.15	0.49
Abdel-Baset et al. (2023) [27,39]	Randomized controlled trial with 3 arms	$n = 99$ (33 per group)	tVNS (6 sessions) vs. tVNS + PNE vs. PNE alone	VAS pain, FIQ, PCS, PDQ, STAI	All groups improved; tVNS + PNE showed highest improvement across all measures	3.60	1.85	0.67
Paccione et al. (2020) [28,33]	Single-blind randomized controlled trial (protocol)	Planned $n = 112$	tVNS vs. Sham tVNS vs. MNRB vs. Sham MNRB (2 weeks, twice daily)	HRV (primary), NRS pain, pain thresholds, quality of life	Protocol; aims to evaluate tVNS and MNRB effects on HRV and pain	0.82	0.52	0.25

tVNS: transcutaneous vagus nerve stimulation; VAS: Visual Analogue Scale; FIQR: Fibromyalgia Impact Questionnaire; PCS: Pain Catastrophizing Scale; SF-36: Short Form Health Survey 36; PDQ: PainDETECT questionnaire; STAI: State-Trait Anxiety Inventory; MNRB: motivational nondirective resonance breathing; PNE: pain neuroscience education.

conchae, allows for targeted stimulation without cardiac risk, making it a safe and feasible technique—reflected in the use of left-sided auricular tVNS in our protocol with Nurosym™.

Comparing our findings to the literature on the three studies specifically addressed the use of tVNS in fibromyalgia [26–28], Kutlu et al. [26] found no additive benefit of tVNS over exercise, except for some quality of life domains. In contrast, Abdel-Baset et al. [27] demonstrated that combining tVNS with pain neuroscience education (PNE) produced superior outcomes across multiple measures compared to either intervention alone. While Paccione et al. [28] primarily focused on autonomic outcomes, they also explored pain perception, aligning with our findings of benefit in autonomic function and sensory processing. Notably, the only outcome common across all three studies was the VAS for pain, which improved in all trials, in Table 3 are described the main characteristics of the aforementioned studies.

The heterogeneity in these results may stem from variability in stimulation parameters, duration, patient characteristics, and outcome tools. Our study, though limited by a small sample size ($n = 25$), lack of control group, and relatively short duration, contributes to this growing body of evidence by showing that even a brief tVNS protocol is feasible and well-tolerated, and can yield multidimensional improvements.

This study contributes to the existing literature by integrating a personalized clinimetric approach, utilizing the COMPASS-31 questionnaire, to assess autonomic and dysautonomic function in patients with fibromyalgia. This methodology provides further insight into the involvement of the vagus nerve in the pathophysiology of the disease. Future studies should focus on protocol optimization, responder profiling, and long-term outcomes. Particularly promising is the potential integration of tVNS with behavioral therapies, such as PNE or mindfulness, to harness synergistic effects. Objective markers like HRV or functional neuroimaging could further elucidate mechanisms of action and guide individualized treatment strategies.

Taken together, these findings advocate for the inclusion of tVNS in the integrative management of fibromyalgia, especially in patients with prominent autonomic symptoms and central sensitization features, or those unresponsive to conventional treatments.

In this real-world pilot study, tVNS via Nurosym™ proved to be a safe, feasible, and well-tolerated intervention for patients with fibromyalgia. The 28-day protocol led to statistically significant improvements in disease severity, autonomic function, central sensitization, and neuropathic-like pain features, as measured by validated clinimetric scales. Notably, the most responsive domains were those related to autonomic dysfunction, with significant reductions in the orthostatic, vasomotor, and pupillomotor subdomains of the COMPASS-31.

The observed moderate improvement in FIQR scores suggests a clinically relevant reduction in the overall symptom burden. Given the multidimensional nature of the FIQR, which includes but is not limited to pain, the observed changes likely reflect global benefits rather than isolated modulation of pain intensity. In addition to its autonomic effects, tVNS may exert broader neuromodulatory actions through anti-inflammatory and analgesic mechanisms, potentially mediated by the cholinergic anti-inflammatory pathway (CAP). These findings reinforce the hypothesis that tVNS, by modulating both peripheral and central pathways, can influence several dimensions of the fibromyalgia phenotype, beyond pain alone. Despite these promising outcomes, the study is limited by its small sample size, short duration, and lack of a control group. Therefore, these results should be interpreted cautiously. Larger, controlled studies with longer follow-up periods are warranted to confirm these preliminary observations and to better delineate the therapeutic role of tVNS in the integrative management of fibromyalgia. Ultimately, tVNS may represent a novel adjunctive strategy in the treatment of fibromyalgia, particularly in patients with prominent autonomic and central sensitization features or in those who are refractory to conventional pharmacological approaches.

Nurosym provider information

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Disclosure of interest

The authors declare that they have no competing interest.

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