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RESEARCH ARTICLE



Self-administered non-invasive vagus nerve stimulation therapy for severe pharmacoresistant restless legs syndrome: outcomes at 6 months

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Summary

Severe pharmacoresistant restless legs syndrome (RLS) is difficult to manage and a source of suffering to patients. We studied the effectiveness at 6 months of an innovative treatment: transauricular vagus nerve stimulation (taVNS) in the left cymba concha in a case series of 15 patients, 53% male, mean (SD) age 62.7 (12.3) years with severe pharmacoresistant RLS (mean [SD] International Restless Legs Rating Scale [IRLS] score of 31.9 [2.9]) at baseline. Following an 8-week non-randomised hospital-based study with eight 1-h sessions of taVNS, patients were trained to administer taVNS at home and were followed up for 6 months. The primary outcome measure was the IRLS score, secondary outcome measures were quality of life, mood disorders using the Hospital Anxiety and Depression scale (HAD) subscales for depression (HADD) and anxiety (HADA). At the 6-month follow-up 13/15 patients continued to use weekly taVNS. Symptom severity decreased (mean [SD] IRLS score 22.2 [9.32] at 6 months, $p = 0.0005$). Four of the 15 patients had an IRLS score of <20 at 6 months and two an IRLS score of 5. Quality of life significantly improved compared to baseline (mean [SD] score at baseline 49.3 [18.1] versus 65.66 [22.58] at 6 months, $p = 0.0005$) as did anxiety and depression symptoms (mean [SD] HADA score at baseline 8.9 [5.4] versus 7.53 [4.42] at 6 months, $p = 0.029$; and HADD score at baseline 5.2 [4.5] versus 4.73 [4.44] at 6 months, $p = 0.03$). Treatment was well tolerated, and no adverse events were reported. Our case series shows a potential role for self-administered taVNS in patients with severe pharmacoresistant RLS. Randomised controlled trials are needed to confirm the utility of taVNS.

KEYWORDS

non-pharmacological intervention, restless legs syndrome, sleep, vagus nerve stimulation

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1 | INTRODUCTION

Restless legs syndrome (RLS) is a common pathology affecting approximately 3.9%–14.3% of the general population. In 2%–3% of the population, treatment is indicated to control symptoms (Allen et al., 2005). Typical RLS presents with limb discomfort in the evening, which is increased by immobility and reduced by movement (Allen et al., 2014). About 80% of patients also have periodic leg movements during sleep, which can fragment sleep (Montplaisir et al., 1997). RLS can lead to a reduced quality of life (QoL), and mood disorders with an increased risk of self-harm (Zhuang et al., 2019). Current treatments for severe idiopathic RLS include dopamine agonists, alpha 2 delta ($\alpha_2\delta$) ligands and opioids (Allen et al., 2018). Patients treated by dopamine agonists are at risk of developing augmentation with the need to modify treatment. In some patients, despite optimal management including frequent changes of treatment, symptoms may remain difficult to control leading to considerable suffering (Chenini et al., 2018; Mitterling et al., 2015). New approaches for treating pharmacoresistant RLS are urgently needed.

Vagus nerve stimulation (VNS) was initially developed for refractory epilepsy (Lulic et al., 2009). Studies show that VNS modulates activity in the nucleus tractus solitarius that projects onto the locus coeruleus, amygdala, hypothalamus, nucleus accumbens, prefrontal cortex, periaqueductal grey, postcentral gyrus and insula among others (Frangos et al., 2015). The development of non-invasive techniques of stimulation has expanded use and non-invasive VNS has been shown to be effective for epilepsy, chronic pain, and depression (Kong et al., 2018; Lulic et al., 2009; Napadow et al., 2012). The first report of potential efficacy in RLS was a case report by Merkl et al. (2007) in a patient with depression treated with duloxetine and VNS. A marked decrease in the patient's RLS symptoms was noted: and this was demonstrated using the International Restless Legs Rating Scale (IRLS), which measures symptom severity with a decrease from 19 at baseline to 8 after VNS (Merkl et al. 2007). We recently published a case series using outpatient transauricular VNS (taVNS) for pharmacoresistant RLS (Hartley et al., 2023). In this non randomised study we showed symptom improvement in around two thirds of patients at 8 weeks and a significant mean reduction in the IRLS score of 7.3. However, outpatient taVNS is time consuming for patients and for practitioners. We developed a method for self-administration of taVNS at home to enable patients to continue their treatment long term. However, the long-term efficacy of taVNS for RLS is not known.

We hypothesised that like pharmacotherapy, taVNS would also gradually lose efficacy over a period of follow-up. The aim of this study was to evaluate the efficacy of taVNS at 6 months on RLS severity measured by the IRLS in patients self-administering taVNS at home.

2 | METHODS

The study followed on from an initial 8-week observational study of taVNS in the hospital setting (Hartley et al., 2023). All patients from

the initial phase were offered taVNS at home at the end of the initial 8-week study with portable stimulators, individualised electrodes and training in self-administration of taVNS.

The study was approved by our local ethics committee N° IRB: IORG0009855 and conducted in compliance with good clinical practice guidelines and the Declaration of Helsinki. All participants provided written informed consent. The study is part of the SMART-VNS™ Project: a Structured Multidisciplinary programme for Advanced Research in Therapy of VNS. The SMART-VNS project is dedicated to the development of research, teaching, and clinical care in the field of VNS therapy. The project has both hospital and academic affiliation: it is based within the Neurophysiology and Neuro-modulation Unit of the Raymond Poincaré Hospital in Garches (AP-HP) and is attached to the Institut National de la Santé et de la Recherche Médicale (INSERM) 1173 research team of the University of Versailles Saint-Quentin-en-Yvelines (UVSQ) and Paris–University of Saclay. It is not industry funded.

2.1 | Patients

A total of 15 patients with RLS were included in the initial study between June 2020 and May 2021 in a tertiary care sleep centre. Initial inclusion criteria were: severe RLS according to the international diagnostic criteria (Allen et al., 2014) with an IRLS score of >20 despite optimal pharmacotherapy, absence of augmentation syndrome as defined by international agreed criteria (García-Borreguero et al., 2007) and a ferritin level of >50 $\mu\text{g/L}$. Patients with augmentation syndrome were excluded as the recommended treatment depending on the severity of augmentation is either modulation of the dosing regimen (i.e., dividing the dose in two), combining a dopamine agonist with another treatment or withdrawal of dopamine agonists (García-Borreguero et al., 2018). Optimal pharmacotherapy was individually defined as the treatment that had been the most successful at reducing symptoms over the past year (dopamine agonists, $\alpha_2\delta$ ligands, and opiate analgesics either as monotherapy or combined therapy). Maximum doses of dopamine agonists to reduce the risk or augmentation syndrome were defined as follows (pramipexole >0.36 mg, ropinirole ≥ 2 mg, rotigotine ≥ 2 mg). Exclusion criteria were pregnancy and breastfeeding, treatment by a molecule known to exacerbate RLS including neuroleptics, antihistamines and antidepressants, psychiatric disorders, and lack of health insurance. Patients were asked to maintain their medication during the study. All patients were reviewed by a senior sleep physician before inclusion.

2.2 | Study design and procedures

Following the 8-week non-randomised hospital-based study with eight 1-h sessions of taVNS, all patients were offered the option of continuing weekly taVNS at home using previously determined effective stimulation settings (Figure 1).

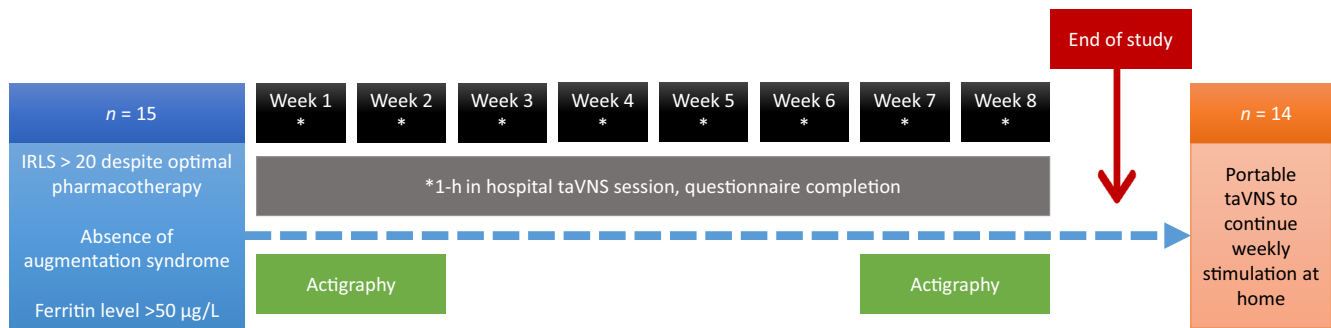


FIGURE 1 Flow chart of study protocol. IRLS, International Restless Legs Rating Scale; taVNS, transauricular vagus nerve stimulation.

2.3 | Intervention

Transcutaneous non-invasive stimulation of the auricular branch of the vagal nerve was performed in the left anterior cymba conchae using a transcutaneous electrical nerve stimulation (TENS) eco Plus (Schwa-medico, Germany). The following stimulation parameters were used: 2 Hz frequency, 200 μ s symmetric square wave impulse width, and an intensity range from 2 to 7 mA titrated to achieve effective stimulation without side-effects (modifications of heart rate or blood pressure, headache, or gastrointestinal discomfort) (Hartley et al., 2023). Stimulation intensity was determined by titration in the first stimulation session: intensity was gradually increased until patients reported discomfort and then reduced below the discomfort threshold. Once the titration threshold has been determined the treatment is painless. Patients report a sensation of pricking or vibration in the ear at the start of stimulation that gradually reduces over the first few minutes but remains perceptible. During the initial hospital stimulation sessions individually designed electrodes, comprising an anode and cathode composition with a brass three-dimensionally (3D)-printed flexible electrode made from thermodynamic polyurethane fibres, were 3D printed with a 3D Flash forge inventor (Flashforge®, China). In hospital taVNS lasted 1 h with simultaneous electroencephalography (EEG) monitoring to observe the stimulation artefact and its diffusion. Towards the end of the hospital-based sessions (sessions five to eight) patients were trained by the Smart-VNS platform team to position the electrode and to use the stimulator independently while stimulation quality was monitored by EEG. All patients at the end of the 8-week initial phase were offered portable taVNS to enable them to continue weekly stimulation sessions at home. Stimulators were programmed with the patients' individualised stimulation parameters. Patients were asked to perform taVNS in the home setting for 1 h once a week. For home taVNS patients were provided with commercially available Schwa-Medico electrodes (reference 101.012–101.013/1), developed for ambulatory auricular stimulation. Patients were trained to monitor the presence of the sensations produced by stimulation: the disappearance of this sensation signal would probably indicate electrode displacement and patients were trained to reposition the electrode.

Patients were advised to perform the sessions lying down or semi-recumbent, and to relax during sessions. Sessions were timed to be

compatible with patients RLS symptoms: e.g., if symptoms were severe in the early evening, patients were advised to perform sessions in the afternoon when their symptoms permitted them to lie down and relax.

Stimulator equipment is relatively inexpensive. The Schwa-Medico stimulator costs ~200 euros and the electrode ~30 euros. The total cost of home stimulation is thus 230 euros. In the setting of the hospital study treatment was offered at no cost to the patient. In the ambulatory setting, while the stimulator was free, patients had to pay for an electrode. The manufacturers recommend that an electrode can be used 15–20 times before replacement.

Adherence was determined by patient self-report.

2.4 | Testing and outcome measures

2.4.1 | Primary outcome measure

Score on the IRLS, which evaluates the severity of RLS symptoms on a scale of 0–40 where a score of >20 is considered severe. The IRLS was initially validated as a clinician administered questionnaire (Walters et al., 2003). We used it as a self-administered questionnaire, which has shown to be reliable and valid compared to the clinician administered version (Sharon et al., 2019). A score of >20 is considered severe.

2.4.2 | Secondary outcome measures

The QoL was measured with the Restless Legs Syndrome Quality of Life questionnaire (RLSQoL) (Abetz et al., 2005), using a French translation developed using the standard technique of translation and backtranslation. The RLSQoL shows good test-retest reliability and is sensitive to small clinical changes (Abetz et al., 2005). Higher scores on the RLSQoL indicate a higher QoL.

Mood disorders were assessed using the subscales of the Hospital Anxiety and depression scale (HAD) for depression (HADD) and anxiety (HADAA), translated and validated in French (Bocéréan & Dupret, 2014). In the adult population a score of <8 on each subscale is considered to indicate the absence of anxiety or depression (Zigmond & Snaith, 1983).

Patients were asked to report side-effects directly to the VNS team by email or telephone and were asked about adverse effects

occurring during ambulatory sessions by questionnaire at the end of the 6-month follow-up period.

Data were collected by self-administered questionnaire at baseline, at the end of the 8-week hospital-based taVNS session, and after 6 months of home-based taVNS.

2.5 | Statistical analysis

Data were collected in Excel and analysed with MATLAB. Quantitative data were presented as means (\pm standard deviations [SDs]), qualitative data as percentage (%). The analysis was performed on an intention-to-treat basis: all 15 patients were included. In all, 14/15 accepted taVNS at home and 13/15 correctly performed the treatment. All 15 patients provided questionnaire follow-up at 6 months. Patients were considered responders if their final IRLS score was <20 and partial responders if their IRLS score reduced by >5 . Chi-square tests were used to compare quantitative data and non-parametric tests for paired data (Wilcoxon) for the IRLS, RLSQoL, HADD and HADA. A supplementary analysis excluding the two outliers who had marked benefit (patient number 8 [P8] and P11) was performed.

3 | RESULTS

3.1 | Patients' characteristics

A total of 15 patients with RLS (53% male), with a mean (SD, range) age of 62.7 (12.3, 27–74) years, were included. All patients had severe RLS with a mean (SD) IRLS score of 31.9 (2.9), and restless legs symptoms had been present on average for a mean (SD) of 15.5 (8.6) years. Patients reported that their restless legs had a negative impact on their QoL (mean [SD] RLSQoL score of 49.3 [18.1]) and symptoms of depression (mean [SD] HADD score of 5.2 [4.5]) and anxiety (mean [SD] HADA score of 8.9 [5.4]) were present (Table 1).

One patient refused home stimulation as he felt that he had received minimal benefit in the initial trial: as a result, 14/15 patients were provided with a stimulator for taVNS sessions at home. Of the patients provided with a stimulator one did not manage to fit the 1 h-long weekly stimulation session into their schedule. As a result, 13/15 performed weekly stimulation sessions.

Patients reported that compared to hospital sessions they had some initial difficulties over the first 2 weeks with electrode placement and electrode stability, probably related to the use of commercially available electrodes, which could have potentially reduced the efficacy of taVNS at home.

3.2 | Effect of taVNS on the severity of RLS

The mean severity of symptoms of RLS, measured by the IRLS, was significantly reduced from baseline to session eight and from baseline to 6 months (mean [SD] IRLS score 31.9 [2.9] versus 24.6 [5.9] versus

22.2 [9.32], $p = 0.0005$, respectively; Table 2 and Figure 2), with no significant change in the whole group from session eight to 6 months. In all, 10 of the 15 patients had an improvement of >5 points on the IRLS, four had an IRLS score of <20 of whom two had an IRLS score of 5.

After the initial hospital sessions, three distinct profiles were identified: 27% of participants were responders with a decrease below an IRLS score of 20, 40% a partial response with an improvement in the IRLS score by >5 points but an IRLS remaining above 20, and 33% were non-responders. Removing the two outliers with a final IRLS score of <5 from the analysis (see Table S1) showed that benefits on the IRLS were maintained with a significant improvement from baseline to 6 months, with a mean (SD) score of 32.53 (2.9) versus 24.84 (6.68) ($p = 0.001$) and no significant change from Week 8 to 6 months, with a mean (SD) score of 26.15 (5.04) versus 24.84 (6.68) ($p = 0.269$).

Four distinct profiles were identified by comparing the results in the initial phase followed by the evolution from 8 weeks to 6 months: (a) continual improvement: five of 15; (b) improvement followed by stability: three of 15; (c) stability during the first 8 weeks followed by improvement: two of 15; and (d) initial improvement followed by a gradual return of symptoms: five of 15. We note that in the 8-week initial protocol, positive results were typically observed towards the end of the sessions.

The two patients who did not continue taVNS at home respectively displayed a small improvement followed by stability (patient who refused home stimulation) and improvement followed by a gradual return of symptoms in the patient who received a home stimulator but did not perform treatment.

3.3 | Effect of taVNS on QoL, anxiety and depression

A significant increase in the RLSQoL score was observed between baseline and session eight. The RLSQoL score then non-significantly decreased from 8 weeks to 6 months follow-up but remained significantly improved compared to the baseline (Table 2, Figure 2).

The mean (SD) baseline HADA score was 8.9 (5.4), indicating the presence of anxiety and 60% of participants had a score of ≥ 8 . This was significantly reduced at 8 weeks and although non-significantly increased at follow-up remained significantly below baseline with 47% having a score of ≥ 8 (Table 2, Figure 2). The mean baseline HADD score was not in the pathological range and once again significantly improved by session eight with a non-significant increase at follow-up although this remained below baseline (Table 2, Figure 2).

3.4 | Side-effects of taVNS

The taVNS was safe and well tolerated. No significant differences were noted in individual heart rate or blood pressure either within individual sessions or across the eight sessions. No adverse effects were reported during the 6-month follow-up period.

TABLE 1 Characteristics of the patients at baseline.

| Patient | Sex | Age, years | Duration of symptoms from start, years | Treatment | Clock time of onset of symptoms with treatment | IRLS score | RLSQoL score | HADA score | HADD score | Mean stimulation intensity, mA | Use of ta VNS at home during 6-month follow-up |
|---------|-----|------------|----------------------------------------|----------------------------------|------------------------------------------------|------------|--------------|------------|------------|--------------------------------|------------------------------------------------|
| P1 | M | 73 | 38 | Gabapentin, tramadol, codeine | 8:00 p.m. | 36 | 25 | 11 | 10 | 5 | Yes |
| P2 | M | 47 | 10 | Gabapentin | 12:00 a.m. | 30 | 75 | 3 | 0 | 6 | No |
| P3 | M | 72 | 17 | Rotigotine | 2:00 a.m. | 31 | 62.5 | 12 | 7 | 5 | Yes |
| P4 | M | 65 | 10 | Pramipexole | 7:00 p.m. | 36 | 50 | 7 | 5 | 4 | Yes |
| P5 | F | 73 | 15 | Pramipexole, tramadol | 4:00 p.m. | 30 | 47.5 | 8 | 2 | 3 | Yes |
| P6 | M | 71 | 19 | Pregabalin, pramipexol, tramadol | 4:00 p.m. | 31 | 67.5 | 6 | 1 | 4 | Yes |
| P7 | F | 69 | 19 | Pregabalin | 6:00 p.m. | 32 | 52.5 | 9 | 7 | 3 | Yes |
| P8 | M | 62 | 11 | Gabapentin | 1:00 a.m. | 32 | 70 | 3 | 2 | 5 | Yes |
| P9 | M | 67 | 7 | Pramipexole, gabapentin | 12:00 a.m. | 35 | 77.5 | 8 | 5 | 7 | No |
| P10 | F | 62 | 14 | Pregabalin, pramipexol, tramadol | 12:00 a.m. | 29 | 77.5 | 5 | 2 | 4 | Yes |
| P11 | F | 62 | 12 | Gabapentin | 9:00 p.m. | 29 | 57.5 | 17 | 7 | 5 | Yes |
| P12 | F | 27 | 5 | Gabapentin | 8:00 p.m. | 29 | 50 | 15 | 8 | 3 | Yes |
| P13 | M | 69 | 29 | Pregabalin, pramipexole, codeine | 1:00 p.m. | 33 | 35 | 5 | 6 | 4 | Yes |
| P14 | F | 59 | 9 | Pramipexole, gabapentin | 7:00 p.m. | 33 | 40 | 15 | 11 | 4 | Yes |
| P15 | F | 74 | 16 | Pregabalin, pramipexole, codeine | 9:00 p.m. | 38 | 7.5 | 21 | 17 | 6 | Yes |

Abbreviations: F, female; HADA, mood disorders using the Hospital Anxiety and Depression scale subscale for anxiety; HADD, mood disorders using the Hospital Anxiety and Depression scale subscale for depression; IRLS, International Restless Legs Rating Scale; M, male; RLSQoL, Restless Legs Syndrome Quality Of Life questionnaire.

TABLE 2 Results of transauricular vagus nerve stimulation treatment: baseline to 6 months.

| Variable, mean (SD) | Baseline | After eighth session of taVNS | After 6 months | p^* (baseline to 6 months) | p^* (8 weeks to 6 months) |
|-----------------------|-------------|-------------------------------|----------------|------------------------------|-----------------------------|
| IRLS score | 31.9 (2.9) | 24.6 (5.9) | 22.2 (9.32) | 0.0005 | 0.111 |
| RLSQoL score | 49.3 (18.1) | 80.0 (19.6) | 65.66 (22.58) | 0.0005 | 0.95 |
| Anxiety HADA score | 8.9 (5.4) | 6.2 (5.0) | 7.53 (4.42) | 0.029 | 0.645 |
| Depression HADD score | 5.2 (4.5) | 4.0 (4.0) | 4.73 (4.44) | 0.03 | 0.759 |

Abbreviations: HADA, mood disorders using the Hospital Anxiety and Depression scale subscale for anxiety; HADD, mood disorders using the Hospital Anxiety and Depression scale subscale for depression; IRLS, International Restless Legs Rating Scale; RLSQoL, Restless Legs Syndrome Quality of Life questionnaire; taVNS, transauricular vagus nerve stimulation.

*Wilcoxon signed-rank test for paired samples.

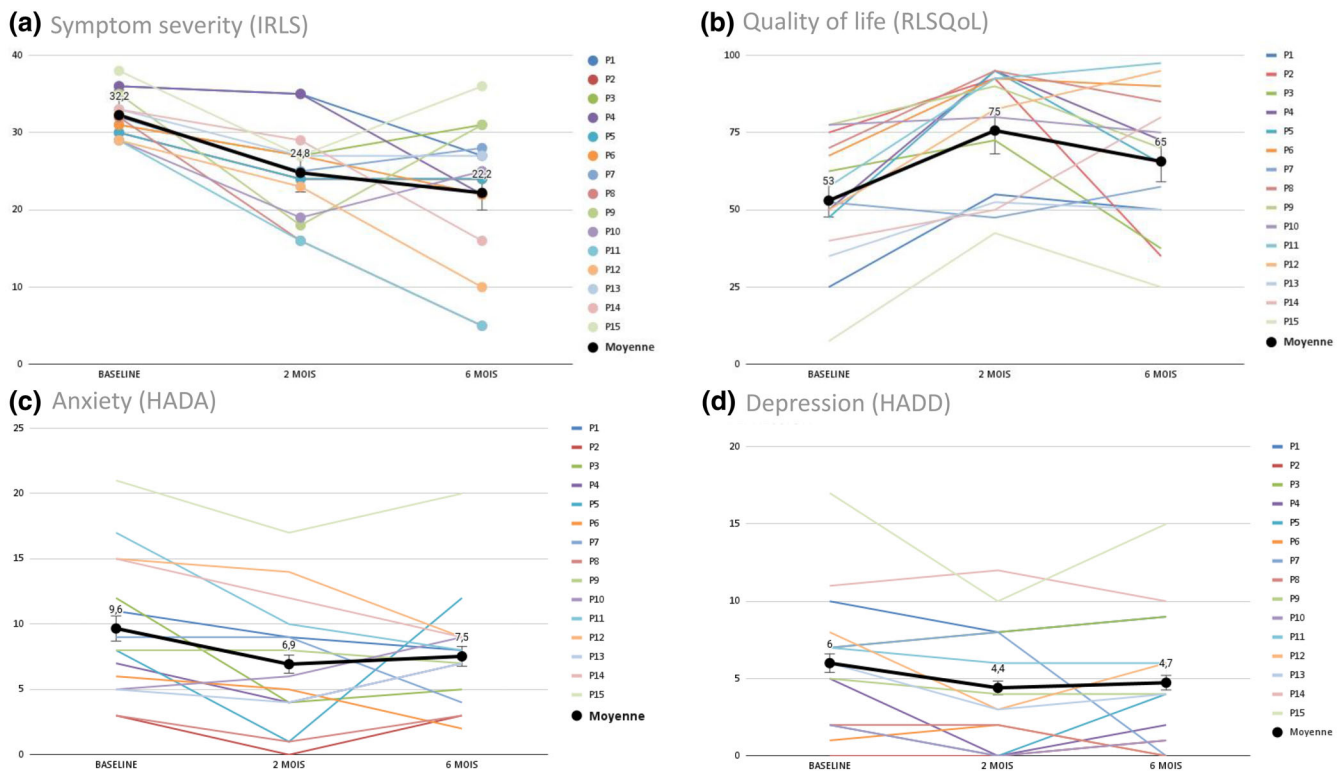


FIGURE 2 Individual evolution of restless legs syndrome (RLS) severity, quality of life (QoL), anxiety and depression from baseline to 6 months with mean indicated in black: (a) symptom severity: International Restless Legs Rating Scale (IRLS); (b) QoL: Restless Legs Syndrome Quality of Life questionnaire (RLSQoL); (c) anxiety mood disorders using the Hospital Anxiety and Depression scale (HAD) subscale for and anxiety (HADA); and (d) depression using the HAD subscale for depression (HADD).

4 | DISCUSSION

In this study evaluating at home self-administrated taVNS following eight sessions of in-hospital administered taVNS in patients with severe pharmacoresistant RLS, we found that at 6 months symptom severity was improved compared to baseline in 14/15 patients measured by the IRLS. In the majority of patients (73%), symptoms although improved remained severe with a score on the IRLS of >20. In two patients, symptoms effectively disappeared. No patient had worsening of his or her symptom severity compared to baseline. Patients were required to continue their baseline treatment during the treatment period so changes in symptoms could be attributed to taVNS. We also found an increase in QoL and a reduction in

symptoms of anxiety and depression at 6 months. taVNS treatment in the ambulatory setting proved to be acceptable to patients and remained safe and well tolerated.

This study adds to the findings of our initial study, which showed that that eight sessions of in-hospital administered taVNS improved the symptoms of RLS in ~60% of participants with severe pharmacoresistant RLS (Hartley et al., 2023). In some patients in whom improvements were not evident at 8 weeks, symptoms continued to improve with the use of ambulatory taVNS, implying that our initial 8-week treatment protocol was too short. In other patients their symptoms stabilised. After an initial marked improvement at 8 weeks, the mean QoL, mean anxiety and mean depression decreased at follow-up but still remained improved compared to baseline.

The pathophysiology of RLS is being gradually elucidated. Onset can be early or late with a clear genetic component, notably in patients with early onset RLS (Trenkwalder et al., 2018). Environmental factors also play a role, notably iron deficiency (Gulyani et al., 2009). RLS involves both sensory and motor systems, with pain and discomfort in the legs leading to an uncontrollable urge to move. These circuits are modulated by descending signals from the dorsal raphe, the locus coeruleus and the A11 region in the dorsal-posterior hypothalamus. Early studies underlined the importance of dopamine, due to the dramatic success of L-DOPA and dopamine agonists in relieving symptoms. RLS is thought to represent a hyperdopaminergic state with subsequent downregulation of postsynaptic receptors, which contributes to the circadian pattern of RLS. The complex excitatory-inhibitory action of dopamine depends on concentration, receptor affinity and receptor actions, explaining why dopamine agonists are effective but also why they lead to the development of augmentation syndrome (paradoxical worsening of symptoms) (Trenkwalder et al., 2018).

The link between iron deficiency and RLS (especially in cases of iron deficiency anaemia) and the response to iron treatment has been known for some time, but more recent studies have shown that brain iron deficiency, which can exist even in patients with normal serum iron (Earley et al., 2000). Brain iron deficiency in animal models leads to downregulation of adenosine A₁ receptors (A₁Rs), a reduction in inhibitory D₁-A₁ heterodimers in the basal ganglia and the spinal cord and an increased sensitivity of glutaminergic cortico-striatal receptors (Ferré, Quiroz, et al., 2017). Adenosine A₁R-A_{2A}R heterodimers act as an on-off switch, and high concentrations of adenosine lead to glutamate release. The importance of glutamate is underlined by the efficacy of $\alpha_2\delta$ ligands, which target glutaminergic neurones, but also by the demonstration of increased glutamate in the basal ganglia on magnetic resonance imaging (Allen et al., 2013). Dopamine affects the glutaminergic system via modulation of the α amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor-evoked responses and *N*-methyl-D-aspartate (NMDA) receptor-evoked responses. This action explains the effect of tramadol and methadone, which act on NMDA receptors (Ferré, Earley, et al., 2017).

To date pharmacological treatments for RLS have targeted the different neurotransmitters, often with good initial success but an effect that can reduce over time. Loss of treatment efficacy is particularly problematic in patients treated with dopamine agonists in whom the development of augmentation syndrome can lead to dramatic dose escalation and worsening of symptoms (Becker et al., 1993; Högl et al., 2011). Studies of pharmacological treatments for RLS in drug naïve or patients post-treatment wash out show that patients with RLS, in common with many other pathologies, experience a placebo effect. In a recent well controlled trial of dipyrindamole a short-term reduction in the IRLS score of 5 was seen in patients treated with placebo (Garcia-Borreguero et al., 2021). However, this population is not comparable with our population of patients with pharmacoresistant RLS, first because symptoms were less severe at baseline with a mean IRLS score of 24 and second because in patients with pharmacoresistant RLS, IRLS scores progressively increase over time:

the Course of RLS (COR) study by Fuhs et al. (2014) of patients with RLS found that 12.5% of patients deteriorated over time and 8.5% reported an increase in symptom severity of >5 points on the IRLS despite treatment. In the Fuhs et al. (2014) study the initial mean IRLS score in the group of patients with symptom aggravation was 16 at inclusion; our patients were far more severe with a mean IRLS score at inclusion of 31.9. We carefully excluded secondary causes of pharmacoresistance and augmentation syndrome (Leu-Semenescu et al., 2018) but both study evidence and clinical experience in this group of patients would lead us to anticipate that without changes in treatment, symptoms would certainly worsen over 6 months with an increase in the IRLS. This is not what we found: on an intention-to-treat analysis, no patient had an IRLS above baseline and 67% had an improvement of ≥ 5 points on the IRLS after 6 months of weekly ambulatory taVNS treatment. We note that the two patients who did not continue with taVNS treatment also remained stable. The demonstration of improvement and/or stability in our patients opens the possibility that taVNS may have a role in patients with augmentation syndrome. Thus, taVNS may have a role either in primary prevention (in addition to dopamine agonists) in order to reduce the incidence of augmentation syndrome over time, or as an adjuvant therapy to reduce the symptoms of augmentation and thus enable the continuation of dopamine agonists for a longer period or to enable withdrawal of dopamine agonists in order to re-establish efficacy. Future studies are needed to explore this potential role.

How taVNS can affect RLS is unknown. The vagus nerve is principally composed of afferent sensory fibres that project to the nucleus of the solitary tract leading to the release of both inhibitory neurotransmitters (gamma-aminobutyric acid) and excitatory (glutamate and aspartate), along with noradrenaline, acetylcholine, and other neuropeptides (Lulic et al., 2009). The nucleus of the solitary tract projects to the locus coeruleus and dorsal raphe magnus, which in turn modulate serotonin and noradrenaline release (Frangos et al., 2015, 2017; Henry, 2002; Komisaruk & Frangos, 2022; Spindler et al., 2019). The vagus nerve modulates key physiological pathways including cerebral blood flow, melanocortin, inflammation, glutamatergic excitotoxicity, noradrenaline and neurotrophic processes (Berthoud et al., 2021; Cai et al., 2014; Neuhuber & Berthoud, 2021). Early studies on VNS used direct stimulation via implanted electrodes, but the development of external stimulation, typically via the cymba concha (taVNS) has extended its use. The efficacy of taVNS in epilepsy, depression, and chronic pain is well known (Chen et al., 2009; Huston, 2012), and in these cases the effect is considered to be due to the effects of taVNS on glutaminergic and dopaminergic systems with modulation of cortical excitability. Given the pathophysiology of RLS and the importance of the dopaminergic and glutamatergic systems, it is probable that VNS in RLS exerts its effects via modulation of these systems. In RLS dysfunctions of the sympathovagal system (Thireau et al., 2017) have been described but their cause and potential role are unclear.

Some patients responded positively during the first 8-week period, but for others, improvements were noted later on. The reasons why some patients are responders and others are non-responders, early responders or late responders are all avenues that should be

investigated in future studies. Available evidence suggests that in animal models taVNS alters the hippocampal and cortical transcriptomes, epigenetically modulating neuronal plasticity (Sanders et al., 2019). Transauricular VNS induces long-term potentiation in vagus nerve-controlled neural circuits and networks by promoting synaptic plasticity (Alvarez-Dieppa et al., 2016). The intensity and repetitive character of the stimulation are crucial criteria for the induction of synaptic modifications necessary for functional switching (Zhang et al., 2004). These modifications may take time and there is evidence from studies on depression that the response rate increases with the duration of treatment (Marangell et al., 2002). Use of the taVNS device in the patients home allows long-term treatment and potentially maximises benefit. In addition, it also increases the number of patients who can be managed by the hospital VNS team. However, efficacy was potentially reduced in patients performing home taVNS as initial difficulties with electrode placement and stability were reported, possibly linked to the use to commercial taVNS electrodes in the home setting. Initial improvements in some patients during the 8-week hospital protocol were followed by stability or deterioration: the lack of a significant improvement in the mean IRLS score for the group from week 8 to 6 months may reflect reduced stimulation efficacy.

Several parameters concerning the delivery of taVNS for RLS remain to be defined. Although several studies have looked at parameters in other indications (for a review see Thompson et al., 2021), no studies have looked at stimulus parameters or frequency of taVNS in RLS, e.g., we do not know if weekly, biweekly or daily sessions would be more effective. Equally, we do not know if the daytime timing of taVNS sessions affects efficacy; performing taVNS requires the patient to rest for 1 h and as immobility triggers RLS, it is clear that patients with severe RLS cannot lie still for 1 h when their symptoms are maximal (typically in the evening). Pragmatically, taVNS has to be performed when symptoms are quiescent (typically in the morning or early afternoon) but whether there is benefit in performing taVNS close to the start of symptoms (e.g., 1–2 h before symptom onset) is not known.

Poorly controlled RLS causes great distress to patients (Leu-Semenescu et al., 2018) with a marked impact on QoL. Marked improvements in QoL were found at 8 weeks, and although this decreased at 6 months it still remained above baseline. We noted improvement in mood. This could be related to reduced symptoms but we note that taVNS is used to treat depression (for a review see Kong et al., 2018) and anxiety in patients with chronic pain (Napadow et al., 2012). After initial marked improvement during the hospital-based protocol no significant change was noted in the results. We do not know why this is; possible causes are reduced efficacy of stimulation in the home setting, a lack of long-term efficacy of taVNS on mood and QoL, or that in pharmacoresistant patients' initial improvements were linked to being offered a potentially useful treatment.

Study limitations: first, and as discussed in our initial paper, our study follows up a small non-randomised pilot study. Without a randomised controlled design, we cannot confirm that the improvements in symptoms either at the end of the protocol or at follow-up are due to taVNS. We did not perform polysomnography (PSG) prior to

inclusion and so cannot exclude underlying obstructive sleep apnea (OSA) or provide objective data on potential improvements in sleep or periodic limb movements of sleep. RLS is more common in patients with OSA and can complicate management; pharmacotherapy used for RLS can also worsen OSA. The effects of VNS on underlying sleep-related breathing disorders is unknown, in the absence of a PSG we cannot comment on potential modifications of respiratory parameters (Romero-Peralta et al., 2019). Ambulatory stimulation was performed by patients at home using a transauricular electrode and a pre-programmed stimulator. In all, 14/15 patients requested ambulatory stimulation and 13/15 stated they used the treatment as recommended. However, we have no data on patient adherence or on whether treatment was correctly performed in the ambulatory setting. Given the initial difficulties reported with electrode placement and electrode stability, we cannot exclude potentially reduced stimulation efficacy. There is no biomarker for RLS, but we measured changes in symptoms on a validated self-administered questionnaire, the IRLS, which is the reference standard for studies of treatment in RLS. Finally, there is no agreement on a biomarker of taVNS effectiveness (Farmer et al., 2021) as data on the evaluation of heart rate variability parameters in left ear taVNS are conflicting (Antonino et al., 2017; Bretherton et al., 2019; Clancy et al., 2014). We confirmed that stimulation was occurring by monitoring the stimulation artefact during each session via EEG recording during the hospital-based sessions. At home, patients relied on self-monitoring of cutaneous sensation to determine whether electrodes were still correctly placed, potentially reducing stimulation efficacy.

5 | CONCLUSION

At the 6-month follow-up of 15 patients with severe pharmacoresistant RLS, taVNS, in combination with optimal pharmacotherapy, was shown to be effective in improving RLS symptoms measured by the IRLS over the short and longer term. Initial highly positive effects on mood and QoL show a tendency to reduced efficacy over the long term. Randomised controlled trials of taVNS in RLS are necessary to confirm a positive short- and long-term effect in RLS and to define optimal treatment modalities.

AUTHOR CONTRIBUTIONS

Sarah HARTLEY: Conceptualization; formal analysis; visualization; writing – original draft; methodology; writing – review and editing; validation; investigation; supervision. **Guillaume BAO:** Data curation; visualization; methodology; investigation; project administration; writing – review and editing; software; validation; conceptualization. **Ashley RUSSO:** Formal analysis; data curation; writing – review and editing; investigation; software; validation. **Marine ZAGDOUN:** Data curation; formal analysis; investigation; writing – review and editing; software; validation. **Sylvain CHEVALLIER:** Data curation; formal analysis; investigation; writing – review and editing; software; validation. **Frédéric LOFASO:** Formal analysis; visualization; methodology; writing – review and editing; funding acquisition; validation;

resources. **Antoine LEOTARD:** Visualization; writing – review and editing; supervision; investigation; methodology; resources. **Eric AZA-BOU:** Conceptualization; formal analysis; visualization; methodology; supervision; project administration; writing – review and editing; funding acquisition; resources; validation.

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CONFLICT OF INTEREST STATEMENT

The authors have no relevant affiliations or financial involvement with any organisation or entity in conflict with the subject matter or materials discussed in the manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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REFERENCES

- Abetz, L., Arbuckle, R., Allen, R. P., Mavradi, E., & Kirsch, J. (2005). The reliability, validity and responsiveness of the restless legs syndrome quality of life questionnaire (RLSQoL) in a trial population. *Health and Quality of Life Outcomes*, 3, 79. <https://doi.org/10.1186/1477-7525-3-79>
- Allen, R. P., Barker, P. B., Horská, A., & Earley, C. J. (2013). Thalamic glutamate/glutamine in restless legs syndrome: Increased and related to disturbed sleep. *Neurology*, 80(22), 2028–2034. <https://doi.org/10.1212/WNL.0b013e318294b3f6>
- Allen, R. P., Picchietti, D. L., Auerbach, M., Cho, Y. W., Connor, J. R., Earley, C. J., Garcia-Borreguero, D., Kotagal, S., Manconi, M., Ondo, W., Ulfberg, J., & Winkelman, J. W. (2018). Evidence-based and consensus clinical practice guidelines for the iron treatment of restless legs syndrome/Willis-Ekbohm disease in adults and children: An IRLSSG task force report. *Sleep Medicine*, 41, 27–44. <https://doi.org/10.1016/J.SLEEP.2017.11.1126>
- Allen, R. P., Picchietti, D. L., Garcia-Borreguero, D., Ondo, W. G., Walters, A. S., Winkelman, J. W., Zucconi, M., Ferri, R., Trenkwalder, C., & Lee, H. B. (2014). Restless legs syndrome/Willis-Ekbohm disease diagnostic criteria: Updated international restless legs syndrome study group (IRLSSG) consensus criteria—History, rationale, description, and significance. *Sleep Medicine*, 15(8), 860–873. <https://doi.org/10.1016/J.SLEEP.2014.03.025>
- Allen, R. P., Walters, A. S., Montplaisir, J., Hening, W., Myers, A., Bell, T. J., & Ferini-Strambi, L. (2005). Restless legs syndrome prevalence and impact: REST general population study. *Archives of Internal Medicine*, 165(11), 1286–1292. <https://doi.org/10.1001/ARCHINTE.165.11.1286>
- Alvarez-Dieppa, A. C., Griffin, K., Cavalier, S., & McIntyre, C. K. (2016). Vagus nerve stimulation enhances extinction of conditioned fear in rats and modulates arc protein, CaMKII, and GluN2B-containing NMDA receptors in the basolateral amygdala. *Neural Plasticity*, 2016, 4273280. <https://doi.org/10.1155/2016/4273280>
- Antonino, D., Teixeira, A. L., Maia-Lopes, P. M., Souza, M. C., Sabino-Carvalho, J. L., Murray, A. R., Deuchars, J., & Vianna, L. C. (2017). Non-invasive vagus nerve stimulation acutely improves spontaneous cardiac baroreflex sensitivity in healthy young men: A randomized placebo-controlled trial. *Brain Stimulation*, 10(5), 875–881. <https://doi.org/10.1016/j.brs.2017.05.006>
- Becker, P. M., Jamieson, A. O., & Brown, W. D. (1993). Dopaminergic agents in restless legs syndrome and periodic limb movements of sleep: Response and complications of extended treatment in 49 cases. *Sleep*, 16(8), 713–716. <https://doi.org/10.1093/SLEEP/16.8.713>
- Berthoud, H. R., Albaugh, V. L., & Neuhuber, W. L. (2021). Gut-brain communication and obesity: Understanding functions of the vagus nerve. *The Journal of Clinical Investigation*, 131(10), e143770. <https://doi.org/10.1172/JCI143770>
- Bocéréan, C., & Dupret, E. (2014). A validation study of the hospital anxiety and depression scale (HADS) in a large sample of French employees. *BMC Psychiatry*, 14(1), 354. <https://doi.org/10.1186/S12888-014-0354-0>
- Bretherton, B., Atkinson, L., Murray, A., Clancy, J., Deuchars, S., & Deuchars, J. (2019). Effects of transcutaneous vagus nerve stimulation in individuals aged 55 years or above: Potential benefits of daily stimulation. *Aging*, 11(14), 4836–4857. <https://doi.org/10.18632/AGING.102074>
- Cai, P. Y., Bodhit, A., Derequito, R., Ansari, S., Abukhalil, F., Thenkabail, S., Ganji, S., Saravanapavan, P., Shekar, C. C., Bidari, S., Waters, M. F., & Hedna, V. S. (2014). Vagus nerve stimulation in ischemic stroke: Old wine in a new bottle. *Frontiers in Neurology*, 5, 107. <https://doi.org/10.3389/FNEUR.2014.00107>
- Chen, S., Li, J., Zhang, L., Dong, X., Gao, W., Mo, J., Chen, H., Xiao, S., & Li, Y. (2009). 5-HT 3 receptors mediate the time-dependent vagal afferent modulation of nociception during chronic food allergen-sensitized visceral hyperalgesia in rats. *Neurogastroenterology and Motility: The Official Journal of the European Gastrointestinal Motility Society*, 21(11), 1222. <https://doi.org/10.1111/J.1365-2982.2009.01335.X>
- Chenini, S., Arnulf, I., Monaca, C. C., & Ghorayeb, I. (2018). French consensus: Pharmacoresistant restless legs syndrome. *Revue Neurologique*, 174(7–8), 522–531. <https://doi.org/10.1016/J.NEUROL.2018.06.003>
- Clancy, J. A., Mary, D. A., Witte, K. K., Greenwood, J. P., Deuchars, S. A., & Deuchars, J. (2014). Non-invasive vagus nerve stimulation in healthy humans reduces sympathetic nerve activity. *Brain Stimulation*, 7(6), 871–877. <https://doi.org/10.1016/J.BRS.2014.07.031>
- Earley, C. J., Connor, J. R., Beard, J. L., Malecki, E. A., Epstein, D. K., & Allen, R. P. (2000). Abnormalities in CSF concentrations of ferritin and transferrin in restless legs syndrome. *Neurology*, 54(8), 1698–1700. <https://doi.org/10.1212/wnl.54.8.1698>
- Farmer, A. D., Strzelczyk, A., Finisguerra, A., Gourine, A. V., Gharabaghi, A., Hasan, A., Burger, A. M., Jaramillo, A. M., Mertens, A., Majid, A., Verkuil, B., Badran, B. W., Ventura-Bort, C., Gaul, C., Beste, C., Warren, C. M., Quintana, D. S., Hämmerer, D., Frer, E., ... Koenig, J. (2021). International consensus based review and recommendations for minimum reporting standards in research on transcutaneous Vagus nerve stimulation (version 2020). *Frontiers in Human Neuroscience*, 14, 568051. <https://doi.org/10.3389/FNHUM.2020.568051>
- Ferré, S., Earley, C., Gulyani, S., & Garcia-Borreguero, D. (2017). In search of alternatives to dopaminergic ligands for the treatment of restless legs syndrome: Iron, glutamate, and adenosine. *Sleep Medicine*, 31, 86–92. <https://doi.org/10.1016/j.sleep.2016.08.019>
- Ferré, S., Quiroz, C., Guitart, X., Rea, W., Seyedian, A., Moreno, E., Casadó-Anguera, V., Díaz-Ríos, M., Casadó, V., Clemens, S., Allen, R. P., Earley, C. J., & García-Borreguero, D. (2017). Pivotal role of adenosine neurotransmission in restless legs syndrome. *Frontiers in Neuroscience*, 11, 722. <https://doi.org/10.3389/fnins.2017.00722>

- Frangos, E., Ellrich, J., & Komisaruk, B. R. (2015). Non-invasive access to the Vagus nerve central projections via electrical stimulation of the external ear: FMRI evidence in humans. *Brain Stimulation*, 8(3), 624–636. <https://doi.org/10.1016/J.BRS.2014.11.018>
- Frangos, E., Richards, E. A., & Bushnell, M. C. (2017). Do the psychological effects of vagus nerve stimulation partially mediate vagal pain modulation? *Neurobiology of Pain (Cambridge, Mass.)*, 1, 37–45. <https://doi.org/10.1016/J.YNPAL.2017.03.002>
- Fuhs, A., Bentama, D., Antkowiak, R., Mathis, J., Trenkwalder, C., & Berger, K. (2014). Effects of short- and long-term variations in RLS severity on perceived health status—The COR-study. *PLoS One*, 9(4), e94821. <https://doi.org/10.1371/JOURNAL.PONE.0094821>
- García-Borreguero, D., Allen, R. P., Benes, H., Earley, C., Happe, S., Högl, B., Kohnen, R., Paulus, W., Rye, D., & Winkelmann, J. (2007). Augmentation as a treatment complication of restless legs syndrome: Concept and management. *Movement Disorders: Official Journal of the Movement Disorder Society*, 22(Suppl 18), S476–S484. <https://doi.org/10.1002/mds.21610>
- García-Borreguero, D., Cano-Pumarega, I., & Marulanda, R. (2018). Management of treatment failure in restless legs syndrome (Willis-Ekbom disease). *Sleep Medicine Reviews*, 41, 50–60. <https://doi.org/10.1016/j.smrv.2018.01.001>
- García-Borreguero, D., García-Malo, C., Granizo, J. J., & Ferré, S. (2021). A randomized, placebo-controlled crossover study with dipyrindamole for restless legs syndrome. *Movement Disorders: Official Journal of the Movement Disorder Society*, 36(10), 2387–2392. <https://doi.org/10.1002/mds.28668>
- Gulyani, S., Earley, C. J., Camandola, S., Maudsley, S., Ferré, S., Mughal, M. R., Martin, B., Cheng, A., Gleichmann, M., Jones, B. C., Allen, R. P., & Mattson, M. P. (2009). Diminished iron concentrations increase adenosine a(2A) receptor levels in mouse striatum and cultured human neuroblastoma cells. *Experimental Neurology*, 215(2), 236–242. <https://doi.org/10.1016/J.EXPNEUROL.2008.10.007>
- Hartley, S., Bao, G., Zagdoun, M., Chevallier, S., Lofaso, F., Leotard, A., & Azabou, E. (2023). Noninvasive Vagus nerve stimulation: A new therapeutic approach for Pharmacoresistant restless legs syndrome. *Neuromodulation: Journal of the International Neuromodulation Society*, 26(3), 629–637. <https://doi.org/10.1016/j.neurom.2022.10.046>
- Henry, T. R. (2002). Therapeutic mechanisms of vagus nerve stimulation. *Neurology*, 59(6 Suppl 4), S3–S14. https://doi.org/10.1212/WNL.59.6_SUPPL_4.S3
- Högl, B., García-Borreguero, D., Trenkwalder, C., Ferini-Strambi, L., Hening, W., Poewe, W., Brenner, S. S., Fraessdorf, M., Busse, M., Albrecht, S., & Allen, R. P. (2011). Efficacy and augmentation during 6 months of double-blind pramipexole for restless legs syndrome. *Sleep Medicine*, 12(4), 351–360. <https://doi.org/10.1016/J.SLEEP.2010.12.007>
- Huston, J. M. (2012). The vagus nerve and the inflammatory reflex: Wandering on a new treatment paradigm for systemic inflammation and sepsis. *Surgical Infections*, 13(4), 187–193. <https://doi.org/10.1089/SUR.2012.126>
- Komisaruk, B. R., & Frangos, E. (2022). Vagus nerve afferent stimulation: Projection into the brain, reflexive physiological, perceptual, and behavioral responses, and clinical relevance. *Autonomic Neuroscience: Basic & Clinical*, 237, 102908. <https://doi.org/10.1016/J.AUTNEU.2021.102908>
- Kong, J., Fang, J., Park, J., Li, S., & Rong, P. (2018). Treating depression with transcutaneous auricular Vagus nerve stimulation: State of the art and future perspectives. *Frontiers in Psychiatry*, 9(FEB), 20. <https://doi.org/10.3389/FPSYT.2018.00020>
- Leu-Semenescu, S., Petiau, C., Charley Monaca, C., & Dauvilliers, Y. (2018). French consensus: Augmentation syndrome in restless legs syndrome. *Revue Neurologique*, 174(7–8), 532–539. <https://doi.org/10.1016/J.NEUROL.2018.06.004>
- Lulic, D., Ahmadian, A., Baaj, A. A., Benbadis, S. R., & Vale, F. L. (2009). Vagus nerve stimulation. *Neurosurgical Focus*, 27(3), E5. <https://doi.org/10.3171/2009.6.FOCUS09126>
- Marangell, L. B., Rush, A. J., George, M. S., Sackeim, H. A., Johnson, C. R., Husain, M. M., Nahas, Z., & Lisanby, S. H. (2002). Vagus nerve stimulation (VNS) for major depressive episodes: One year outcomes. *Biological Psychiatry*, 51(4), 280–287. [https://doi.org/10.1016/S0006-3223\(01\)01343-9](https://doi.org/10.1016/S0006-3223(01)01343-9)
- Merkel, A., Brakemeier, E. L., Danker-Hopfe, H., & Bajbouj, M. (2007). Vagus nerve stimulation improves restless legs syndrome associated with major depression: A case report [3]. *Journal of Clinical Psychiatry*, 68(4), 635–636. <https://doi.org/10.4088/jcp.v68n0423c>
- Mitterling, T., Heidebreder, A., Stefani, A., Fritz, J., Ulmer, H., Poewe, W., & Högl, B. (2015). Natural course of restless legs syndrome/Willis-Ekbom disease: Long-term observation of a large clinical cohort. *Sleep Medicine*, 16(10), 1252–1258. <https://doi.org/10.1016/J.SLEEP.2015.05.028>
- Montplaisir, J., Boucher, S., Poirier, G., Lavigne, G., Lapierre, O., & Lespérance, P. (1997). Clinical, polysomnographic, and genetic characteristics of restless legs syndrome: A study of 133 patients diagnosed with new standard criteria. *Movement Disorders: Official Journal of the Movement Disorder Society*, 12(1), 61–65. <https://doi.org/10.1002/mds.870120111>
- Napadow, V., Edwards, R. R., Cahalan, C. M., Mensing, G., Greenbaum, S., Valovska, A., Li, A., Kim, J., Maeda, Y., Park, K., & Wasan, A. D. (2012). Evoked pain analgesia in chronic pelvic pain patients using respiratory-gated auricular vagal afferent nerve stimulation. *Pain medicine (Malden, Mass.)*, 13(6), 777–789. <https://doi.org/10.1111/J.1526-4637.2012.01385.X>
- Neuhuber, W. L., & Berthoud, H. R. (2021). Functional anatomy of the vagus system—Emphasis on the somato-visceral interface. *Autonomic Neuroscience: Basic & Clinical*, 236, 102887. <https://doi.org/10.1016/J.AUTNEU.2021.102887>
- Romero-Peralta, S., Cano-Pumarega, I., García-Malo, C., Agudelo Ramos, L., & García-Borreguero, D. (2019). Treating restless legs syndrome in the context of sleep disordered breathing comorbidity. *European Respiratory Review: An Official Journal of the European Respiratory Society*, 28(153), 190061. <https://doi.org/10.1183/16000617.0061-2019>
- Sanders, T. H., Weiss, J., Hogewood, L., Chen, L., Paton, C., McMahan, R. L., & Sweatt, J. D. (2019). Cognition-enhancing Vagus nerve stimulation alters the epigenetic landscape. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, 39(18), 3454–3469. <https://doi.org/10.1523/JNEUROSCI.2407-18.2019>
- Sharon, D., Allen, R. P., Martínez-Martin, P., Walters, A. S., Ferini Strambi, L., Högl, B., Trotti, L. M., Buchfuhrer, M., Swieca, J., Bogan, R. K., Zak, R., Hensley, J. G., Schaefer, L. A., Marelli, S., Zucconi, M., Stefani, A., Holzknacht, E., Olvera, V., Meaklim, H., ... Becker, P. M. (2019). Validation of the self-administered version of the international restless legs syndrome study group severity rating scale—The sIRLS. *Sleep Medicine*, 54, 94–100. <https://doi.org/10.1016/J.SLEEP.2018.10.014>
- Spindler, P., Bohlmann, K., Straub, H. B., Vajkoczy, P., & Schneider, U. C. (2019). Effects of vagus nerve stimulation on symptoms of depression in patients with difficult-to-treat epilepsy. *Seizure*, 69, 77–79. <https://doi.org/10.1016/J.SEIZURE.2019.04.001>
- Thireau, J., Farah, C., Molinari, N., Bouliou, F., Torrelles, L., Winkelmann, J., Scholz, S., Richard, S., Dauvilliers, Y., & Marmigère, F. (2017). MEIS1 variant as a determinant of autonomic imbalance in restless legs syndrome. *Scientific Reports*, 7, 46620. <https://doi.org/10.1038/srep46620>
- Thompson, S. L., O'Leary, G. H., Austelle, C. W., Gruber, E., Kahn, A. T., Manett, A. J., Short, B., & Badran, B. W. (2021). A review of parameter settings for invasive and non-invasive Vagus nerve stimulation (VNS)

- applied in neurological and psychiatric disorders. *Frontiers in Neuroscience*, 15, 709436. <https://doi.org/10.3389/fnins.2021.709436>
- Trenkwalder, C., Allen, R., Högl, B., Clemens, S., Patton, S., Schormair, B., & Winkelmann, J. (2018). Comorbidities, treatment, and pathophysiology in restless legs syndrome. *The Lancet Neurology*, 17(11), 994–1005. [https://doi.org/10.1016/S1474-4422\(18\)30311-9](https://doi.org/10.1016/S1474-4422(18)30311-9)
- Walters, A., LeBrocq, C., Dear, A., Hening, W., Rosen, R., Allen, R., & Trenkwalder, C. (2003). Validation of the international restless legs syndrome study group rating scale for restless legs syndrome. *Sleep Medicine*, 4(2), 121–132.
- Zhang, Y., McGuire, M., White, D. P., & Ling, L. (2004). Serotonin receptor subtypes involved in vagus nerve stimulation-induced phrenic long-term facilitation in rats. *Neuroscience Letters*, 363(2), 108–111. <https://doi.org/10.1016/j.neulet.2004.03.067>
- Zhuang, S., Na, M., Winkelmann, J. W., Ba, D., Liu, C. F., Liu, G., & Gao, X. (2019). Association of Restless Legs Syndrome with Risk of suicide and self-harm. *JAMA Network Open*, 2(8), e199966. <https://doi.org/10.1001/JAMANETWORKOPEN.2019.9966>

- Zigmond, A., & Snaith, R. (1983). The hospital anxiety and depression scale. *Acta Psychiatrica Scandinavica*, 67, 361–370.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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