Noninvasive Vagus Nerve Stimulation: A New Therapeutic Approach for Pharmacoresistant Restless Legs Syndrome

Sarah Hartley, Guillaume Bao, Marine Zagdoun, Sylvain Chevallier, Frédéric Lofaso, Antoine Leotard, Eric Azabou

To cite this version:

Sarah Hartley, Guillaume Bao, Marine Zagdoun, Sylvain Chevallier, Frédéric Lofaso, et al.. Noninvasive Vagus Nerve Stimulation: A New Therapeutic Approach for Pharmacoresistant Restless Legs Syndrome. Neuromodulation, 2022, 26 (3), 10.1016/j.neurom.2022.10.046. hal-03921967
Noninvasive Vagus Nerve Stimulation: A New Therapeutic Approach for Pharmacoresistant Restless Legs Syndrome

Sarah Hartley, BMBChir; Guillaume Bao, MSc; Marine Zagdoun, MSc; Sylvain Chevallier, PhD; Frédéric Lofaso, MD, PhD; Antoine Leotard, MD; Eric Azabou, MD, PhD

ABSTRACT

Aims: This work aimed to study the effect of noninvasive vagus nerve stimulation on severe restless legs syndrome (RLS) resistant to pharmacotherapy.

Materials and Methods: Patients with severe pharmacoresistant RLS were recruited from a tertiary care sleep center. Intervention was one-hour weekly sessions of transauricular vagus nerve stimulation (tVNS) in the left cymba concha, for eight weeks. The primary outcome measure was the score on the International Restless Legs Rating Scale (IRLS); secondary outcome measures were quality of life (Restless Legs Syndrome Quality of Life scale [RLSQOL]), mood disorders using the Hospital Anxiety and Depression scale subscale for depression (HADD) and Hospital Anxiety and Depression scale subscale for anxiety (HADA), and objective sleep latency, sleep duration, efficiency, and leg movement time measured by actigraphy.

Results: Fifteen patients, 53% male, aged mean 62.7 ± 12.3 years with severe RLS, reduced quality of life, and symptoms of anxiety and depression, were included. The IRLS improved from baseline to session eight: IRLS 31.9 ± 2.9 vs 24.6 ± 5.9 \( p = 0.0003 \). Of these participants, 27% (4/15) had a total response with a decrease below an IRLS score of 20; 40% (6/15) a partial response with an improvement in the IRLS > 5 but an IRLS above 20; and 33% (5/15) were nonresponders. After tVNS, quality of life improved (RLSQOL 49.3 ± 18.1 vs 80.0 ± 19.6 \( p = 0.0005 \)), as did anxiety (HADA 8.9 ± 5.4 vs 6.2 ± 5.0 \( p = 0.001 \)) and depression (HADD 5.2 ± 4.5 vs 4.0 ± 4.0 \( p = 0.01 \)). No significant change was found in actigraphic outcome measures.

Conclusions: In this pilot study, tVNS improved the symptoms of RLS in 66% of participants (10/15) with severe pharmacoresistant RLS, with concomitant improvements in quality of life and mood. Randomized controlled trials evaluating therapeutic efficacy of tVNS in RLS are needed to confirm these promising findings.

Keywords: Neuromodulation, nonpharmacologic intervention, restless syndrome, sleep, vagus nerve stimulation

Conflict of Interest: The authors reported no conflict of interest.

INTRODUCTION

Restless legs syndrome (RLS) is a relatively frequent condition, occasionally affecting approximately 7% of the population. In 2% to 3% of the population, the symptoms are sufficiently severe to require treatment. The classic presentation of limb discomfort in the evenings, increased by immobility and decreased by moving the limbs, is accompanied in 80% of patients by periodic leg movements during sleep, when regular foot and leg flexion can fragment sleep. Treatments for severe idiopathic RLS include dopamine agonists, alpha 2 delta ligands, and opiate analgesics. Despite optimal treatment and in the absence of augmentation...
syndrome, some patients have intractable symptoms that are difficult to manage despite frequent changes of treatment, are a source of great suffering, and can lead to a reduced quality of life, mood disorders, and an increased risk of self-harm. Patients with RLS have been shown to have increased cardiovascular risk. This may be linked to autonomic dysfunction found in patients with RLS. Analysis of heart rate variability (HRV) shows modified sympathovagal regulation in patients homozygous for rs2300478 in the MEIS1 locus, with sleep fragmentation during periodic leg movements leading to sympathetic activation. Vagus nerve stimulation (VNS) has been shown to be beneficial in epilepsy, depression, chronic pain, and inflammatory diseases. Studies show that VNS modulates activity in the nucleus tractus solitarius, which projects to many areas of the brain, including the locus coeruleus, amygdala, hypothalamus, nucleus accumbens, prefrontal cortex, peri-aqueductal gray, postcentral gyrus, and insula. Both VNS using implanted stimulators and transauricular vagal nerve stimulation (tVNS) using low dose electrical stimulation of the external area of the ear innervated by the auricular branch of the vagal nerve have been shown to reduce epileptic seizure frequency and to modulate pain perception. tVNS has also shown effects on mood, with reduced depression. It has been suggested that these effects on mood may also modulate pain perception. Given the effectiveness of new antiepileptics in the treatment of RLS and the anticonvulsant effect of VNS, there has been interest in the effects of VNS on RLS. A single case of treatment by vagal nerve stimulation was reported by Merkl in a patient with depression and RLS, treated with duloxetine, with a decrease in symptom severity measured by the International Restless Legs Rating Scale (IRLS) from 19 to 8.

We hypothesized that treatment by tVNS would reduce the symptoms of RLS. The aim of this nonrandomized pilot study was to evaluate the feasibility and the effect of tVNS on patients with severe RLS despite optimal pharmacotherapy. The primary outcome measure was the effect on RLS measured by the IRLS. Secondary outcome measures included the effect of tVNS on sleep, leg movements, quality of life, and mood, and feasibility (recruitment, retention, and delivery of stimulation in the hospital setting).

MATERIALS AND METHODS

Patients

Fifteen patients with RLS were included in this pilot study between June 2020 and May 2021, in a tertiary care sleep center. The study was approved by our local ethics committee, number international review board (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(TM) Project: A Structured Multidisciplinary program for Advanced Research in Vagus Nerve Stimulation Therapy.

The inclusion criteria were severe RLS following international diagnostic criteria with an IRLS > 20 despite optimal pharmacotherapy, absence of augmentation syndrome as defined by international agreed criteria, and a ferritin level > 50 μg/L. Optimal pharmacotherapy was defined for each patient as treatment by dopamine agonists, alpha 2 delta ligands, and opioid analgesics (either as monotherapy or combination therapy) that was the most successful at reducing symptoms over the past year. Patients taking doses of dopamine agonists above recommended levels were temporarily excluded until doses had been reduced, owing to the high risk of augmentation syndrome (pramipexole > 0.36 mg, Rotigotrine > 2 mg, Rotigotrine > 2 mg). The exclusion criteria were pregnancy and breastfeeding, known psychiatric disorders, treatment by a molecule known to exacerbate RLS, and lack of health insurance.

All patients were reviewed by a senior sleep physician before inclusion. Patients were asked not to change their medication during the study. The study was approved by our local ethics committee, number IRB: IORG0009855, and conducted in compliance with good clinical practice guidelines and the Declaration of Helsinki. All participants provided written informed consent.

Study Design and Procedures

This was an open-label pilot study comprising eight one-hour sessions of tVNS over eight weeks. After informed consent and inclusion, each session consisted of completion of questionnaires followed by a one-hour–long tVNS protocol. In addition, during weeks 1 and 2 and weeks 7 and 8, participants wore two actigraphs (AWD4, CamNtech, Cambridge, UK), one on the nondominant wrist and one on the ankle (Fig. 1).

Interventions

tVNS was performed using a standardized protocol and is described following the international guidelines for VNS studies. Intervention was one-hour weekly sessions of tVNS in the left cymba concha, over eight weeks. We chose a weekly hour-long stimulation protocol to maximize study participation.

Transcutaneous noninvasive stimulation of the auricular branch of the vagal nerve using a TENS eco Plus (Schwa-medico, Ehringshausen, Germany) was performed using a constant voltage,
afferent unidirectional stimulation in the left anterior cymba conchae. The stimulation parameters used were 2 Hz frequency, 200-millisecond symmetric square wave impulse width, and intensity range between 2 mA and 7 mA, depending on patient sensitivity. Current was titrated starting at an intensity of 2 mA in the first session, to achieve effective stimulation without stimulation causing pain or discomfort. The electrode used was individually designed to maximize cutaneous contact, using an anode and cathode composition with a brass 3-dimensional (3D) printed flexible electrode using thermodynamic polyurethane fibers. Individualized electrode printing was performed with a 3D Flashforge inventor (Flashforge, Jinhua, China). Each session of tVNS lasted an hour, with simultaneous electroencephalogram (EEG) monitoring to observe the stimulation artifact during the session. At the end of the study, all patients were offered portable tVNS to enable them to continue weekly stimulation at home.

Testing and Outcome Measures

The primary outcome measure was the score on the IRLS, which evaluates the severity of RLS symptoms on a scale of 0 to 40 over the last seven days, in which a score > 20 is considered severe. The IRLS was initially validated as a clinician administered questionnaire; we used it as a self-administered questionnaire, which has been shown to be reliable and valid compared with the clinician-administered version.

Secondary outcome measures were quality of life as measured with the Restless Legs Syndrome Quality of Life scale (RLSQOL), using a French translation developed using the standard technique of translation and backtranslation. The RLSQOL summary score is calculated based on items 1 to 5, 7 to 10, and 13. Each five-point scale is coded so that 1 equals most severe and 5 equals least severe. The score is then transformed to a 0 to 100 score. Higher scores on the RLSQOL indicate a higher quality of life. The RLSQOL shows good test-retest reliability and is sensitive to small clinical changes.

Mood disorders were assessed using the Hospital Anxiety and Depression scale subscale for depression (HADD) and Hospital Anxiety and Depression scale subscale for anxiety (HADA), translated and validated in French. In the adult population, a score < 8 on each subscale is considered to indicate the absence of anxiety or depression.

Sleep latency, sleep duration, sleep fragmentation, and leg movements were measured by actigraphy using two actigraphs (AWD4 CamNtech, Cambridge, UK), one on the nondominant wrist and one on the ankle during the night. Patients wore the actigraphs for two weeks at the beginning and two weeks at the end of the study. Actigraphs were worn only at night; patients were asked to put on the actigraphs when going to bed. Data were analyzed for week 1 and week 2. Simultaneous sleep diaries were completed to estimate lights out and lights on for each night. Analysis was performed using the validated sleep analysis tool (CamNtech) with night-by-night correction for lights on and lights off. Wrist-worn actigraphy was used for sleep parameters, with visual verification of sleep onset enabling calculation of sleep latency and sleep duration. The fragmentation index was defined as the sum of the moving time (%) plus immobile bouts lasting < 1 minute (%) present during the period of actigraphically defined sleep, and is considered a measure of sleep fragmentation. Ankle-worn actigraphy was used to measure leg movements; moving time was calculated as the mobile time expressed as a percentage of time in bed.

Adverse effects were monitored assessing heart rate, blood pressure, and questionnaires on the occurrence of pain, headache, nausea, dizziness, intestinal upset, or other uncomfortable symptoms at each session.

Statistical Analysis

Data were collated in Excel (Microsoft, Redmond, WA) and analyzed with MATLAB (MathWorks, Natick, MA). Quantitative data were presented as means ± SD, qualitative data as percentage (%). Patients were considered responders if their final IRLS was < 20 and partial responders if their IRLS score decreased by > 5. Chi² tests were used to compare quantitative data and nonparametric tests for paired data (Wilcoxon) for the IRLS, RLSQOL, HADD, and HADA.

RESULTS

Patients’ Characteristics at Baseline

Fifteen patients with RLS, (53% male) aged from 27 to 74 years, mean 62.7 ± 12.3 years, were included. All patients had severe RLS, with a mean IRLS score of 31.9 ± 2.9; symptoms had a negative impact on their quality of life (mean RLSQOL 49.3 ± 18.1), and symptoms of depression (mean HADD 5.2 ± 4.5) and anxiety (mean HADA 8.9 ± 5.4) were present (table 1).

Effect of tVNS on the Severity of RLS

The mean severity of symptoms of RLS measured by the IRLS was significantly reduced from session 1 to session 8 (31.9 ± 2.9 vs 24.8 ± 5.9, respectively) (table 2). The correlation coefficient for the IRLS over time was r² = 0.13 (Supplementary Data Fig. S5). However, three distinct profiles were identified: 27% of participants (4/15) had a total response with a decrease below an IRLS score of 20; 40% (6/15) a partial response with an improvement in the IRLS > 5 but an IRLS remaining above 20; and 33% (5/15) were nonresponders. We found that positive effects on RLS were not observed by patients immediately but instead toward the end of the protocol (Fig. 2). Fourteen of the 15 patients opted to continue tVNS at home.

Effect of tVNS on Quality of Life, Anxiety, and Depression

A significant increase in the RLSQOL was observed between baseline and session 8 (table 2). The mean baseline HADA score was 8.9 ± 5.4, indicating the presence of anxiety, and 60% of participants had a score ≥ 8. This was significantly reduced by session 8. The mean baseline HADA score was not in the pathological range and once again significantly improved overall by session 8 (Fig. 3).

Effect of tVNS on Sleep and Nocturnal Leg Movements

Wrist actigraphy was used to measure sleep latency, sleep duration, and sleep fragmentation. Mean sleep latency 44.4 ± 35.9 vs 20.9 ± 14.6 minutes p = 0.067 showed a nonsignificant trend toward improvement, but no significant differences were found in either estimated sleep duration or the fragmentation index (table 2). Ankle actigraphy was used to measure nocturnal leg movements. No significant difference was found in either the percentage movement time or the fragmentation index (Fig. 4).

Side Effects of tVNS

tVNS was safe and well tolerated. No side effects were reported after the sessions. No significant differences were noted in...
individual heart rate or blood pressure either within individual sessions or across the eight sessions.

Feasibility of tVNS

Information about the project was rapidly disseminated within the patient community because the project was funded by a patient group dedicated to RLS. Recruitment of patients was rapid, with a long waiting list of patients keen to participate. Delivering weekly one-hour sessions within the physiology department ensured that stimulation was effective, and required a technician dedicated to tVNS working on several simultaneous research projects. Programs were timed to allow sequential eight-week sessions by avoiding major holiday periods. No patient included in the study dropped out, and questionnaire data were complete for all patients, although some actigraphic records were incomplete owing to patients forgetting to wear the actigraph or to technical failure.

DISCUSSION

Our findings indicate that tVNS is successful in alleviating the symptoms of RLS in approximately 66% of participants (10/15) with severe pharmacoresistant RLS. Patients were required to continue their baseline treatment during the treatment period so that changes in symptoms could be attributed to tVNS. We also found an increase in quality of life and a reduction in symptoms of anxiety and depression. This concomitant improvement in quality of life and mood with the symptoms of RLS after tVNS reflects the burden of RLS. Moreover, we found delivering tVNS in the physiology department setting to be feasible regarding recruitment, retention, data handling, and the intervention. tVNS was safe and well tolerated.

To our knowledge, this study is the first to look at the use of tVNS in patients with restless legs, apart from a single case study reported by Merkl.14 We included only patients with severe pharmacoresistant RLS. Current medical treatments for RLS include iron supplementation, dopamine agonists, alpha-2-delta (α2δ) ligand antiepileptics, and opioids7,23–27 but these are not always effective.5,28 Dopamine agonists are probably the most effective treatment but expose patients to the risk of developing augmentation syndrome, with an incidence of 6% to 8% over six months and 9% per year over ten years for patients treated by pramipexole.29,30 Patients with augmentation syndrome were excluded from our study because in these patients, withdrawal of dopamine agonists is the first line of treatment.31 Poorly controlled RLS causes great

<p>| Table 1. Individual Participant Baseline Data and Stimulation Intensity |
|--------------------------|--------------------------|--------------------------|--------------------------|</p>
<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age (y)</th>
<th>Age at first symptoms (y)</th>
<th>Treatment</th>
<th>Hour of onset of symptoms with treatment</th>
<th>IRLS</th>
<th>RLSQOL</th>
<th>HADA</th>
<th>HADD</th>
<th>Mean stimulation intensity (mA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1</td>
<td>M</td>
<td>73</td>
<td>35</td>
<td>Gabapentin, Tramadol, Codeine</td>
<td>20:00</td>
<td>36</td>
<td>25</td>
<td>11</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>P2</td>
<td>M</td>
<td>47</td>
<td>37</td>
<td>Gabapentin</td>
<td>00:00</td>
<td>30</td>
<td>75</td>
<td>3</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>P3</td>
<td>M</td>
<td>72</td>
<td>55</td>
<td>Rotigotine</td>
<td>02:00</td>
<td>31</td>
<td>62.5</td>
<td>12</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>P4</td>
<td>M</td>
<td>65</td>
<td>55</td>
<td>Pramipexole</td>
<td>19:00</td>
<td>36</td>
<td>50</td>
<td>7</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>P5</td>
<td>F</td>
<td>73</td>
<td>58</td>
<td>Pramipexole Tramadol</td>
<td>16:00</td>
<td>30</td>
<td>47.5</td>
<td>8</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>P6</td>
<td>M</td>
<td>71</td>
<td>52</td>
<td>Pregabalin Pregabalin, Pramipexol, Tramadol</td>
<td>16:00</td>
<td>31</td>
<td>67.5</td>
<td>6</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>P7</td>
<td>F</td>
<td>69</td>
<td>50</td>
<td>Pregabalin</td>
<td>18:00</td>
<td>32</td>
<td>52.5</td>
<td>9</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>P8</td>
<td>M</td>
<td>62</td>
<td>51</td>
<td>Gabapentin</td>
<td>01:00</td>
<td>32</td>
<td>70</td>
<td>3</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>P9</td>
<td>M</td>
<td>67</td>
<td>60</td>
<td>Pramipexole Gabapentin</td>
<td>00:00</td>
<td>35</td>
<td>77.5</td>
<td>8</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>P10</td>
<td>F</td>
<td>62</td>
<td>48</td>
<td>Pregabalin Pregabalin, Tramadol</td>
<td>00:00</td>
<td>29</td>
<td>77.5</td>
<td>5</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>P11</td>
<td>F</td>
<td>62</td>
<td>50</td>
<td>Gabapentin</td>
<td>21:00</td>
<td>29</td>
<td>57.5</td>
<td>17</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>P12</td>
<td>F</td>
<td>27</td>
<td>22</td>
<td>Gabapentin</td>
<td>20:00</td>
<td>29</td>
<td>50</td>
<td>15</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>P13</td>
<td>M</td>
<td>69</td>
<td>40</td>
<td>Pregabalin Pregabalin, Codeine</td>
<td>13:00</td>
<td>33</td>
<td>35</td>
<td>5</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>P14</td>
<td>F</td>
<td>59</td>
<td>50</td>
<td>Pramipexole Gabapentin</td>
<td>19:00</td>
<td>33</td>
<td>40</td>
<td>15</td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td>P15</td>
<td>F</td>
<td>74</td>
<td>58</td>
<td>Pregabalin Pregabalin, Codeine</td>
<td>21:00</td>
<td>38</td>
<td>7.5</td>
<td>21</td>
<td>17</td>
<td>6</td>
</tr>
</tbody>
</table>

F, female; M, male.

| Table 2. Results of tVNS Treatment: Baseline vs End of Session Eight. |
|--------------------------|--------------------------|--------------------------|
| Outcome measures | Baseline | After 8th session of tVNS | p Value* |
| IRLS | 31.9 ± 2.9 | 24.6 ± 5.9 | 0.0003 |
| RLSQOL | 493 ± 18.1 | 80.0 ± 196 | 0.0005 |
| Anxiety HADA | 89 ± 5.4 | 6.2 ± 5.0 | 0.001 |
| Depression HADD | 5.2 ± 4.5 | 4.0 ± 4.0 | 0.01 |
| Actigraphy wrist | Sleep latency (min) | 444 ± 35.9 | 20.9 ± 14.6 | 0.067 |
| Estimated sleep time (h) | 84 ± 5.5 | 81 ± 5.7 | 0.61 |
| Fragmentation index | 62.3 ± 35 | 56.6 ± 26.3 | 0.89 |
| Actigraphy ankle | Moving time % | 21.6 ± 19.2 | 21.7 ± 17.6 | 0.83 |
| Fragmentation index | 63.2 ± 43 | 62.8 ± 36.3 | 0.83 |

*Wilcoxon signed-rank test for paired samples.
suffering to patients in whom chronic pain and continual leg movements deprive them of sleep despite maximal treatment. Pharmacoresistant RLS is relatively frequent: in a large study, more than 8.5% of patients with RLS reported an increase in symptom severity despite treatment of more than 5 points on the IRLS. In many patients, despite careful assessment for secondary causes of pharmacoresistance, no cause is found, and inadequate symptom control despite frequent treatment change is a source of suffering.

The underlying causes of RLS remain unclear. RLS has sensory and motor manifestations: both circuits are modulated by descending signals from the dorsal raphe, the locus coeruleus, and the A11 region in the dorsal-posterior hypothalamus. The principal neurotransmitter in the A11 nucleus is dopamine, which has both excitatory and inhibitory effects depending on concentration, receptor affinity, and receptor actions. Dopamine agonists that target the inhibitory D3 subtype are, at least initially, effective in treating RLS, although long-term treatment leads to upregulation of excitatory D1 receptors in the spinal cord and the development of augmentation syndrome. Iron deficiency plays a role in dopamine function, with low iron concentrations in the substantia nigra in RLS, and clinical improvements noted with iron treatment. Other neurotransmitters play a role: adenosine forms inhibitory D1–A1 heterodimers in the basal ganglia and the spinal cord; iron deficiency also leads to a hypoadenosinergic state, which would reduce the presence of inhibitory heterodimers. Finally, the efficacy of α2δ

Figure 2. Evolution of symptom severity measured by the IRLS. a. Individual evolution of symptoms across the eight sessions with mean indicated in black. b. Mean evolution of symptoms at baseline (session 1) and at the final session (session 8). [Color figure can be viewed at www.neuromodulationjournal.org]

Figure 3. Individual evolution across the eight sessions of secondary outcomes measures with mean indicated in black. a. Quality of life measured by the RLSQOL. b. Anxiety measured by the HADA. c. Depression measured by the HADD. [Color figure can be viewed at www.neuromodulationjournal.org]
ligands such as gabapentin and pregabalin implies a role for glutamate because their action targets glutaminergic neurons in key regions for the causation of RLS symptoms. It has been suggested that the interplay between the dopaminergic and glutaminergic systems through the effects of dopamine on the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid-receptor-evoked responses and N-methyl-D-aspartate (NMDA)-receptor-evoked responses may also explain the effectiveness of molecules that affect NMDA receptors, notably tramadol and methadone.

The mechanism by which tVNS influences RLS is not known. However, tVNS is known to modulate pain perception and cortical excitability. The vagus nerve comprises approximately 80% afferent sensory fibers carrying information from the periphery to the brain. In the central nervous system, the vagus primarily projects to the nucleus of the solitary tract and releases excitatory neurotransmitters (glutamate and aspartate), inhibitory neurotransmitter (γ-aminobutyric acid [GABA]), acetylcholine, norepinephrine, and other neuropeptides for signal transduction. The projections of the solitary tract to brainstem nuclei (locus coeruleus and dorsal raphe magnus) modulate serotonin and norepinephrine release to the entire brain. There is experimental evidence for the role of the vagus nerve in regulating a number of distinct, important physiological pathways, including cerebral blood flow, melatonin, inflammation, glutamatergic excitotoxicity, norepinephrine, and neurotrophic processes. Through efferent and afferent fibers, the vagus nerve regulates numerous central and peripheral key processes.

It modulates monoaminergic nuclei in the brainstem, with effects on the GABAergic, serotonergic and dopaminergic networks. On the basis of these properties, VNS has been used for decades to treat epilepsy, depression, chronic pain, and inflammatory diseases. In light of the proven dysfunctions of the dopaminergic and sensorimotor networks in the pathophysiology of RLS, the therapeutic effects of VNS on RLS could be at least partly explained by the above cited anticonvulsant, serotonergic, and dopaminergic properties of the vagus nerve.

Changes in mood have been found in previous studies of tVNS; indeed, VNS is used to treat depression (Kong et al. for a review) and has been shown to reduce anxiety in patients receiving VNS for chronic pain. Improvements in mood could be due either to a direct effect of tVNS or to a reduction in symptoms. In the latter case, change would be found only in responders to tVNS. Our study did not find this, but we note that the sample size was small. Changes in mood can modulate nociception, and it is possible that mood changes underlie the observed improvements in RLS symptoms and RLSQOL. We were unable to show a significant difference between RLSQOL and HADD/HADA in responders vs nonresponders; it is possible that concomitant changes in mood influenced the results.

We did not find changes in actigraphy, although there was a trend to an improvement in sleep latency. Actigraphy tends to overestimate sleep duration in the presence of long periods of wake after sleep onset, which was often reported by patients with RLS. However, we found an abnormally long mean sleep onset latency of 44 minutes before tVNS, which normalized to a mean of 20.9 minutes after the last session, although this difference was not significant. The estimated sleep duration was within normal limits, but the fragmentation index both before and after tVNS remained high, implying significant sleep fragmentation.

Patients with severe RLS not only feel the need to move their legs before falling asleep and during periods of wake in the night, but 80% of patients have also periodic leg movements (PLM). Our study funding did not include polysomnography, which permits accurate measurement of PLM. A possible objective composite measure of both movements during wake and movements during

![Figure 4](https://www.neuromodulationjournal.org)
sleep (PLM) could be percentage moving time measured by actigraphy during the period in bed. Changes in a patient over time would potentially reflect an effect of treatment. We analyzed moving time from lights out to lights on, which would include both periods with PLM and periods of leg movement due to RLS during wake. Although RLS symptoms vary from night to night, the night-to-night variability of PLM in patients with severe RLS measured by polysomnography has been shown to be low.\textsuperscript{12} To capture potential variability in RLS symptoms, we performed actigraphy across two weeks (weeks 1 and 2, and weeks 7 and 8) and analyzed the results for week 1 and week 8. We did not indicate significant changes in leg movements measured by actigraphy placed at the ankle. We did not perform polysomnography before tVNS, and thus, we do not know whether all patients had PLM during sleep at baseline. Finally, we note that actigraphy using AWD4 actigraphs placed on the ankle is not a sensitive measure of nocturnal movements.\textsuperscript{13}

**Study Limitations**

Our study is a small, nonrandomized pilot study designed to test the feasibility and effect of tVNS in a population of patients with severe RLS. Patients with pharmacoresistant RLS are distressed by their symptoms and symptomatic despite regular changes of medication, even when augmentation syndrome has been excluded. The feeling that no more treatment modalities are available is a source of stress, and inclusion in our study was a relief to many, increasing the possibility of a placebo effect on RLS symptoms, mood, and quality of life. Without a randomized controlled design, we cannot confirm that the improvements in symptoms were due to tVNS. There is no biomarker for RLS, but we measured changes in symptoms on a validated autoquestionnaire, the IRLS, which is the reference standard for studies of treatment in RLS. We did not use sufficiently sensitive actigraphy to determine whether leg movements were affected by treatment. We were not able to show a difference in secondary outcomes linked to responder profile, which may be attributed to the small size of the responder vs nonresponder subgroups. By performing stimulation sessions in a hospital setting, we were able to control the quality of stimulation, but this limited the frequency of sessions.

Finally, no consensus exists on a biomarker of effectiveness of tVNS.\textsuperscript{16} In this study, we monitored the presence of each stimulation during the sessions using the stimulation artifact measured through EEG recording. Measuring effectiveness of tVNS through HRV assessment, specifically the low frequency:high frequency (LF:HF) ratio, could have been an option; however, studies of left ear tVNS have found heterogenous results with both a decrease\textsuperscript{24,25} and increase of the LF:HF ratio.\textsuperscript{26,27} We will measure HRV parameters in our upcoming randomized study, which will have a larger sample size.

Our study found that tVNS was feasible in the setting of a neurophysiology department. Challenges to delivering tVNS for patients with RLS are centered around the need for trained technicians and appropriate stimulation and monitoring equipment. We did not find recruitment or retention to be a problem; indeed, our study was so popular that we rapidly built up a waiting list. Patients found the titration phase of tVNS slightly uncomfortable because the current was progressively increased, but of the patients recruited for the study, all finished the eight sessions and were offered the use of an individually programmed stimulator for ambulatory use. We do not know the optimal frequency or timing of tVNS sessions for RLS; our choice of one session a week during the day was chosen to optimize patient adherence and technician time. Studies in chronic gastroenterologic pain have used multiple daily sessions.\textsuperscript{38,39} Future studies will look at reducing in-hospital sessions and increasing the use of ambulatory sessions, which will enable us to increase the frequency of stimulation to reduce technician time per patient and to increase cost-effectiveness.

**CONCLUSIONS**

RLS is responsible for chronic pain, prolonged sleep onset latency, sleep fragmentation, and anxiety-depressive disorders and has a major impact on the quality of life.\textsuperscript{28} This pilot study of tVNS in patients with severe pharmacoresistant RLS shows that weekly sessions of one-hour tVNS for eight weeks improve symptoms, mood, and quality of life without significant side effects. Further randomized controlled trials of tVNS in RLS are necessary to confirm a positive effect in RLS.

**Acknowledgements**

The authors thank all patients for participating in the study and all the members of the Department of Physiology for various supports, particularly Didier Lajoie, Miakelle Bohic, and Jennifer Bidot for their helpful assistance during the initiation phase of the SMART-VNS\textsuperscript{TM} project.

**Authorship Statements**

Sarah Hartley was responsible for the conceptualization, formal analysis, investigation, methods, visualization, writing–original draft, and review and editing the manuscript. Eric Azabou was responsible for the conceptualization, data curation, formal analysis, investigation, methods, project administration, visualization, writing–review, and editing. Guillaume Bao, Antoine Leotard, and Frédéric Lofaso were responsible for the formal analysis, methods, visualization, and writing–review and editing of the manuscript. Sylvain Chevallier and Marine Zagdoun were responsible for the formal analysis, methods, and writing–review and editing of the manuscript. All authors have approved the final manuscript.

**How to Cite This Article**


**SUPPLEMENTARY DATA**

To access the supplementary material accompanying this article, visit the online version of *Neuromodulation: Technology at the Neural Interface* at [www.neuromodulationjournal.org](http://www.neuromodulationjournal.org) and at [https://doi.org/10.1016/j.neurom.2022.10.046](https://doi.org/10.1016/j.neurom.2022.10.046).


COMMENT

In this study the authors report of the effects of VNS on severe RLS resistant to pharmacotherapy. The authors found that one-hour weekly sessions of tVNS over eight weeks, significantly improved quality of life, anxiety, and depression scores in two-thirds of treated patients. The manuscript is well written, and the results provide a framework for modifying current clinical practice in the treatment of pharmacoresistant RLS.

Christopher Wilson, MD
Avon, IN, USA