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ORIGINAL ARTICLE

# Transcutaneous auricular vagus nerve stimulation improves dysautonomia in patients with hypermobile Ehlers–Danlos syndrome

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## Abstract

**Background** Autonomic nervous system dysfunction is highly prevalent in hypermobile Ehlers–Danlos syndrome (hEDS) and contributes substantially to multisystem symptoms and reduced quality of life. Neuroimmune dysregulation and chronic low-grade inflammation are increasingly recognized as key mechanisms underlying these manifestations. Transcutaneous auricular vagus nerve stimulation (taVNS) may restore autonomic balance and engage the cholinergic anti-inflammatory pathway.

**Methods** In this prospective, single-center, open-label pilot study, fourteen consecutive female patients with hEDS and disabling dysautonomia (Composite Autonomic Symptom Score-31 [COMPASS-31] > 20) underwent weekly 60-minute taVNS sessions for eight weeks. Autonomic symptoms were assessed weekly using COMPASS-31. Quality of life was evaluated at baseline and week 8 using the 36-Item Short-Form Health Survey (SF-36).

**Results** taVNS was well tolerated, with no serious adverse events. The mean COMPASS-31 total score decreased significantly from 44.6 ± 12.7 at baseline to 28.3 ± 15.4 at week 8 (−36.5%, $p < 0.001$). Significant improvements were observed in orthostatic intolerance, gastrointestinal, vasomotor, and secretomotor domains. The SF-36 total score increased by 27.7% ($p = 0.07$), with statistically significant improvements in physical functioning, physical role, bodily pain, general health, and vitality.

**Conclusions** In this pilot study, taVNS was safe and associated with clinically meaningful improvements in dysautonomia in patients with hEDS. These findings support further randomized controlled studies incorporating objective autonomic and neuroimmune biomarkers.

**Keywords** Hypermobile Ehlers–Danlos syndrome · Dysautonomia · Neuroimmunology · Vagus nerve · Transcutaneous auricular vagus nerve stimulation · Inflammation

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## Introduction

Hypermobile Ehlers–Danlos syndrome (hEDS) is the most common subtype of the Ehlers–Danlos syndromes (EDS), a heterogeneous group of inherited connective tissue disorders. Unlike other EDS subtypes, hEDS lacks an identified molecular etiology, and diagnosis remains clinical, based on established criteria encompassing generalized joint hypermobility, musculoskeletal complications, and systemic manifestations [1]. Beyond joint instability and chronic pain, hEDS is increasingly recognized as a multisystem disorder with prominent autonomic nervous system involvement.

Dysautonomia affects up to 90% of patients with hEDS when systematically assessed and represents a major driver of disability and impaired quality of life [2, 3]. Clinical manifestations include orthostatic intolerance and postural orthostatic tachycardia syndrome (POTS), gastrointestinal dysmotility, vasomotor instability, genitourinary dysfunction, fatigue, and neuropsychiatric symptoms [2, 4–6]. Despite its high prevalence and impact, dysautonomia in hEDS remains poorly treated, with current management largely limited to symptomatic and supportive measures.

Accumulating evidence suggests that hEDS may involve immune dysregulation and altered neuroimmune communication. Mast cell activation, innate immune abnormalities, and chronic low-grade inflammation have been proposed as contributors to autonomic instability and symptom amplification [7, 8]. These observations support the concept of hEDS as a disorder of connective tissue–neuroimmune interactions rather than a purely mechanical condition.

Transcutaneous auricular vagus nerve stimulation (taVNS) provides a non-invasive approach to engage vagal afferents via the auricular branch of the vagus nerve. taVNS has been shown to modulate autonomic balance, reduce sympathetic activity, and influence inflammatory signaling, with an excellent safety profile [9–14]. However, data regarding its use in hEDS-associated dysautonomia remains scarce. Several recent studies explored the benefits of taVNS in people with various chronic conditions involving dysautonomia such as POTS, fibromyalgia and chronic fatigue syndrome and suggest that vagus nerve stimulation could be a safe and promising therapeutic option for these patients [11, 15–18]. Therefore, the present pilot study aimed to evaluate the association between taVNS and changes in dysautonomia severity and quality of life in patients with hEDS, relevant to a gut–brain axis dysfunction.

## Materials and methods

### Study design and patients

This prospective, single-center, open-label pilot study enrolled fourteen consecutive female patients with HSD and disabling dysautonomia referred by a national Reference Center for Non-Vascular Ehlers-Danlos Syndromes of our hospital from October 2023 to July 2025. All were clinically evaluated by a senior physician specialist of hEDS prior to inclusion. The patients were diagnosed with hEDS, according to current diagnostic criteria [1]. Patients were included in the study if they met the diagnostic criteria for hEDS with associated disabling dysautonomia defined by a Composite Autonomic Symptom Score-31 (COMPASS-31) score > 20 and a rather poor quality of life (SF36 < 50) at baseline, and if genetic testing, using next generation sequencing gene panel analysis, had excluded other EDS subtypes and differential diagnosis. Pregnant patients, those with severe psychiatric disorders, and those with a pacemaker or an auditory implant were not eligible.

The study was approved by the local ethics committee (IRB No.: IORG0009855) and conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent. Table 1 summarizes characteristics of patients at baseline before the taVNS treatment. Patients and their treating physicians were instructed to keep their maintenance therapy stable during the 8 weeks of tAVNS treatment. Any unavoidable medication changes were to be reported; however, no such events were reported.

### Intervention

taVNS was delivered at the hospital-based VNS comprehensive center, affiliated with the neurophysiology department, to the left cymba conchae using a commercially available device (TENS Eco+, Schwa Medico™ Germany) following established methodological recommendations [9, 10, 19–21]. Sessions lasted 60 min and were conducted once weekly for eight weeks. Each session was conducted in an individual room and supervised by a nurse, who maintained continuous real-time video monitoring of the stimulation throughout the entire session duration. Stimulation parameters included a frequency of 2 Hz, 200 µs pulse width, and individualized current intensity (1–8 mA). Stimulation intensity was individually titrated using a dual standardized procedure combining both objective and subjective criteria. First, real-time EEG monitoring was used to verify the propagation of the 2 Hz stimulation artifact to scalp electrodes T3 and C3, thereby

**Table 1** Baseline characteristics of the included patients

| Characteristic | Value ($n=14$) |
|---|---|
| Sex, female, n (%) | 14 (100) |
| Age, years, mean ± SD (range) | 37 ± 12 (15–55) |
| Autonomic dysfunction | |
| COMPASS-31 total score, mean ± SD | 44.6 ± 12.7 |
| Patient with COMPASS-31 > 20, n (%) | 14 (100) |
| COMPASS-31 subdomains, mean ± SD | |
| Orthostatic intolerance | 4.9 ± 2.6 |
| Gastrointestinal | 11.3 ± 3.6 |
| Vasomotor | 2.7 ± 1.5 |
| Secretomotor | 3.1 ± 0.9 |
| Bladder | 3.0 ± 2.1 |
| Pupillomotor | 7.9 ± 2.9 |
| Quality of life (SF-36), mean ± SD | 30.3 ± 9.8 |
| Sub domains of SF-36, mean ± SD | |
| Physical functioning | 41.8 ± 26 |
| Physical Role | 7.1 ± 20.6 |
| Bodily pain | 29.8 ± 16.5 |
| General health | 30.1 ± 8.0 |
| Vitality | 25.4 ± 14.3 |
| Social functioning | 32.7 ± 12.0 |
| Emotional Role | 26.2 ± 32.5 |
| Mental health | 49.4 ± 23.7 |
| Main comorbidities, n (%) | |
| Orthostatic intolerance / POTS | 9 (64) |
| Functional gastrointestinal disorder | 10 (71) |
| Chronic pain syndrome | 12 (86) |
| Anxiety disorder | 8 (57) |
| Previous autonomic-targeted treatment, n (%) | |
| Beta-blockers | 5 (36) |
| Fludrocortisone or midodrine | 3 (21) |
| Non-pharmacological measures only | 6 (43) |

Values are presented as mean ± standard deviation (SD) unless otherwise indicated. COMPASS-31: Composite Autonomic Symptom Score-31; SF-36: 36-Item Short Form Health Survey; POTS: postural orthostatic tachycardia syndrome; taVNS: transcutaneous auricular vagus nerve stimulation

confirming effective signal diffusion along auricular vagus nerve pathways. Second, stimulation intensity was adjusted to each participant's sensory threshold, defined as the lowest intensity eliciting a clearly perceptible yet non-painful auricular sensation. This combined objective–subjective titration protocol was systematically applied at the beginning of each session and readjusted when necessary, during the one-hour stimulation period.

taVNS was proposed as an adjunct to the best available standard of care, within the context of a prospective observational research protocol. As described above, treatment was delivered under optimal conditions, within a specialized center and with individual nursing supervision, ensuring protocol adherence and patient safety throughout the study. Patients were instructed to maintain their existing treatments unchanged throughout the study protocol, so that any observed changes could be attributed to the taVNS intervention.

## Outcome measures

Autonomic symptoms were assessed using COMPASS-31, a validated instrument sensitive to changes in autonomic dysfunction severity [22–25]. Quality of life was evaluated using the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36), a widely validated measure of physical and mental health domains [26–28]. Assessments were performed weekly, before each taVNS intervention.

## Safety monitoring

Safety assessments were performed at each weekly visit in conjunction with the clinical evaluations conducted before the taVNS sessions. Adverse events were prospectively and systematically assessed throughout the study, with particular attention to known taVNS-related effects, including local discomfort, skin irritation, and transient autonomic

symptoms. Adverse events were collected by both nurses and physicians using a standardized self-reported side-effect questionnaire administered at every session. Reported adverse events were subsequently documented in the weekly medical reports completed by the supervising physician.

In addition, each stimulation session was conducted under continuous nursing supervision with real-time monitoring throughout the 60-minute intervention period, allowing immediate identification and management of any stimulation-related symptoms..

### Statistical analysis

Data distribution was assessed using the Shapiro–Wilk test. Given the small sample size and non-normal distribution of most variables, paired comparisons between baseline (S01) and end-of-treatment (S08) were performed using Wilcoxon signed-rank tests, with results reported as means±standard deviation. The Wilcoxon test statistic (W) and the rank-biserial correlation coefficient (r) were reported as a measure of effect size, interpreted as small ($r \geq 0.1$), medium ($r \geq 0.3$), or large ($r \geq 0.5$). To characterize the longitudinal trajectory of outcomes across all eight weekly sessions, linear regression was applied, with session number as the independent variable. For multiple comparisons, including COMPASS-31 subdomain analyses and quality-of-life subscales, p-values were corrected using the Benjamini–Hochberg false discovery rate (FDR) procedure. Statistical significance was set at $p < 0.05$. All analyses were conducted using Python (version 3.x).

## Results

### Safety and tolerability

All 14 patients completed the eight-week protocol. Mean age was 37 ± 12 years. Table 1 summarizes characteristics of patients at baseline before the taVNS treatment, including their comorbidities. Baseline autonomic impairment was severe, with a mean COMPASS-31 score of 44.6 ± 12.7, confirming disabling dysautonomia (Table 1). Ten patients had functional gastrointestinal disorders, including 2 with irritable bowel syndrome (IBS), 5 with functional dyspepsia, and 3 with functional constipation. No cardiovascular or neurological adverse effects attributable to taVNS were observed. Mild transient local sensations (tingling or warmth) were reported in 5 (36%) patients but did not lead to discontinuation, consistent with previous taVNS safety studies [16] (Fig 1).

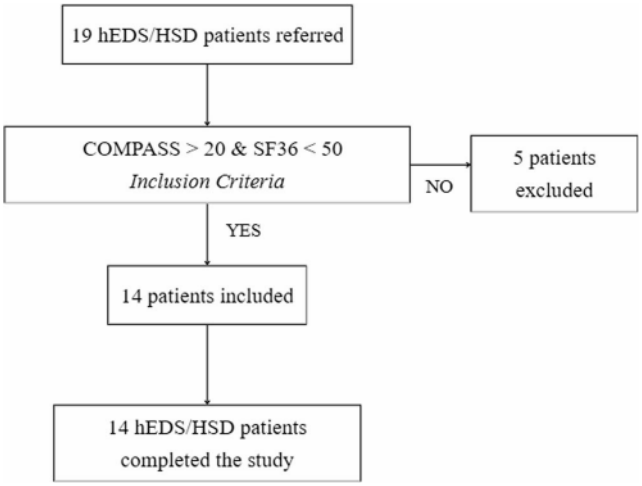


**Fig. 1** Participant flowchart

### Effects on dysautonomia

The mean COMPASS-31 total score decreased significantly from baseline to week 8 (44.6±12.7 vs. 28.3±15.4; W=4, Z=−2.90, $p=0.004$; $r=0.78$, large effect), representing a mean reduction of 36.5%. Notably, 5 out of 14 patients (35.7%) fell below the clinical threshold of 20 at week 8, compared to none at baseline. After FDR correction, this result remained significant (p_FDR=0.033). Subdomain analyses with FDR correction revealed significant improvements in the gastrointestinal domain (11.3±3.6 vs. 5.2±4.0; W=3.5, Z=−3.08, $p=0.002$, p_FDR=0.012; $r=0.82$). Orthostatic intolerance (4.9±2.6 vs. 3.0±3.3; W=6.5, Z=−2.14, $p=0.032$, p_FDR=0.089, $r=0.57$), vasomotor domain (2.7±1.5 vs. 1.4±1.8; W=2.5, Z=−2.55, $p=0.010$, p_FDR=0.055, $r=0.68$) and pupillomotor domains (7.9±2.9 vs. 6.1±3.9; W=9.5, Z=−2.09, $p=0.036$, p_FDR=0.089, $r=0.56$) showed nominal significance but did not survive FDR correction. Secretomotor and bladder domains showed non-significant reductions ($p=0.285$ and $p=0.223$, respectively). Fig. 2; Table 2 show changes in autonomic symptoms following the taVNS regarding the mean total COMPASS-31 score, as well as each of its subdomain with marked improvements in the gastrointestinal domain.

### Effects on quality of life

The mean SF-36 total score increased from 30.3±9.8 to 38.7±15.9 (W=23, Z=−1.85, $p=0.068$; $r=0.50$), approaching but not reaching statistical significance. After FDR correction, this trend was not retained (p_FDR=0.122). Among

SF-36 subdomains, physical functioning showed a significant improvement (41.8±26.0 vs. 48.6±29.0; W=8, Z=−1.99, $p$=0.045), as did physical role functioning (7.1±20.6 vs. 28.6±41.4; W=0, Z=−2.02, $p$=0.041) and mental health/well-being (49.4±23.7 vs. 59.1±25.9; W=13, Z=−2.27, $p$=0.022). None of these subdomain effects survived FDR correction (p_FDR range: 0.081–0.090), indicating that results should be interpreted with caution in the context of the sample size. Social functioning, emotional role, bodily pain, general health, and vitality trended positively but did not reach nominal significance (Fig. 3).

### Effects on pain

Pain was assessed using the Bodily Pain subscale of the SF-36, where higher scores reflect less pain and better functioning. Mean scores increased from 29.8±16.5 at baseline to 37.7±20.4 at week 8 (W=14, Z=−1.69, $p$=0.089, p_FDR=0.134; $r$=0.45, medium effect), representing a trend toward improvement that did not reach statistical significance after FDR correction (Fig. 4).

## Discussion

In this prospective pilot study, transcutaneous auricular vagus nerve stimulation was safe and associated with significant improvements in autonomic symptoms in patients with hypermobile Ehlers–Danlos syndrome. The magnitude of reduction in overall COMPASS-31 scores suggests a clinically meaningful effect in a population characterized by severe and disabling dysautonomia. Indeed, an average COMPASS-31 score of 44.45 (similar as in our pilot study before treatment : 44.6) is acknowledged as reflecting a substantial autonomic symptom burden [29]. The predictive validity of Composite Autonomic Symptom Score-31 based on gold standard (cardiac autonomic reflex test score ≥ 2) has been assessed [30], supporting the significance of a shift of the score from 44.6 to 28.3, even if to prove total recovery of dysautonomia, the expected final COMPASS-31 score is expected to be below 12.5. In comparison a decrease > 10 points of the COMPASS-31 is considered to be high enough to demonstrate benefit on dysautonomia and support a drug prescription [31].

Improvements were particularly pronounced in orthostatic intolerance and gastrointestinal domains, two symptom clusters that are highly prevalent and burdensome in hEDS. These findings are consistent with the established role of the vagus nerve in cardiovascular reflex control and gastrointestinal motility [32–34]. The observed domain-specific responses support the biological plausibility of vagal neuromodulation as a targeted approach to dysautonomia in this condition, consistently with prior reports of taVNS effects on autonomic regulation [11, 35].

Moreover, the vagus nerve occupies a central position at the interface between the nervous and immune systems. Through the inflammatory reflex, vagal efferent signaling modulates cytokine production, immune activation and restoration of autonomic balance, while afferent pathways convey peripheral inflammatory signals to the brain [34–36]. In addition, vagal pathways play a key role in gut–brain communication, cardiovascular reflexes, and visceral homeostasis [32–34]. Vagus nerve stimulation has demonstrated therapeutic efficacy in inflammatory, neurological, and psychiatric disorders, highlighting its potential as a neuromodulatory strategy targeting neuroimmune dysfunction [36, 37]. Given accumulating evidence of immune dysregulation, mast cell involvement, and innate immune abnormalities in hEDS [7], modulation of vagal–immune signaling represents a particularly relevant therapeutic avenue. The improvements in gastrointestinal symptoms further align with emerging concepts of gut–brain–immune axis dysfunction in hEDS.

Bodily Pain subscale may not be sensitive enough to capture significance on such a small and heterogeneous population as in this pilot study. Indeed, taVNS has been acknowledged to improve chronic low back pain, for instance, in a bigger population of patients ($n$ = 25), supported by a MRI marker, the functional connectivity of the descending pain modulation system and reward network [38].

Quality-of-life outcomes only showed a favorable trend in physical functioning. The increase in the SF-36 total score did not reach conventional statistical significance, likely due to the limited sample size. Interestingly, these findings are consistent with prior studies demonstrating improvements in physical and functional outcomes following vagal neuromodulation in other chronic inflammatory and autonomic disorders [39–41].

Our 8-one hour-session-protocol using 2 Hz frequency has already been assessed with other populations of patients, like restless legs syndrome [9, 10] or Long COVID [19] showing good compliance, tolerability and efficiency in rather severe and/or vulnerable patients. Given the neuro-autonomic symptoms like chronic fatigue, dysautonomia and chronic pain shared by Ehlers-Danlos and Long COVID patients, as well as the recent discovery of an overlapping gene network between them [42], we chose to assess the same stimulation protocol on both populations. Indeed, we valued the minimal stimulation able to improve severe patients, one-hour session once a week instead of twice a day [20], delivered at suprathreshold intensities, at hospital during 8 weeks (instead of a 4-week-at-home protocol) in order to be sure that the stimulation was done properly (good contact of the electrode on the ear, compliance

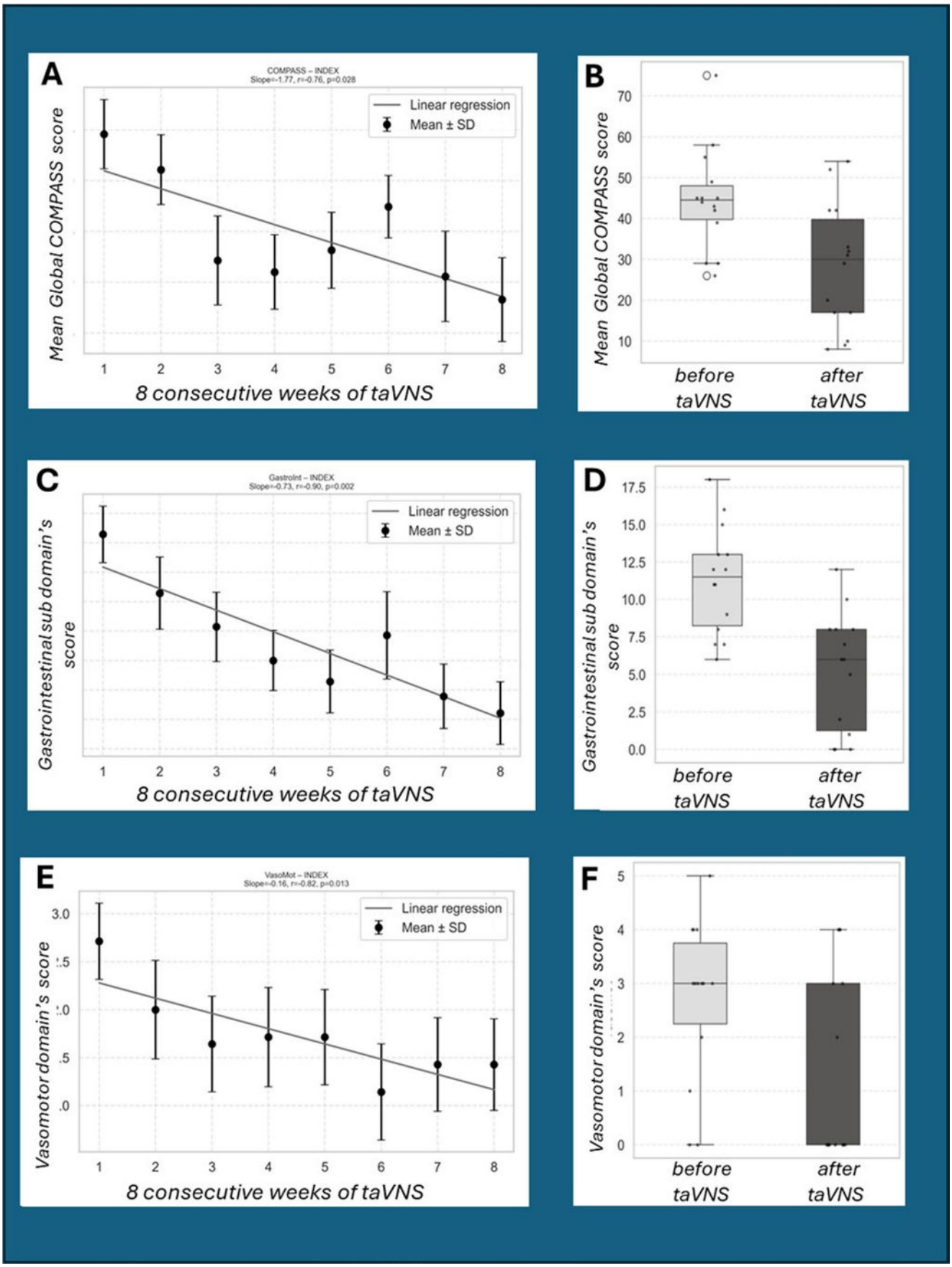
A
COMPASS – INDEX
Slope=-1.77, r=-0.76, p=0.028
Linear regression
Mean ± SD
Mean Global COMPASS score
8 consecutive weeks of taVNS
B
Mean Global COMPASS score
before taVNS
after taVNS
C
GastroInt – INDEX
Slope=-0.73, r=-0.90, p=0.002
Linear regression
Mean ± SD
Gastrointestinal sub domain's score
8 consecutive weeks of taVNS
D
Gastrointestinal sub domain's score
before taVNS
after taVNS
E
VasoMot – INDEX
Slope=-0.16, r=-0.82, p=0.013
Linear regression
Mean ± SD
Vasomotor domain's score
8 consecutive weeks of taVNS
F
Vasomotor domain's score
before taVNS
after taVNS

**Fig. 2** Longitudinal changes in autonomic symptoms assessed by the Composite Autonomic Symptom Score-31 (COMPASS-31) following transcutaneous auricular vagus nerve stimulation (taVNS). (**A**) Linear regression analysis illustrating the weekly evolution of the mean total COMPASS-31 score over the 8 consecutive weeks of taVNS treatment. (**B**) Boxplots comparing mean total COMPASS-31 scores at baseline (week 0) and after completion of the 8-week taVNS protocol (week 8). (**C**) Linear regression analysis showing the weekly evolution of the mean gastrointestinal subdomain score of the COMPASS-31 over the 8-week treatment period. (**D**) Boxplots comparing mean gastrointestinal subdomain scores at baseline and at week 8. (**E**) Linear regression analysis depicting the weekly evolution of the mean vasomotor subdomain score of the COMPASS-31 over the 8-week treatment period. (**F**) Boxplots comparing mean vasomotor subdomain scores at baseline and at week 8

of the patient facing a delay before efficiency of that technique). Last, we stick to our 2 Hz frequency protocol instead of the usual 25 Hz one [20]. Indeed, superiority of 25 Hz tVNS over 1 Hz tVNS over 20 weeks could not be proven in patients with drug-resistant epilepsy for instance [43]. Moreover, a preclinical randomized controlled study [44] clearly demonstrates the anti- inflammatory effect of taVNS in lipopolysaccharide- treated C57BL/6 mice, comparing 2 pulse frequencies (15–25 Hz), the lower 15 Hz frequency being systematically significantly more efficient!

Nevertheless, several limitations should be acknowledged. The open-label design and absence of a sham-controlled group preclude definitive conclusions regarding efficacy and placebo effects. The small sample size limits its generalizability and statistical power, particularly for quality-of-life outcomes. In addition, reliance on self-reported measures, while clinically relevant, underscores the need for objective autonomic and biological endpoints.

Future randomized controlled trials should incorporate objective autonomic metrics such as heart rate variability, baroreflex sensitivity, and tilt-table testing, alongside neuroimmune biomarkers including cytokine profiles and mast cell mediators. Integration of microbiome analyses may further elucidate the role of the gut–brain axis in mediating responses to taVNS in hEDS.

## Conclusion

This pilot study provides preliminary evidence that transcutaneous auricular vagus nerve stimulation is safe and associated with clinically meaningful improvements in dysautonomia in patients with hypermobile Ehlers–Danlos syndrome. The observed benefits are consistent with known vagal functions and support the plausibility of this intervention within a gut–brain axis framework.

These valuable exploratory findings warrant confirmation in larger, sham-controlled trials incorporating objective autonomic and immunological biomarkers to better define mechanisms and therapeutic potential. Vagal neuromodulation may represent a promising, non-invasive treatment strategy for dysautonomia in hEDS, a condition with still substantial unmet clinical needs.

**Table 2** Changes in autonomic symptoms and quality of life parameters following taVNS

| Variable | Baseline (S1) | Week 8 (S8) | W | Z | *p* | p_FDR | *r* | Effect size |
|---|---|---|---|---|---|---|---|---|
| | Mean ± SD | Mean ± SD | Wilcoxon | Approx. | Raw | BH-corrected | Rank-biserial | Interpretation |
| COMPASS-31 Total | 44.6 ± 12.7 | 28.3 ± 15.4 | 4 | -2.90 | **0.004** | **0.033** | 0.78 | *Large* |
| Orthostatic intolerance | 4.9 ± 2.6 | 3.0 ± 3.3 | 6.5 | -2.14 | **0.032** | 0.090 | 0.57 | *Large* |
| Vasomotor | 2.7 ± 1.5 | 1.4 ± 1.8 | 2.5 | -2.55 | **0.010** | 0.055 | 0.68 | *Large* |
| Secretomotor | 3.1 ± 0.9 | 2.7 ± 1.4 | 22 | -0.98 | 0.285 | 0.321 | 0.26 | *Small* |
| Gastrointestinal | 11.3 ± 3.6 | 5.2 ± 4.0 | 3.5 | -3.08 | **0.002** | **0.033** | 0.82 | *Large* |
| Bladder | 3.0 ± 2.1 | 2.4 ± 1.7 | 19.5 | -1.20 | 0.223 | 0.286 | 0.32 | *Medium* |
| Pupillomotor | 7.9 ± 2.9 | 6.1 ± 3.9 | 9.5 | -2.09 | **0.036** | 0.090 | 0.56 | *Large* |
| SF-36 Total Score | 30.3 ± 9.8 | 38.7 ± 15.9 | 23 | -1.85 | 0.068 | 0.122 | 0.49 | *Medium* |
| Physical Functioning | 41.8 ± 26.0 | 48.6 ± 29.0 | 8 | -1.99 | **0.045** | 0.090 | 0.53 | *Large* |
| Physical Role | 7.1 ± 20.6 | 28.6 ± 41.4 | 0 | -2.02 | **0.041** | 0.090 | 0.54 | *Large* |
| Bodily Pain | 29.8 ± 16.5 | 37.7 ± 20.4 | 14 | -1.69 | 0.089 | 0.134 | 0.45 | *Medium* |
| General Health | 30.1 ± 8.0 | 36.0 ± 10.2 | 16.5 | -1.77 | 0.075 | 0.123 | 0.47 | *Medium* |
| Vitality | 25.4 ± 14.3 | 31.1 ± 17.8 | 25 | -1.10 | 0.270 | 0.321 | 0.29 | *Small* |
| Social Functioning | 32.7 ± 12.0 | 42.1 ± 23.1 | 20 | -1.49 | 0.133 | 0.184 | 0.40 | *Medium* |
| Emotional Role | 26.2 ± 32.5 | 26.2 ± 39.6 | 13.5 | -0.09 | 0.933 | 0.964 | 0.02 | *Negligible* |
| Mental Health | 49.4 ± 23.7 | 59.1 ± 25.9 | 13 | -2.27 | **0.022** | 0.081 | 0.61 | *Large* |

S1 = Session 1 (baseline); S8 = Session 8 (end of 8-week treatment). $n = 14$ for all variables. For each variable: first line = mean ± SD; second line (italic) = median [Q1–Q3]. W = Wilcoxon signed-rank test statistic; Z = approximated Z-score. r = rank-biserial correlation (effect size): Large ≥ 0.5, Medium ≥ 0.3, Small ≥ 0.1 (Cohen, 1992). p_FDR = Benjamini–Hochberg false discovery rate correction. SF-36: higher scores = better health. COMPASS-31. Bold values: $p < 0.05$. Green = significant; amber = medium effect; grey = non-significant/negligible. *p* values were obtained using Wilcoxon signed-rank tests and Benjamini–Hochberg false discovery rate (FDR) procedure. COMPASS-31: Composite Autonomic Symptom Score-31; SF-36: 36-Item Short Form Health Survey; taVNS: transcutaneous auricular vagus nerve stimulation

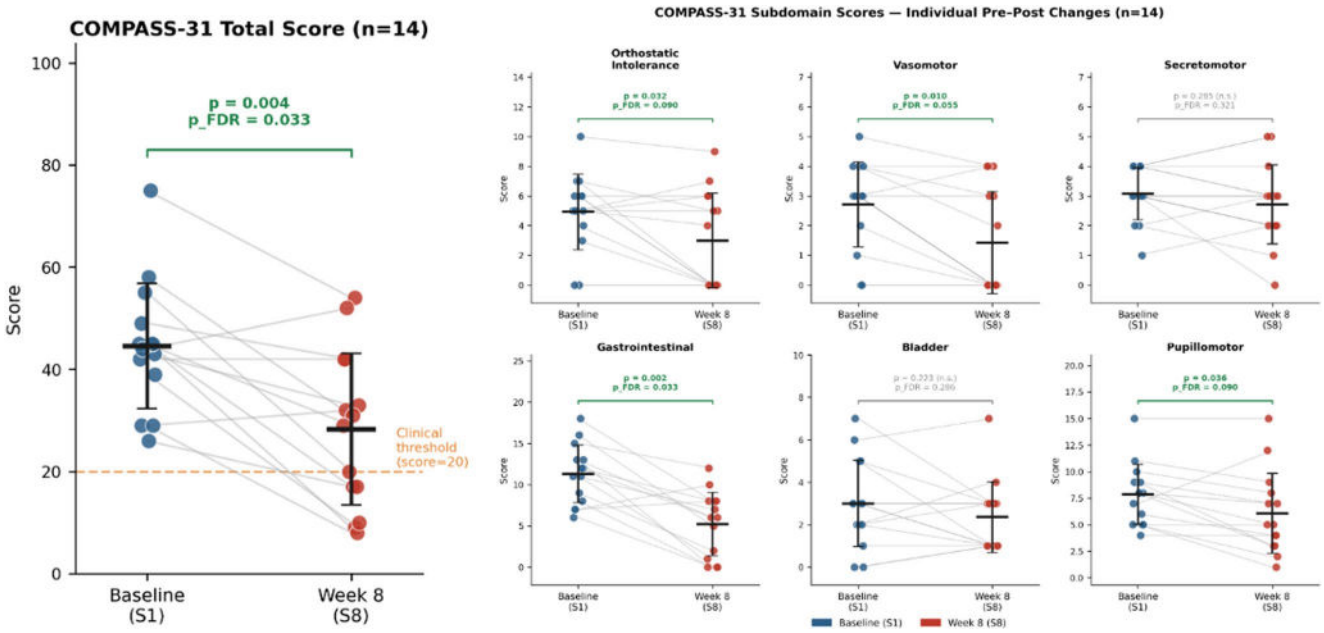


**Fig. 3** Pre versus Post transcutaneous auricular vagus nerve stimulation (taVNS) changes in autonomic symptoms assessed by the Composite Autonomic Symptom Score-31 (COMPASS-31)

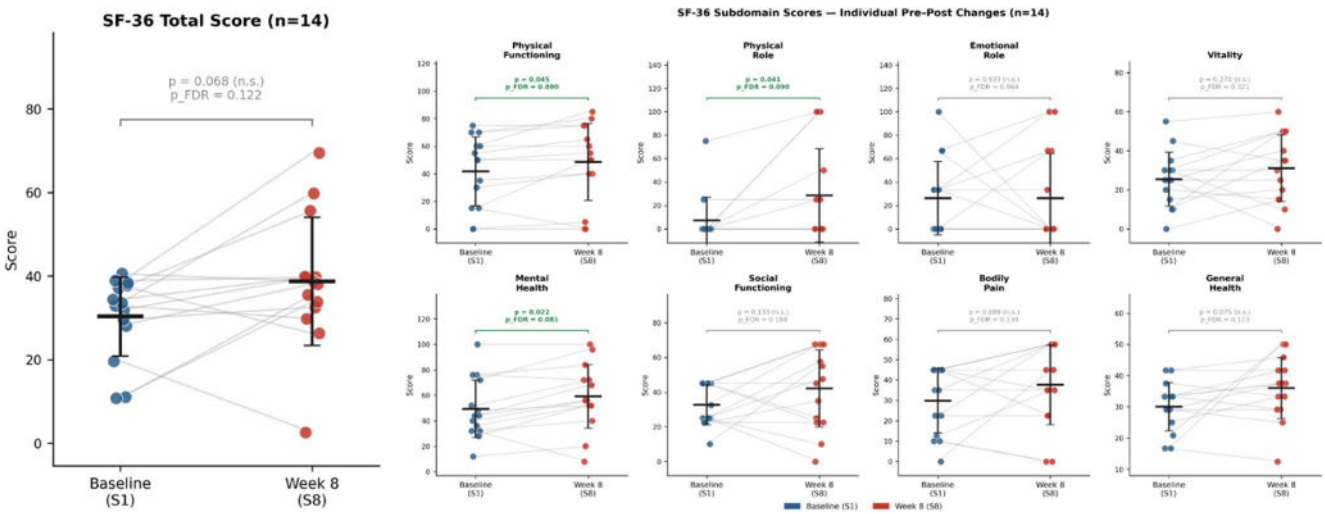


**Fig. 4** Pre and Post transcutaneous auricular vagus nerve stimulation (taVNS) changes in quality-of-life symptoms assessed by the Short-Form 36 Index (SF-36)

**Supplementary Information** The online version contains supplementary material available at https://doi.org/10.1007/s10072-026-09420-7.

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## Declarations

**Ethical statement** The study was approved by our local ethics committee (IRB No.: IORG0009855) and was conducted in accordance with the Declaration of Helsinki and institutional ethical standards. All patients provided their informed signed consent.

**Competing interests** The authors declare that they have no conflict of interest.

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