Vagal nerve stimulation and fibromyalgia: an additional therapeutic option

G. Dolcini[1], M. Favretti[1], D. Franculli[2], G. Buoncuore[3], G. Pellegrino[4,5], M. Di Carlo[6], P. Sarzi-Puttini[4,5], F. Conti[3], C. Iannuccelli[7], M. Di Franco[3]

[1]Department of Molecular Medicine, Sapienza University of Rome; [2]Department of Medicine, Acquapendente Civil Hospital; [3]Department of Internal Clinical, Anaesthesiologic and Cardiovascular Sciences, Sapienza University of Rome; [4]Department of Rheumatology, IRCCS Galeazzi-Sant'Ambrogio Hospital, Milan; [5]Department of Biochemical and Clinical Sciences, University of Milan; [6]Rheumatology Unit, Carlo Urbani Hospital, Università Politecnica delle Marche, Jesi; [7]Rheumatology Unit, AOU Policlinico Umberto I, Sapienza University of Rome, Italy.

Abstract

Objective

Fibromyalgia (FM) is a chronic syndrome characterised by widespread pain, sleep, mood and cognitive disturbances, asthenia and muscle stiffness. The aetiopathogenesis of FM is not fully understood, but autonomic nervous system dysfunction could play a fundamental role in the development of chronic pain and could alter serum levels of neuro-inflammatory mediators like Brain Derived Neurotrophic Factor (BDNF). Transcutaneous vagus nerve stimulation (tVNS) is a non-invasive bioelectronic technique that increases parasympathetic nervous system activity and there is growing evidence that it can modulate nociception and improve mood and sleep quality.
The aim of this pilot study was to evaluate the efficacy of auricular vagal neuromodulation therapy (AVNT™) in reducing disease severity and improving sleep quality of FM patients; secondly, to evaluate fluctuations in serum BDNF levels after treatment.

Methods

Eighteen patients with FM, underwent AVNT™ treatment consisting of 30-minute stimulation, 5 times a week, for 4 consecutive weeks.

Results

After two weeks of treatment, an early reduction in the WPI score (p=0.03) was detected, then confirmed at week 4 (p=0.004). At week 4, significant reduction either in the revised Fibromyalgia Impact Questionnaire (rFIQ) total score (p=0.02), rFIQ general health (p=0.002) and symptoms (p<0.001) components and the Pittsburgh Sleep Quality Index (PSQI) level (p=0.02) was also detected. No significant changes in BDNF levels were found either after two or four weeks of treatment.

Conclusion

In conclusion, our preliminary results show that the treatment with AVNT™ reduced disease severity and improved sleep quality in FM patients.

Key words

fibromyalgia, chronic pain, sleep disorders, vagus nerve stimulation, autonomic dysfunction, brain derived neurotrophic factor

Giulio Dolcini, MD
Martina Favretti, MD
Daniele Franculli, MD
Giorgia Buoncuore, MD
Greta Pellegrino, MD
Marco Di Carlo, MD
Piercarlo Sarzi-Puttini, MD
Fabrizio Conti, MD
Cristina Iannuccelli, MD, PhD
Manuela Di Franco, MD

Please address correspondence to:
Cristina Iannuccelli
U.O. di Reumatologia,
AOU Policlinico Umberto I,
Sapienza Università di Roma,
Viale del Policlinico 155,
00161 Roma, Italy.
E-mail:
c.iannuccelli@policlinicoumberto1.it

Received on April 25, 2025; accepted in revised form on June 2, 2025.

Funding: medical writing was funded through a donation by AbbVie Srl.

Competing interests: none declared.

Introduction

Fibromyalgia (FM) is a common cause of chronic widespread pain, and is characterised by diffuse musculoskeletal pain (1, 2) sleep disturbances, asthenia, headache, muscle stiffness, cognitive dysfunction, depression and anxiety.

FM is fairly common, with a 3.4% prevalence (3, 4), and a female:male ratio of 3:1. FM pathogenesis is still not completely understood and genetic, immunological, inflammatory, endocrinological and psychosocial factors have been linked to the development of FM symptoms (5, 6). The absence of alterations detectable in blood tests and diagnostic imaging places FM in the singular condition of not presenting any reliable diagnostic marker (7). In FM, treatment must be tailored in every single patient, targeting primarily the most distressing symptoms (8). The most effective strategy is based on a multidisciplinary approach that combines both pharmacological and non-pharmacological interventions (9-11). However, even this multimodal approach has a low success rate, and international research is currently evaluating different possible treatments.

The autonomic nervous system (ANS) is a complex network composed of functional and neurochemical distinctive components (sympathetic, parasympathetic, and enteric system), which are bidirectionally linked to differential responses to stressors in order to maintain internal homeostasis (12-14). In case of chronic stress, the response of the ANS becomes dysfunctional (15). Due to hyperactivation/hyporeactivity of the sympathetic system and a dysfunction of the parasympathetic system, the body loses the ability to respond properly to stressful situations, which lead to symptoms like fatigue, stiffness (16, 17), reduced physical capacity (18), and sleep disturbances (19). Therefore, the possible role of the ANS dysfunction in the pathogenesis of chronic pain syndromes raised interest over the years (20, 21).

The vagus nerve (VN), mediator of the parasympathetic system, regulates multiple functions and can be targeted for therapeutic purposes. Vagus nerve stimulation (VNS) regulates ANS activity through the electrical stimulation of the VN, modulating seizure threshold, mood and possibly analgesia (8). Either invasive, minimally invasive, and non-invasive approaches are nowadays available and have been applied in the treatment of different chronic pain pathologies (22-31). Trans-auricular VNS (taVNS) and specifically auricular vagal neuromodulation therapy (AVNT™) preferentially stimulate the afferent auricular branch of the VN through electrodes positioned at the external ear (32).

Studies on rats implanted with VNS devices suggested that this treatment may increase the production of brain derived neurotrophic factor (BDNF) (33-35), a neurotrophin with a role in pain, memory, and mood regulation, which levels are reduced in depression, chronic pain states and FM (36-39).

Because of these evidences, the primary objective in this pilot study was to evaluate the efficacy of AVNT™ on disease severity in a cohort of patients affected by FM. Secondary objectives were to evaluate the influence of AVNT™ on sleep quality, the different effects of 2 or 4 weeks of treatment on disease severity, sleep quality, and BDNF levels, and the persistence of any symptom improvement 4 weeks after treatment discontinuation.

Materials and methods

This was a longitudinal, single-centre pilot study that used AVNT™ in a group of FM patients attending to the out-patient Fibromyalgia clinic of the AOU Policlinico Umberto I, Rome. Starting from March 2023, patients affected by FM, according to the 2016 revised American College of Rheumatology (ACR) diagnostic criteria (40), were consecutively enrolled for the study. Demographic data, comorbidities, and pharmacological and non-pharmacological therapies were recorded for every enrolled patient.

To be eligible, patients had to be between 18 and 65 years of age, on stable pharmacological and non-pharmacological therapy for at least 3 months, and able to read and understand the informed consent. Exclusion criteria included a diagnosis or history of ac-

tive cancer, acute or chronic infections, stage II or higher renal failure, and heart failure NHYA class II to IV. Patients with a history of cardiac arrhythmia or epilepsy, pregnant patients and patients affected by a psychotic disorder and/or under psychiatric treatment were also excluded. Lastly, a diagnosis of an immune-mediated rheumatic disease was considered another exclusion criterion.

Study participants underwent AVNT™ treatment using the Parasym® Device kit, with application of the auricular electrode placed at the tragus of the external ear. The Parasym® device has been developed and patented for safely and effectively delivering AVNT™, previously referred to as Low level tragus stimulation. It was decided to use AVNT™ delivered through the Parasym™ device because of the safety and the highly scientifically backed up technology having been used in more than 40 clinical trials. Unlike invasive devices, non-invasive devices have only mild adverse events, that may include regional discomfort, skin irritation, transient muscle stiffness, and pain (41, 42). AVNT™ delivered through the Parasym™ in particular has shown to be a safe and tolerable approach also in vulnerable populations (43).

The Parasym® device kit contains a stimulation unit and a lead with a small ear clip electrode (Fig. 1). The clip-on electrode is placed on the tragus of the left outer ear, where targeted micro pulses of electrical current stimulate the auricular branch of the VN. All patients were stimulated for 30 minutes/day, in the same daily time slot (from 02:00 to 06:00 pm), five times a week (from Monday to Friday), for four consecutive weeks (from May 15, 2023, to June 12, 2023).

The Parasym® device was set up at frequency within 1–30 Hz and pulse width within 50–250 μs, while the current intensity could be adjusted from 0.1 to 36 mA during each session based on the pain threshold. Therefore, before initiating the stimulation, patients were given an explanation regarding how to adjust stimulation intensity: slowly increasing the intensity by one level per second and stopping as soon as a slight tingling sensation was felt on the stimulation zone.

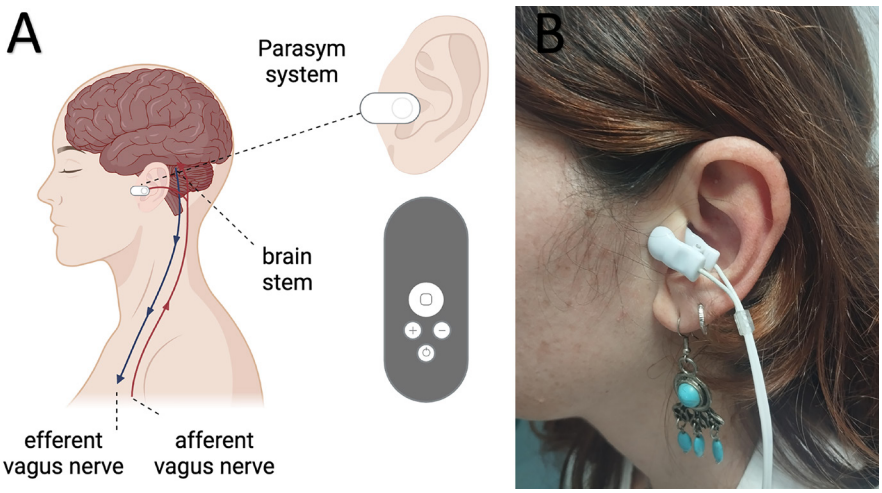

Fig. 1. Parasym® device kit (**A**) and electrode placing of the Parasym® device (**B**).

Disease severity was assessed using different clinimetric indices validated for FM: pain scored on 0-10 mm visual analogue scale (VAS pain), revised Fibromyalgia Impact Questionnaire (rFIQ), Widespread Pain Index (WPI), and Symptoms Severity Scale (SSS). Sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI). For each patient, both disease severity and sleep quality were assessed before starting the treatment (T0), at two weeks after the treatment started (T2), and at the end of the last treatment session (T4).

At the end of each session the stimulation intensity achieved was recorded and patients were asked to report any adverse event occurred during the previous day. Any adverse event observed in clinical practice was reported in accordance with local pharmacovigilance regulations. At the end of the last treatment session, patients were asked to respond to a satisfaction questionnaire regarding their experience with the treatment. Finally, a follow-up visit was performed four weeks after the end of the treatment and disease severity and sleep quality indices were re-evaluated.

In order to evaluate serum BDNF levels, a 15 mL venous blood sample was collected at T0, T2, and T4. Serum was immediately separated from blood sample through and stored at -20°C. After sample were defrosted, BDNF serum levels were measured using a commercial Double Antibody Sandwich ELISA kit (RAB0026, Sigma-Aldrich, Merck KGaΛ, Darmstadt, Germany), following the manufacturer's instruction. The sensitivity of BDNF detection was 80 pg/mL.

Table I. Baseline characteristics of the patients included in the study.

	Baseline characteristics n=18
Age, mean (SD)	
Years	42.1 (11.6)
Sex, n (%)	
Female	13 (70)
Male	5 (30)
Disease duration, median (IQR)	
Months	91 (169)
Smoke, n (%)	5 (27.7)
Body mass index, mean (SD)	25.5 (5.5)
Educational level, n (%)	
Degree	6 (33.3)
Graduation	12 (66.6)
Pharmacological therapy, n (%)	
Muscle relaxants	5 (27.7)
NSAID	9 (50)
Antidepressants	5 (27.7)
Non-pharmacological therapy, n (%)	
Physical exercise	7 (38.8)

NSAID: non-steroidal anti-inflammatory drug.

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Sapienza University of Rome (protocol code 0298/2023 date of approval: 30/03/2023). Informed consent was obtained from all subjects involved in the study.

Statistical analysis

Categorical variables are reported as absolute and relative frequency (%).

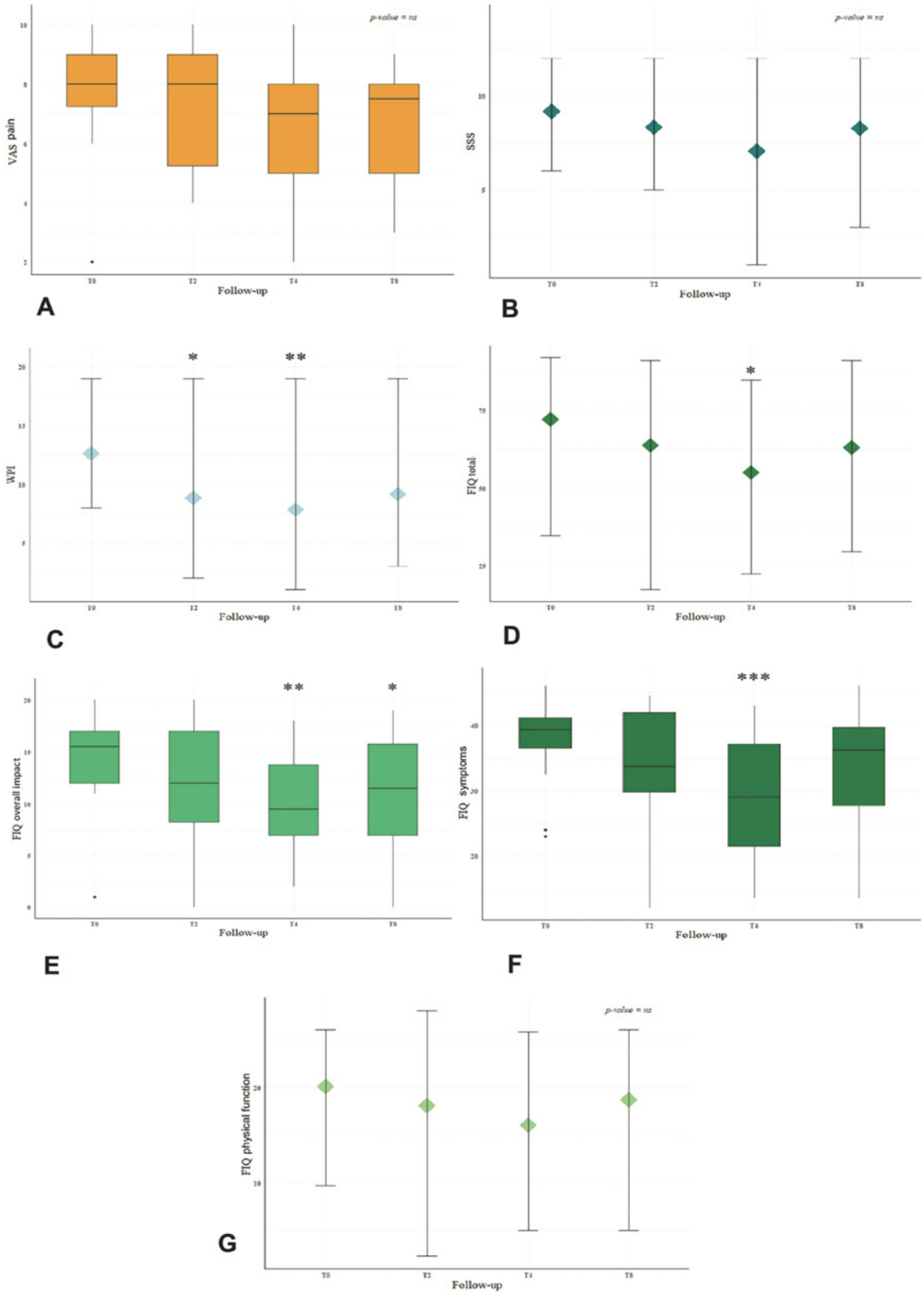

Fig. 2. Effect of taVNS on disease severity. Evolution of (**A**) VAS pain, (**B**) SSS C, (**C**) WPI score, (**D**) rFIQ total score, (**E**) rFIQ overall impact component, (**F**) rFIQ symptoms component, and (**G**) rFIG physical function component.
rFIQ: revised Fibromyalgia Impact Questionnaire; SSS: Symptoms Severity Scale; VAS visual analogue scale; WPI: Widespread Pain Index.

Table II. Comparisons of disease severity scores and sleep quality level between baseline and follow-up evaluations.

Variables	Baseline	Follow-up 2 weeks	Follow-up 4 weeks	Follow-up 8 weeks	F / χ^2	*p*-value
VAS pain						
Median (IQR)	8.00 (2.25)	8.00 (4.00)	7.00 (3.25)	7.00 (3.00)	$\chi^2 = 7.62$	0.05*
rFIQ total						
Mean (SD)	72.1 (12.8)	63.7 (19.4)	55.1 (18.1)	61.75 (17.7)	F = 8.89	**<0.001**†
rFIQ physical function						
Mean (SD)	20.0 (3.91)	18.0 (6.05)	16.0 (5.35)	18.28 (5.55)	F = 6.07	**0.001**†
rFIQ overall impact						
Median (IQR)	15.5 (5.25)	12.0 (9.25)	9.50 (7.50)	10.0 (8.00)	$\chi^2 = 14.6$	**0.002***
rFIQ symptoms						
Median (IQR)	39.2 (5.88)	33.7 (14.3)	29.0 (16.7)	34.5 (11.5)	$\chi^2 = 20.7$	**<0.001***
WPI						
Mean (SD)	12.6 (3.74)	8.83 (4.71)	7.83 (4.16)	8.58 (3.04)	F = 10.2	**<0.001**†
SSS						
Mean (SD)	9.16 (1.97)	8.33 (2.30)	7.05 (3.22)	8.11 (2.61)	F = 5.78	**0.001**†
PSQI						
Mean (SD)	13.1 (3.11)	12.0 (4.24)	9.22 (3.78)	11.47 (5.12)	F = 9.03	**<0.001**†
BDNF ng/mL						
Median (IQR)	76.57 (68.46)	81.88 (93.1)	83.43 (61.0)	--	$\chi^2 = 1.09$	ns*

BDNF: brain derived neurotrophic factor; rFIQ: revised Fibromyalgia Impact Questionnaire: PSQI: Pittsburgh Sleep Quality Index; SSS: Symptoms Severity Scale; VAS: visual analogue scale; WPI: Widespread Pain Index.
*Friedman test; †ANOVA.

Normally distributed variables are reported as mean and standard deviation (SD), while non-normally distributed variables are reported as median and interquartile range (IQR). The conformity of the continuous variable to the Normal distribution was examined using the Shapiro-Wilk test.

For normally distributed variables, the effect of AVNT™ on disease severity scores and sleep quality level was estimated using the repeated-measures analysis of variance (ANOVA) method, performing different models for each dependent variable considered (rFIQ total, rFIQ physical function component, WPI, SSS, PSQI). Multiple comparisons were subsequently made using the Tukey-Kramer test. For non-normally distributed data, the effect of AVNT™ on disease severity scores and serum BDNF levels was estimated using the Friedman test. Different tests were performed for the assessment of each dependent variable considered (VAS pain, rFIQ general impact, rFIQ symptoms, serum BDNF levels). Multiple comparisons were subsequently made using the Nemenyi test.

For missing data adjustment, the LOCF (last observation carried forward) method was applied.

All statistical analyses were performed using R software (R studio v. 4.3.1).

Results

Between March and May 2023, eighteen patients were included in this pilot study. Seventeen patients completed all the four weeks' treatment protocol. Only one patient dropped out at the end of the third week for reasons unrelated to the trial. Baseline clinical and demographic characteristics of the study participants are shown in Table I.

Outcomes

Compared to the baseline, no significant differences were found after two and four weeks of treatment in the average value of the VAS pain and SSS score (Fig. 2A, B).

After two weeks of treatment, the WPI scores went from an average value of 12.6±3.74 to an average value of 8.83±4.71 (Table II), showing an early significant reduction (p=0.03) (Table III, Fig. 2C). After four weeks of treatment, the average value of the WPI score was 7.83±4.16 and a significant difference compared to the average baseline value was also observed (p=0.004).

No significant changes were found neither in the rFIQ scores nor in the PSQI level after two weeks of treatment. After four weeks of treatment, a significant reduction of the rFIQ scores (total, overall impact and symptoms components) (Fig. 2D-2E-2F), and of the PSQI level were seen as compared to the baseline (Fig. 3); however, no significant differences were found for the rFIQ physical function component after four weeks of treatment (Fig. 2G).

The average rFIQ total score went from 72.1±12.8 to 55.1±18.1 (p=0.02). The median rFIQ overall impact component went from 15.5 (IQR=5.25) to 9.5 (IQR=7.50) (Z -0.879; p=0.002), while the median rFIQ symptoms component passed from 39.2 (IQR=5.88) to 29.0 (IQR=16.70) (Z -1.145; p<0.001). Lastly, the average PSQI level decreased from 13.1±3.11 to 9.22±3.78 (p=0.02).

At the follow-up visit performed four weeks post-treatment, both disease severity and sleep quality had deteriorated, indicating a substantial return to baseline levels. However, the rFIQ overall impact component, which had a median value of 10.0 (IQR=8.00) four weeks after the end of treatment, remained significantly improved when compared to the median baseline value (Z -0.207; p=0.04).

Compared to the baseline, no significant differences were found after two and four weeks of treatment in the median BDNF serum levels (Fig. 4).

Adverse events

Adverse events observed in clinical practice were reported in accordance

Table III. Pairwise comparisons of VAS pain, rFIQ (total and physical function, overall impact and symptoms components), WPI, SSS, and PSQI at each period.

	Mean rank	Z score	*p*-value§
VAS pain			
2 weeks - baseline	2.64 - 3.03	1.145	ns
4 weeks - baseline	2.14 - 3.03	-0.697	ns
8 weeks - baseline	2.19 - 3.03	-0.448	ns
rFIQ overall impact			
2 weeks - baseline	2.58 - 3.33	1.087	ns
4 weeks - baseline	1.89 - 3.33	-0.879	**0.002**
8 weeks - baseline	2.19 - 3.33	-0.207	**0.04**
rFIQ symptoms			
2 weeks- baseline	2.53 - 3.44	0.701	ns
4 weeks - baseline	1.53 - 3.44	-1.145	**<0.001**
8 weeks - baseline	2.50 - 3.44	0.443	ns
	Mean difference (IC 95%)		***p-value*§§**
rFIQ total			
2 weeks - baseline	-8.39 (-23.6, 6.82)		ns
4 weeks - baseline	-17.1 (-32.3, -1.8)		**0.02**
8 weeks - baseline	-9.08 (-24.2, 6.13)		ns
FIQ physical function			
2 weeks - baseline	-1.99 (-6.66, 2.67)		ns
4 weeks - baseline	-4.05 (-8.72, 0.61)		ns
8 weeks - baseline	-1.37 (-6.04, 3.29)		ns
WPI			
2 weeks - baseline	-3.77 (-7.40, -0.1)		**0.03**
4 weeks - baseline	-4.77 (-8.40, -1.1)		**0.004**
8 weeks - baseline	-3.44 (-7.07, 0.18)		ns
SSS			
2 weeks - baseline	-0.83 (-3.09, 1.42)		ns
4 weeks - baseline	-2.11 (-4.37, 0.14)		ns
8 weeks - baseline	-0.88 (-3.14, 1.37)		ns
PSQI			
2 weeks - baseline	-1.11 (-4.73, 2.51)		ns
4 weeks - baseline	-3.94 (-7.56, -0.3)		**0.02**
8 weeks - baseline	-1.50 (-5.12, 2.12)		ns

rFIQ: revised Fibromyalgia Impact Questionnaire; PSQI: Pittsburgh Sleep Quality Index; SSS: Symptoms Severity Scale; VAS: visual analogue scale; WPI: Widespread Pain Index.
§ For pairwise comparisons the Nemenyi test was applied.
§§For pairwise comparisons the Tukey-Kramer test was applied.

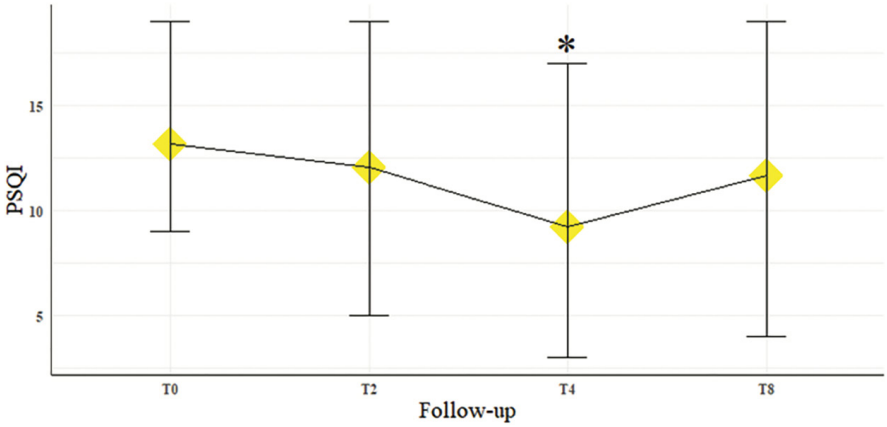

Fig. 3. Effect of taVNS on sleep quality. Evolution of PSQI level.
PSQI: Pittsburgh Sleep Quality Index.

with local pharmacovigilance regulations according to the following definition: "Any harmful clinical event that occurs in a patient or subject involved in a clinical trial who has been administered a medicinal product, and which does not necessarily have a causal relationship with this treatment" (44). Adverse events that persisted at least 24h during the treatment are listed in Table IV. During the entire duration of the treatment no serious or unexpected adverse reactions occurred. All symptoms not present before the start of the treatment have been considered as adverse effects (despite the fact that some of these reported side effects are potentially not related to the treatment, and instead being related to the diversified nature of FM symptoms).

Satisfaction questionnaire

According to the satisfaction questionnaire filled out by each patient at the end of the treatment, 16 out of 18 patients experienced the occurrence of at least one side effect but only one patient considered that the side effects outweighed the benefits of the treatment. Most of the patients reported a high satisfaction rate, despite the appearance of some mild side effects. In particular, 13 out of 18 patients noted an improvement in their quality of life, while 14 out of 18 patients experienced an improvement of their sleep quality. By contrast, only 7 out of 18 patients reported lowering perceived pain (Fig. 5). Moreover, 17 out of 18 patients would be willing to repeat the treatment and 16 out of 18 patients would recommend it to other patients affected by FM. On a 0-10 mm scale, AVNT therapy was rated 7.8.

Discussion

FM treatment requires a multidisciplinary collaboration among different healthcare specialists, such as rheumatologists, neurologists, psychiatrists, pain specialists, psychologists, gynaecologists, and others. Non-pharmacological interventions are considered the first line treatment, and those with the most effective evidence include: patient education, physical exercise and cognitive behavioural therapy. In patients with severe and difficult to treat symptoms, pharmacological strategies should be added, starting with centrally acting drugs such as antidepressants and anticonvulsants (11). However, treatment of FM remains extremely challenging, and it is characterised by poor success rate. Data reveals that

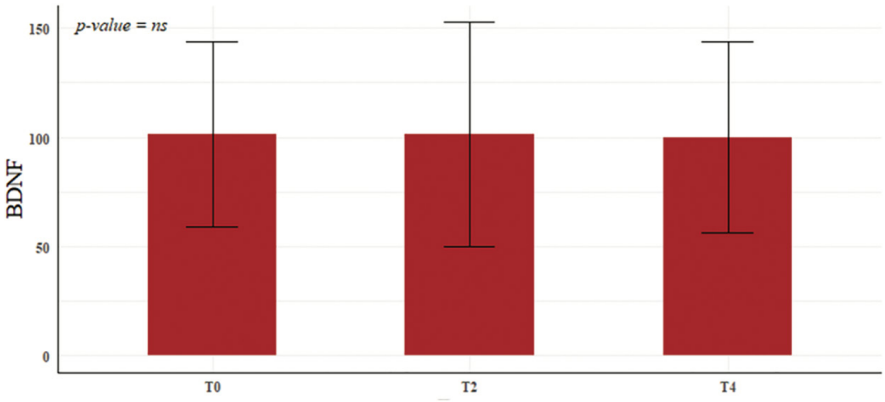

Fig. 4. Effect of taVNS on serum BDNF level. BDNF: brain derived neurotrophic factor.

Table IV. Adverse events occurred during the study (lasting at least 24h hour).

Adverse events	n (%)
Cervical pain	**1 (5%)**
Neurological	**12 (6%)**
Headache	7 (38%)
Blurred vision	4 (22%)
Paraesthesia	1 (5%)
Psychiatric	**2 (11%)**
Panic attack	1 (5%)
Concentration deficit	1 (5%)
Others	**16 (8%)**
Asthenia	9 (50%)
Confusion	6 (33%)
Drowsiness	1 (5%)
Adverse events	**n (%)**
Local	**7 (38%)**
Paraesthesia	4 (22%)
Erythema	3 (16%)
Gastrointestinal	**7 (38%)**
Nausea	*6 (33%)*
Heartburn	*1 (5%)*
ORL	**8 (44%)**
Dizziness	7 (38%)
Tinnitus	1 (5%)
Cardiological	**2 (11%)**
Palpitations	1 (5%)
Hypotension	1 (5%)

treatment adherence in FM patients is suboptimal. On one hand, pain and fatigue commonly interfere with patient's compliance to constant physical activity sessions (45). On the other side, only a minority of patients continue taking medications due to perceived lack of efficacy or development of side effects (46). AVNT™ could be an interesting additional treatment option, since it may be able to overcome critical issues in patient treatment thanks to its ease of use, the possible efficacy on many symptoms, the low long-term costs and the good tolerability.

The present pilot study showed a substantial improvement of disease severity in FM patients that underwent AVNT™ and, at the end of treatment, 11 out of the 17 patients (64%) no longer met the 2016 ACR/EULAR diagnostic criteria for FM. Data obtained from this investigation have the advantage of having evaluated disease severity and sleep quality indices at different time points, allowing to confirm the hypothesis that AVNT™ efficacy may be linked to the length of stimulation period. However, these benefits disappeared four weeks after the end of stimulation, suggesting that the effects of AVNT™ on autonomic dysfunction may be temporary and reversible.

As long as we know, this study is the first one demonstrating that AVNT™ therapy may be an effective strategy for the treatment of sleep disorders in FM patients. Sleep disturbance is a recurrent and disabling symptom in FM and it increases FM severity and reduces the overall quality of life (47). Nowadays, sleep disorders are treated using drugs such as pregabalin or amitriptyline combined with non-pharmacological therapies, but the results are frequently unsatisfying (48). In this context, the use of AVNT™ therapy could offer a promising approach for sleep quality improvement. Unlike previous studies, we did not find any significant differences in the perceived pain. However, it must be noted that pain intensity measured by VAS pain, although extremely used in clinical studies, is an unreliable outcome measure in case of chronic pain (49). Patients affected by chronic pain are less likely to report significant changes in perceived pain, even when their global impression of change in response to a particular treatment is positive.

Although there is large literature regarding the promising efficacy of vagal neuromodulation for the treatment of different pathologies associated with ANS dysfunction (50-53), to date only three other studies evaluated the use of auricular VNS in FM. Kutlu *et al*. (54) compared two groups of FM patients, one assigned to taVNS in combination with physical exercise and the other one treated with physical exercise only. As in the present study, the taVNS treatment was performed five weekdays for four weeks, with each session taking 30 minutes, while the stimulation parameters were set differently (10 Hz frequency and pulse width of less than 500 μs). After four weeks of intervention, both groups showed a notable improvement in disease severity, measured by FIQ and VAS pain, quality of life, evaluated using the Short-Form (SF)-36 life quality scale, and depression and anxiety levels, measured by the Beck Depression Scale and the Beck Anxiety Scale respectively. Comparing the two groups before and after the treatment, it was shown that the combined treatment group had better results; however, significant statistical differences between groups were only demonstrated in some domains of the SF-36 questionnaire.

Asma *et al*. (55) compared the effect of tVNS and pain neuroscience education (PNE) on 99 patients with FM. Patients were divided into 3 groups (33 patients each): group A received 6 sessions of tVNS twice weekly (25 Hz for 30 min), group B received 6 sessions of tVNS twice weekly (25 Hz for 30 min) and 3 sessions of PNE once weekly (for 30 min) and group C received 3 sessions of PNE once weekly (for 30 min). After 3 weeks of intervention, the 3 groups showed significant improvement of FM symptoms assessed by VAS, FIQ, Pain catastrophising scale questionnaire (PCS-Q, Pain DETECT questionnaire (PD-Q) and State Trait Anxiety Inventory (STAI Q)), but group B

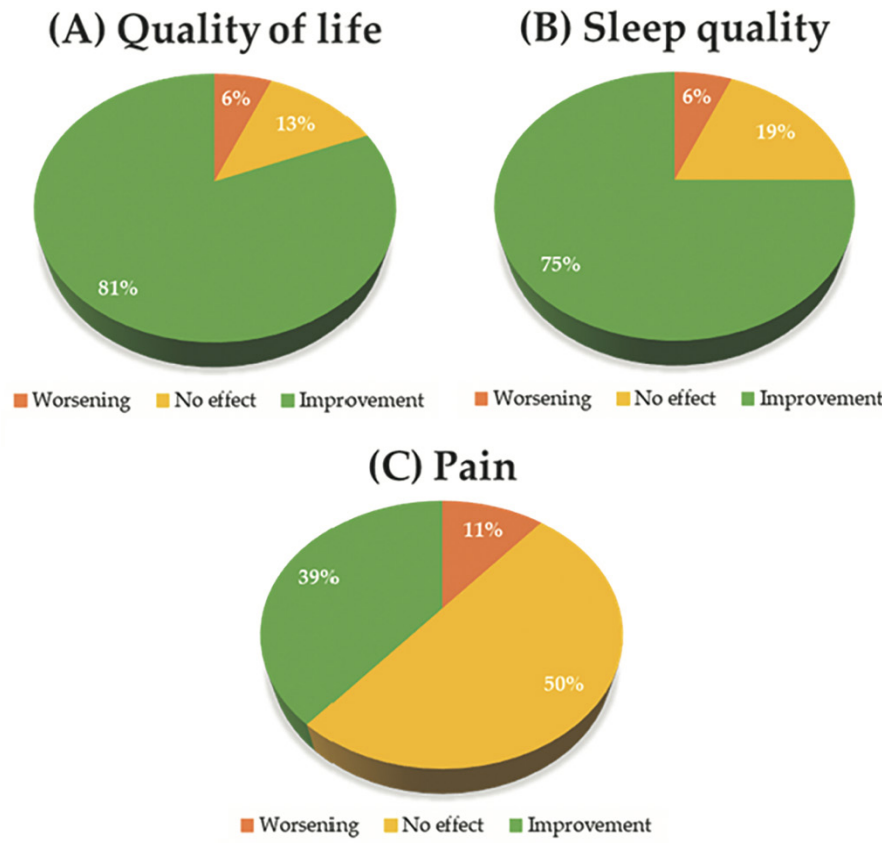

Fig. 5. Results of the satisfaction questionnaire. Perceived efficacy of taVNS on (**A**) quality of life, (**B**) sleep quality and (**C**) pain.

showed the best results percentage of improvement.

Paccione *et al*. (56) evaluated and compared the efficacy of two weeks of active and sham tVNS in a group of 57 FM patients. After 2 weeks of treatment, significant differences were found for overall FM severity and current pain intensity in the active tVNS group; however, similar results were also obtained in the group undergoing sham tVNS. The results of this study also did not show any significant changes in heart rate variability (HRV), a method commonly used to measure autonomic function, before and after tVNS treatment. It must be highlighted that this study used a different treatment protocol compared to the one used in the present study, as tVNS was administered 15 minutes twice a day for a total duration of two weeks.

The enrolled patients experienced side effects rates similar to the one reported in other studies (56). The most frequent side effects comprehended asthenia, nausea, dizziness, and headache. It is important to note that most of the side effects reported did not persist for more than 48 hours at a time under any circumstances. Side effects such as redness, erythema and tingling at the administration site disappeared when the stimulation intensity was reduced and the site was changed (from left to right ear and vice versa). Adverse events such as dizziness, confusion, and blurred vision were reported more frequently in the first days of stimulation, while they tended to disappear with intensity reduction.

Moreover, the present work evaluated BDNF serum levels variation, but did not detect any significant changes after treatment administration when compared to baseline levels, which is in line with the results obtained by Lang *et al*. (57) on a population of depressive patients treated with VNS. It should be noted that the studies reporting a significant increase in BDNF levels following stimulation were conducted in animal models using chronic stimulation delivered through implanted devices. Therefore, it can be hypothesised that longer protocols of stimulation over time would be able to induce serum BDNF level changes similar to the one observed in rats. Moreover, 5 out of 18 patients of our cohort (27.7%) were treated with antidepressants and current data suggest that these drugs may elicit their effects by increasing BDNF levels (58). Therefore, the effect of AVNT™ treatment on serum BDNF levels in our modest cohort may have been masked by antidepressant medications.

Being an exploratory pilot study, the result of this work are still preliminary and presents some limitations related to the low number of patients enrolled, the absence of a control group treated with a sham AVNT™ approach (which does not allow to completely rule out a possible placebo effect), and the absence of a direct measurement of ANS dysfunction, such as HRV measure. Moreover, since VNS is a relatively new technology, it must also be considered that several research gaps remain regarding this treatment, as addressed in recent reviews (59-61), like the need to determine optimal dosage for different pain conditions, incorporate measures for intervention fidelity, investigate long-term outcomes, and explore co-occurring symptoms and outcomes across different sociodemographic variables; however, the cymba concha and the internal tragus seem the best areas for vagal neuromodulation.

Conclusions

This pilot study showed that AVNT™ treatment is able to reduce disease severity and improve sleep quality in a cohort of 17 FM patients, despite less consistent variation in their perceived pain. Most of the improvements were demonstrated after four weeks of treatment, even if an early reduction in the WPI score was observed after two weeks. After the treatment, 11 out of the 17 patients (64%) no longer met the 2016 ACR/EULAR diagnostic criteria for FM. However, it was also demonstrated a short persistence of these benefits, with further worsening of disease severity and sleep quality four weeks after the end of treatment. The treatment was well tolerated by patients, despite the occurrence of mild adverse effects.

Despite the current lack of consensus regarding the optimal stimulation parameters and duration of AVNT™ therapy, its favourable usability profile, potential efficacy across a broad range of fibromyalgia-related symptoms, and relatively low long-term costs position AVNT™ as a promising adjunct within multimodal treatment paradigms for FM. Its integration may contribute to improved patient-reported outcomes and overall quality of life. The preliminary findings of this pilot investigation warrant confirmation through rigorously designed studies with larger cohorts and appropriate control conditions.

References

1. ATZENI F, CAZZOLA M, BENUCCI M, DI FRANCO M, SALAFFI F, SARZI-PUTTINI P: Chronic widespread pain in the spectrum of rheumatological diseases. *Best Pract Res Clin Rheumatol* 2011; 25: 165-71. https://doi.org/10.1016/j.berh.2010.01.011
2. DI CARLO M, BIANCHI B, SALAFFI F *et al*.: Fibromyalgia: one year in review 2024. *Clin Exp Rheumatol* 2024; 42: 1141-49. https://doi.org/10.55563/clinexprheumatol/mbyi1n
3. HÄUSER W, BRÄHLER E, ABLIN J, WOLFE F: Modified 2016 American College of Rheumatology Fibromyalgia Criteria, the Analgesic, Anesthetic, and Addiction Clinical Trial Translations Innovations Opportunities and Networks-American Pain Society Pain Taxonomy, and the Prevalence of Fibromyalgia. *Arthritis Care Res* 2021; 73: 617-25. https://doi.org/10.1002/acr.24202
4. QUEIROZ LP: Worldwide epidemiology of fibromyalgia. *Curr Pain Headache Rep* 2013; 17: 356. https://doi.org/10.1007/s11916-013-0356-5
5. AL SHARIE S, VARGA SJ, AL-HUSINAT L *et al*.: Unraveling the complex web of fibromyalgia: a narrative review. *Med Kaunas Lith* 2024; 60: 272. https://doi.org/10.3390/medicina60020272
6. GHAVIDEL-PARSA B, BIDARI A: The cross-talk of the pathophysiologic models in fibromyalgia. *Clin Rheumatol* 2023; 42: 3177-87. https://doi.org/10.1007/s10067-023-06778-3
7. FAVRETTI M, IANNUCCELLI C, DI FRANCO M: Pain biomarkers in fibromyalgia syndrome: current understanding and future directions. *Int J Mol Sci* 2023; 24: 10443. https://doi.org/10.3390/ijms241310443
8. HÄUSER W, PERROT S, CLAUW DJ, FITZCHARLES M-A: Unravelling fibromyalgia-steps toward individualized management. *J Pain* 2018; 19: 125-34. https://doi.org/10.1016/j.jpain.2017.08.009
9. GIUSTI EM, CASTELNUOVO G, MOLINARI E: Differences in multidisciplinary and interdisciplinary treatment programs for fibromyalgia: a mapping review. *Pain Res Manag* 2017; 2017: 7261468. https://doi.org/10.1155/2017/7261468
10. HÄUSER W, BERNARDY K, ARNOLD B, OFFENBÄCHER M, SCHILTENWOLF M: Efficacy of multicomponent treatment in fibromyalgia syndrome: a meta-analysis of randomized controlled clinical trials. *Arthritis Rheum* 2009; 61: 216-24. https://doi.org/10.1002/art.24276
11. MACFARLANE GJ, KRONISCH C, DEAN LE *et al*.: EULAR revised recommendations for the management of fibromyalgia. *Ann Rheum Dis* 2017; 76: 318-28. https://doi.org/10.1136/annrheumdis-2016-209724
12. GIBBONS CH: Basics of autonomic nervous system function. *Handb Clin Neurol* 2019; 160: 407-18. https://doi.org/10.1016/b978-0-444-64032-1.00027-8
13. GOLDSTEIN DS: Linking the extended autonomic system with the homeostat theory: new perspectives about dysautonomias. *J Pers Med* 2024; 14: 123. https://doi.org/10.3390/jpm14010123
14. MILLER DB, O'CALLAGHAN JP: Neuroendocrine aspects of the response to stress. *Metabolism* 2002; 51: 5-10. https://doi.org/10.1053/meta.2002.33184
15. CHROUSOS GP, GOLD PW: The concepts of stress and stress system disorders. Overview of physical and behavioral homeostasis. *JAMA* 1992; 267: 1244-52
16. FURLAN R, COLOMBO S, PEREGO F *et al*.: Abnormalities of cardiovascular neural control and reduced orthostatic tolerance in patients with primary fibromyalgia. *J Rheumatol* 2005; 32: 1787-93.
17. MARTÍNEZ-LAVÍN M, HERMOSILLO AG, MENDOZA C *et al*.: Orthostatic sympathetic derangement in subjects with fibromyalgia. *J Rheumatol* 1997; 24: 714-18.
18. SISTO SA, TAPP W, DRASTAL S *et al*.: Vagal tone is reduced during paced breathing in patients with the chronic fatigue syndrome. *Clin Auton Res* 1995; 5: 139-43. https://doi.org/10.1007/bf01826195
19. MENDEZ M, BIANCHI AM, VILLANTIERI O, CERUTTI S: Time-varying analysis of the heart rate variability during REM and non REM sleep stages. *Conf Proc IEEE Eng Med Biol Soc* 2006; 2006: 3576-79. https://doi.org/10.1109/iembs.2006.260067
20. COHEN H, NEUMANN L, KOTLER M, BUSKILA D: Autonomic nervous system derangement in fibromyalgia syndrome and related disorders. *Isr Med Assoc J* 2001; 3: 755-60.
21. MARTÍNEZ-LAVÍN M, HERMOSILLO AG: Autonomic nervous system dysfunction may explain the multisystem features of fibromyalgia. *Semin Arthritis Rheum* 2000; 29: 197-99. https://doi.org/10.1016/s0049-0172(00)80008-6
22. ARANOW C, ATISH-FREGOSO Y, LESSER M *et al*.: Transcutaneous auricular vagus nerve stimulation reduces pain and fatigue in patients with systemic lupus erythematosus: a randomised, double-blind, sham-controlled pilot trial. *Ann Rheum Dis* 2021; 80: 203-8. https://doi.org/10.1136/annrheumdis-2020-217872
23. FARMER AD, ALBUSODA A, AMARASINGHE G *et al*.: Transcutaneous vagus nerve stimulation prevents the development of, and reverses, established oesophageal pain hypersensitivity. *Aliment Pharmacol Ther* 2020; 52: 988-96. https://doi.org/10.1111/apt.15869
24. KOOPMAN FA, CHAVAN SS, MILJKO S *et al*.: Vagus nerve stimulation inhibits cytokine production and attenuates disease severity in rheumatoid arthritis. *Proc Natl Acad Sci USA* 2016; 113: 8284-89. https://doi.org/10.1073/pnas.1605635113
25. KRUSCHE-MANDL I, KAIDER A, STARLINGER J *et al*.: Implementation of electrical auricular acupuncture and low frequency modulated electric current therapy in pain management of patients with knee osteoarthritis: a randomized pilot trial. *J Clin Med* 2019; 8: 1229. https://doi.org/10.3390/jcm8081229
26. LANGE G, JANAL MN, MANIKER A *et al*.: Safety and efficacy of vagus nerve stimulation in fibromyalgia: a phase I/II proof of concept trial. *Pain Med Malden Mass* 2011; 12: 1406-13. https://doi.org/10.1111/j.1526-4637.2011.01203.x
27. MEINTS SM, GARCIA RG, SCHUMAN-OLIVIER Z *et al*.: The effects of combined respiratory-gated auricular vagal afferent nerve stimulation and mindfulness meditation for chronic low back pain: a pilot study. *Pain Med Malden Mass* 2022; 23: 1570-81. https://doi.org/10.1093/pm/pnac025
28. MULTON S, SCHOENEN J: Pain control by vagus nerve stimulation: from animal to man... and back. *Acta Neurol Belg* 2005; 105: 62-7.
29. RANDICH A, GEBHART GF: Vagal afferent modulation of nociception. *Brain Res Brain Res Rev* 1992; 17: 77-99. https://doi.org/10.1016/0165-0173(92)90009-b
30. SHI X, HU Y, ZHANG B, LI W, CHEN JD, LIU F: Ameliorating effects and mechanisms of transcutaneous auricular vagal nerve stimulation on abdominal pain and constipation. *JCI Insight* 2021; 6: e150052. https://doi.org/10.1172/jci.insight.150052
31. VENBORG J, WEGEBERG A-M, KRISTENSEN S, BROCK B, BROCK C, PFEIFFER-JENSEN M: The effect of transcutaneous vagus nerve stimulation in patients with polymyalgia rheumatica. *Pharmaceuticals* (Basel) 2021; 14: 1166. https://doi.org/10.3390/ph14111166
32. ELLRICH J: Transcutaneous auricular vagus nerve stimulation. *J Clin Neurophysiol* 2019; 36: 437-42. https://doi.org/10.1097/wnp.0000000000000576
33. BIGGIO F, GORINI G, UTZERI C *et al*.: Chronic vagus nerve stimulation induces neuronal plasticity in the rat hippocampus. *Int J Neuropsychopharmacol* 2009; 12: 1209-21. https://doi.org/10.1017/S1461145709000200
34. DURIC V, MCCARSON KE: Hippocampal neurokinin-1 receptor and brain-derived neurotrophic factor gene expression is decreased in rat models of pain and stress. *Neuroscience* 2005; 133: 999-1006. https://doi.org/10.1016/j.neuroscience.2005.04.002
35. JIN Z, DONG J, WANG Y, LIU Y: Exploring the potential of vagus nerve stimulation in treating brain diseases: a review of immunologic benefits and neuroprotective efficacy. *Eur J Med Res* 2023; 28: 444. https://doi.org/10.1186/s40001-023-01439-2
36. BAUMEISTER D, EICH W, SAFT S *et al*.: No evidence for altered plasma NGF and BDNF levels in fibromyalgia patients. *Sci*

Rep 2019; 9: 13667. https://doi.org/10.1038/s41598-019-49403-7
37. IANNUCCELLI C, LUCCHINO B, GIOIA C *et al*.: Gender influence on clinical manifestations, depressive symptoms and brain-derived neurotrophic factor (BDNF) serum levels in patients affected by fibromyalgia. *Clin Rheumatol* 2022; 41: 2171-78. https://doi.org/10.1007/s10067-022-06133-y
38. MARTINEZ JE, GUIMARÃES I: Fibromyalgia - are there any new approaches? *Best Pract Res Clin Rheumatol* 2024; 38: 101933. https://doi.org/10.1016/j.berh.2024.101933
39. RANZOLIN A, DUARTE ALBP, BREDEMEIER M *et al*.: Evaluation of cytokines, oxidative stress markers and brain-derived neurotrophic factor in patients with fibromyalgia - a controlled cross-sectional study. *Cytokine* 2016; 84: 25-28. https://doi.org/10.1016/j.cyto.2016.05.011
40. WOLFE F, CLAUW DJ, FITZCHARLES M-A *et al*.: 2016 revisions to the 2010/2011 fibromyalgia diagnostic criteria. *Semin Arthritis Rheum* 2016; 46: 319-29. https://doi.org/10.1016/j.semarthrit.2016.08.012
41. MERTENS A, RAEDT R, GADEYNE S, CARRETTE E, BOON P, VONCK K: Recent advances in devices for vagus nerve stimulation. *Expert Rev Med Devices* 2018; 15: 527-39. https://doi.org/10.1080/17434440.2018.1507732
42. REDGRAVE J, DAY D, LEUNG H *et al*.: Safety and tolerability of Transcutaneous Vagus Nerve stimulation in humans; a systematic review. *Brain Stimulat* 2018; 11: 1225-38. https://doi.org/10.1016/j.brs.2018.08.010
43. First report of safety and tolerability of auricular vagal neuromodulation therapy in cardiovascular patients | Request PDF. ResearchGate 2025. https://www.researchgate.net/publication/379731321_First_report_of_safety_and_tolerability_of_auricular_vagal_neuromodulation_therapy_in_cardiovascular_patients (accessed March 11, 2025).
44. Guideline on good pharmacovigilance practices (GVP) - Module VI – Collection, management and submission of reports of suspected adverse reactions to medicinal products (Rev 2) n.d.
45. MAJDOUB F, BEN NESSIB D, FERJANI HL *et al*.: Non-pharmacological therapies in fibromyalgia: new horizons for physicians, new hopes for patients. *Musculoskeletal Care* 2023; 21: 603-10. https://doi.org/10.1002/msc.1741
46. LIU Y, QIAN C, YANG M: Treatment patterns associated with ACR-recommended medications in the management of fibromyalgia in the United States. *J Manag Care Spec Pharm* 2016; 22: 263-71. https://doi.org/10.18553/jmcp.2016.22.3.263
47. TÜRKOĞLU G, SELVI Y: The relationship between chronotype, sleep disturbance, severity of fibromyalgia, and quality of life in patients with fibromyalgia. *Chronobiol Int* 2020; 37: 68-81. https://doi.org/10.1080/07420528.2019.1684314
48. HÄUSER W, FITZCHARLES M-A: Facts and myths pertaining to fibromyalgia. *Dialogues Clin Neurosci* 2018; 20: 53-62. https://doi.org/10.31887/DCNS.2018.20.1/whauser
49. BREIVIK H: Fifty years on the Visual Analogue Scale (VAS) for pain-intensity is still good for acute pain. But multidimensional assessment is needed for chronic pain. *Scand J Pain* 2016; 11: 150-52. https://doi.org/10.1016/j.sjpain.2016.02.004
50. HANEEF Z, SKREHOT HC: Neurostimulation in generalized epilepsy: a systematic review and meta-analysis. *Epilepsia* 2023; 64: 811-20. https://doi.org/10.1111/epi.17524
51. KAMEL LY, XIONG W, GOTT BM, KUMAR A, CONWAY CR: Vagus nerve stimulation: an update on a novel treatment for treatment-resistant depression. *J Neurol Sci* 2022; 434: 120171. https://doi.org/10.1016/j.jns.2022.120171
52. PERRIN AJ, PARIANTE CM: Endocrine and immune effects of non-convulsive neurostimulation in depression: A systematic review. *Brain Behav Immun* 2020; 87: 910-20. https://doi.org/10.1016/j.bbi.2020.02.016
53. VILLAR-MARTINEZ MD, GOADSBY PJ: Non-invasive neuromodulation of the cervical vagus nerve in rare primary headaches. *Front Pain Res* (Lausanne) 2023; 4: 1062892. https://doi.org/10.3389/fpain.2023.1062892
54. KUTLU N, ÖZDEN AV, ALPTEKIN HK, ALPTEKIN JÖ: The impact of auricular vagus nerve stimulation on pain and life quality in patients with fibromyalgia syndrome. *BioMed Res Int* 2020; 2020: 8656218. https://doi.org/10.1155/2020/8656218
55. ABDEL-BASET AM, ABDELLATIF MA, AHMED HHS, EL SHAARAWY NK: Pain neuroscience education versus transcutaneous vagal nerve stimulation in the management of patients with fibromyalgia. *Egypt Rheumatol* 2023; 45: 191-95. https://doi.org/10.1016/j.ejr.2023.03.001
56. PACCIONE CE, STUBHAUG A, DIEP LM, ROSSELAND LA, JACOBSEN HB: Meditative-based diaphragmatic breathing vs. vagus nerve stimulation in the treatment of fibromyalgia-A randomized controlled trial: Body vs. machine. *Front Neurol* 2022; 13: 1030927. https://doi.org/10.3389/fneur.2022.1030927
57. LANG UE, BAJBOUJ M, GALLINAT J, HELLWEG R: Brain-derived neurotrophic factor serum concentrations in depressive patients during vagus nerve stimulation and repetitive transcranial magnetic stimulation. *Psychopharmacology* (Berl) 2006; 187: 56-59. https://doi.org/10.1007/s00213-006-0399-y
58. BJÖRKHOLM C, MONTEGGIA LM: BDNF - a key transducer of antidepressant effects. *Neuropharmacology* 2016; 102: 72-79. https://doi.org/10.1016/j.neuropharm.2015.10.034
59. HAYS SA, RENNAKER RL, KILGARD MP: How to fail with paired VNS therapy. *Brain Stimulat* 2023; 16: 1252-58. https://doi.org/10.1016/j.brs.2023.08.009
60. CHEN J, KUANG H, CHEN A *et al*.: Transcutaneous auricular vagus nerve stimulation for managing pain: a scoping review. *Pain Manag Nurs* 2025; 26: 33-39. https://doi.org/10.1016/j.pmn.2024.11.006
61. PELLOW K, HARRISON J, TUCKER P, HARPER B: Effectiveness of non-invasive vagus nerve stimulation vs heart rate variability biofeedback interventions for chronic pain conditions: a systematic review. *Scand J Pain* 2025; 25(1). https://doi.org/10.1515/sjpain-2024-0037