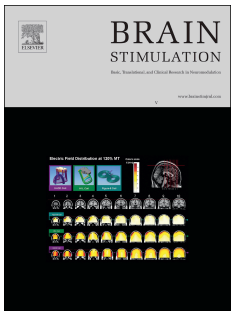
Journal Pre-proof



Vagus nerve stimulation for the treatment of narcolepsy

Yaroslav Winter, Katharina Sandner, Claudio L.A. Bassetti, Martin Glaser, Dumitru Ciolac, Andreas Ziebart, Ali Karakoyun, Assel Saryyeva, Joachim Krauss, Florian Ringel, Sergiu Groppa

PII: S1935-861X(24)00002-0

DOI: https://doi.org/10.1016/j.brs.2024.01.002

Reference: BRS 2532

To appear in: *Brain Stimulation*

Received Date: 24 August 2023

Revised Date: 10 December 2023

Accepted Date: 2 January 2024

Please cite this article as: Winter Y, Sandner K, Bassetti CLA, Glaser M, Ciolac D, Ziebart A, Karakoyun A, Saryyeva A, Krauss J, Ringel F, Groppa S, Vagus nerve stimulation for the treatment of narcolepsy, *Brain Stimulation* (2024), doi: https://doi.org/10.1016/j.brs.2024.01.002.

Vagus nerve stimulation for the treatment of narcolepsy

Running Title: VNS for narcolepsy treatment

Yaroslav Winter[a,b], Katharina Sandner[a], Claudio L.A. Bassetti[c], Martin Glaser[d], Dumitru Ciolac[e], Andreas Ziebart[f], Ali Karakoyun[f], Assel Saryyeva[g], Joachim Krauss[g], Florian Ringel[d], Sergiu Groppa[e]

[a] Mainz Comprehensive Epilepsy and Sleep Medicine Center, Department of Neurology, University Medical Center of the Johannes Gutenberg University Mainz, Mainz, Germany

[b] Department of Neurology, Philipps-University Marburg, Germany

[c] Department of Neurology, Inselspital, University Hospital of Bern, University of Bern, Switzerland

[d] Department of Neurosurgery, University Medical Center of the Johannes Gutenberg University Mainz, Mainz, Germany

[e] Department of Neurology, Focus Program Translational Neuroscience (FTN), Rhine Main Neuroscience Network (rmn^2), University Medical Center of the Johannes Gutenberg University Mainz, Mainz, Germany

[f] Department of Neurosurgery, University Hospital Mannheim, University of Heidelberg, Mannheim, Germany

[g] Department of Neurosurgery, Medical School Hannover, MHH, Hannover, Germany

Corresponding author:

Yaroslav Winter, MD, MSc

Mainz Comprehensive Epilepsy and Sleep Medicine Center, Johannes Gutenberg-University, Langenbeckstrasse 1, D-55131 Mainz, Germany

Email: yaroslav.winter@unimedizin-mainz.de

Number of words in abstract: 227
Number of words in introduction: 792
Number of words in discussion: 844
Number of words in main text: 2709
Number of Figures: 2
Number of Tables: 3

Abstract

Background and Objective: No study on neurostimulation in narcolepsy is available until now. Arousal- and wake-promoting effects of vagus nerve stimulation (VNS) have been demonstrated in animal experiments and are well-known as side effects of VNS therapy in epilepsy and depression. The objective was to evaluate the therapeutic effect of VNS on daily sleepiness and cataplexies in narcolepsy.

Methods: In our open-label prospective comparative study, we included narcolepsy patients who were treated with VNS because of depression or epilepsy and compared them to controls without narcolepsy treated with VNS for depression or epilepsy (18 patients in each group, aged 31.5±8.2 years). We evaluated daily sleepiness (Epworth Sleepiness Scale, ESS) and the number of cataplexies per week before the implantation of VNS and at three and six month follow-ups.

Results: Compared to baseline (ESS: 15.9±2.5) patients with narcolepsy showed a significant improvement on ESS after three months (11.2±3.3, $p < 0.05$) and six months (9.6±2.8, $p < 0.001$) and a trend to reduction of cataplexies. No significant ESS-improvement was observed in patients without narcolepsy (14.9±3.9, 13.6±3.7, 13.2±3.5, $p = 0.2$ at baseline, three and six months, correspondingly). Side effects did not differ between the study groups.

Conclusion: In this first evaluation of VNS in narcolepsy, we found a significant improvement of daily sleepiness due to this type of neurostimulation. VNS could be a promising non-medical treatment in narcolepsy.

Keywords: Narcolepsy, vagus nerve stimulation, excessive daytime sleepiness, cataplexy

Abbreviations: BDI-II: Beck Depression Inventory II; ESS: Epworth Sleepiness Scale; MSLT: Multiple Sleep Latency Test; NT1: narcolepsy type 1; NT2: narcolepsy type 2; REM: rapid eye movement; SSRI: selective serotonin reuptake inhibitors; VNS: vagus nerve stimulation; WCR: weekly cataplexy rate.

Introduction

Narcolepsy is a rare, chronic disease associated with the abnormal regulation of the sleep-wake cycle[1]. A distinction is made between the two types of narcolepsy. Narcolepsy type 1 (NT1) is characterized by the occurrence of cataplexy and orexin deficiency[2]. Orexin (or hypocretin) secreted by neurons in the lateral hypothalamus, increases the activity of multiple brain regions that maintain wakefulness[1]. In patients with NT1, the loss of orexin-producing neurons results in poor maintenance of wakefulness and reduced suppression of rapid eye movement (REM) sleep[2].

Excessive daytime sleepiness (EDS) is usually the first and most disabling symptom of narcolepsy. Clinically, it presents as an increased need for sleep accompanied by automatic behavior and imperative sleep attacks, which intensify during monotonous activities[2]. Cataplexy is another specific symptom of narcolepsy and occurs only in patients with NT1[1]. The primary goal of therapy for patients with narcolepsy is to reduce excessive daytime sleepiness and cataplexies[3]. This can be achieved through a long-term behavioral therapy and pharmacological treatments[1, 3, 4].

Approximately 30-40% of patients suffer from refractory sleepiness despite drug therapy[5]. Tolerance can develop after prolonged therapy, resulting in the loss of efficacy and continuous increase of dose of medication[6]. Good adherence to pharmacological therapy is observed in only 55% of patients[5]. In addition, patients with narcolepsy have a number of comorbidities, such as obstructive sleep apnea (29-33%), obesity (21-32%), arterial hypertension (20-25%), hyperlipidemia (18-25%), anxiety (22-27%) and depression (40-45%) predisposing them to polytherapies and increased risk of drug interactions[3, 7]. Therefore, a further search for new non-pharmacological treatment options is necessary. Neurostimulation has never been investigated in narcolepsy until now. It would improve the adherence and reduce the drug load in these patients. In order to prove its efficacy, neurostimulative approaches should consider the minimal important difference of about 2.5 on the Epworth Sleepiness Scale (ESS) or ≥25%

reduction of EDS compared to baseline, which are known from approvals of narcolepsy therapy by Food and Drug Administration (FDA) or European Medicines Agency (EMA)[8, 9].

Vagus nerve stimulation (VNS) is already being used successfully as a non-drug therapy option for diseases such as epilepsy and depression. As a side effect, increased alertness and reduced sleepiness has already been observed during VNS therapy in patients with epilepsy[10]. Arousal- and wake-promoting effects of VNS have also been demonstrated in animal experiments, including animal models of neurological diseases[11-13].

There are various theories explaining the mechanisms by which VNS might influence wakefulness and alertness (Figure 1). The loss of orexin-producing neurons in the lateral hypothalamus in patients with narcolepsy reduces the activating effects on the locus coeruleus and the basal forebrain accompanied by the decrease in cortical excitation[14]. By its mechanism of action, VNS seems to stimulate these structures, specifically inciting the noradrenergic effects on the locus coeruleus and the cholinergic effects of the basal forebrain[15, 16]. In their mouse model study, Collins et al[12] showed that VNS leads to activation of cholinergic and noradrenergic fibers in the cortex and induces widespread excitation of the cortex. This induced a behavioral change with an increased state of arousal in the mice. This activation persisted in anaesthetized mice, leading the authors to conclude that motor activity alone could not explain this activation. Therefore, they concluded that the VNS, by activating subcortical structures such as the noradrenergic locus coeruleus (over the nucleus of the solitary tract[17]) and the cholinergic basal forebrain, leads to broad activation of the cortex, which in turn leads to behavioral changes with an increased state of arousal.

In the rat model of traumatic brain injury, Dong et al[13] showed that VNS causes the upregulation of orexin-A and the expression of orexin receptor type 1 in the prefrontal cortex. VNS seems to contribute to a better recovery of consciousness in comatose rats after traumatic brain injury, so that a wake-promoting effect of VNS could be postulated.

Other possible effects on wakefulness and alertness are increased cerebral blood flow and an influence on the sleep structure by VNS. In patients with depression and VNS, increased cerebral blood flow in the left posterior limb of the internal capsule, the medial putamen, the

right dorsal anterior cingulate, the right superior temporal gyrus, the left cerebellum and the left dorsolateral prefrontal cortex has been demonstrated[18, 19]. This seems to play a role in the wakefulness and antidepressant effects of VNS[13, 18, 19]. Valdes-Cruz et al[20] also showed that VNS has an effect on sleep structure, which in turn could be involved in the possible wake-promoting effects. Vagus nerve stimulation increased the slow-wave sleep and upregulated the sleep spindles, delta activity and ponto-geniculo-occipital waves in cats.

The aim of this study was to evaluate the effect of VNS on the daytime sleepiness and cataplexy in patients with narcolepsy and to assess its safety profile in these patients.

Methods

Standard Protocol Approvals, Registrations, and Patient Consents

For all participants written informed consent in accordance with the Declaration of Helsinki was obtained before participation and the study was approved by the ethics committee.

Study design and clinical evaluation

Patients aged ≥18 years who had narcolepsy with or without cataplexy (types 1 or 2) and received VNS for the treatment of epilepsy or major depressive disorder (in-label VNS treatment) were included in our study. Narcolepsy was diagnosed according to the International Classification of Sleep Disorders – third edition[21]. The diagnosis was confirmed by polysomnography and a multiple sleep latency test (MSLT), showing two or more sleep onset REM periods and a mean sleep latency of eight minutes or less. All included patients scored >10 on ESS.

Patients without narcolepsy, who received VNS for treatment of depression or epilepsy served as controls. The rationale for inclusion of patients without narcolepsy was to investigate if there is a disease-specific improvement of daily sleepiness in narcolepsy due to VNS in comparison to a general reduction of sleepiness associated with other chronic diseases.

All study participants were treated in the Mainz Comprehensive Epilepsy and Sleep Medicine Center, which is integrated in the Department of Neurology of the University Medical Center of the Johannes Gutenberg University Mainz, Germany. The included patients were participants

in two registries - the Mainz Epilepsy Register (MAINZ-EPIREG) and the Mainz Sleep Register (MAINZ-SLEEPREG). Three months before the baseline (VNS-implantation) and during the entire study period till the last follow-up, patients stayed on unchanged medication for narcolepsy and other concomitant disorders. Implantation of vagus nerve stimulators was performed in the neurosurgical departments from the three German university hospitals - University Medical Center Mainz, University Hospital Mannheim and Medical School Hannover. All patients had the SenTiva Modell 1000 generator implanted, which allows for programming of both daytime and nighttime stimulations with two different regimes. The planned increasing doses regimen after the implantation was based on the dosing guidelines of the manufacture. The initial parameter after the implantation were as follows:

During the day time (8:00 am till 8:00 pm): output current of 0.25 mA, signal frequency of 30 Hz, pulse width of 250 µsec, signal Off-time of 5 minutes and signal On-time of 30 seconds during the day time.

During the night time (8:00 pm till 8:00 am): output current of 0.25 mA, signal frequency of 30 Hz, pulse width of 250 µsec, signal Off-time of 5 minutes and signal On-time of 30 seconds.

The output current during the day time was increased by 0.25mA every two weeks untill the target dose of 2.0mA. In case of side effects preventing the increase of ouput current, the ouput current would have been kept unchanged at the last tolerated dose. In our study population, no side effects occurred that would have prevented the target dose from being reached. All patients have reached the target dose (2.0mA during the day time) after 8 weeks and mantained it during the observational period of 6 months. The applied simulation parameters are appropriate for the use in comorbidities, such as sleep apnea, and therefore no exclusion of patients becase of their comorbidities was performed. Our study was registered at ClinicalTrials.gov (NCT05321355).

To evaluate the effect of VNS on daytime sleepiness, ESS-score was assessed one week prior the VNS implantation (baseline) and at the time points three and six months after the implantation. The assessment of cataplexy frequency was performed by calculation of the average number of cataplexies per week (weekly cataplexy rate, WCR) at the same time

points. Depression was estimated by means of Beck Depression Inventory II (BDI-II). The safety assessment was based on patients' diaries.

Statistical analysis

The statistical analysis was performed using IBM SPSS Statistics Version 23.0 (IBM Corp., Armonk, NY, USA). Data are presented as mean and standard deviation (SD) or median and range.

The between-group differences in demographical and clinical parameters at baseline were assessed by applying a t-test. The repeated measures ANOVA with post-hoc tests was used to compare the changes in ESS, WCR and BDI-II over time. Statistical significance was assumed at a P-value of < 0.05.

Multiple regression analysis was used to prove if the influence of VNS-therapy on the ESS in narcolepsy was independent from the improvement of depression.

Data availability

The de-identified data of subjects are available from the corresponding author upon a reasonable request.

Results

Demographics and clinical characteristics

A total of 36 patients (18 with narcolepsy and 18 controls) were included in the study. Data on demographics and clinical parameters did not differ between the two groups and are shown in Table 1. The indication for VNS implantation was epilepsy in 22 (61.1%) patients and depression in 14 (38.9%) patients. Ten (55.6%) patients had NT1 and eight (44.4%) patients had NT2. Patients with narcolepsy received the following medications: 44.4% (n = 8) modafinil, 16.7% (n = 3) methylphenidate, 38.9% (n = 7) pitolisant, 22.2% (n = 4) solriamfetol, 22.2% (n = 4) sodium oxybate, 27.8% (n = 5) selective serotonin reuptake inhibitors (SSRI) and 11.1% (n = 2) clomipramine.

Clinical outcome

The mean value of the ESS at the baseline was 15.4 ± 3.3 (Table 1). In patients with narcolepsy, there was a significant improvement in ESS after three months (11.2 ± 3.3, $p < 0.05$) and six months (9.6 ± 2.8, $p < 0.01$) compared to baseline 15.9 ± 2.5 (Figure 2). No significant improvement in ESS was observed in patients without narcolepsy. The mean BDI-II value in patients with depression was 18.4 ± 9.7 and in patients with epilepsy 3.4 ± 4.8. The improvement in the ESS in patients with narcolepsy undergoing VNS-treatment was independent from the changes in BDI-II scores. No significant ESS-improvement was observed in patients without narcolepsy (14.9±3.9, 13.6±3.7, 13.2±3.5, $p = 0.2$ at baseline, three and six months, correspondingly, Table 1). In multiple regression analysis, the effect of VNS on ESS was independent from the improvement of depression measured by BDI-II (Table 3).

In patients with narcolepsy, there was a trend in WCR improvement after six months (1.8 ± 2.1) compared to baseline (3.9 ± 4.5) but it did not reach a statistically significant difference ($p = 0.09$). The mean WCR after three months was 2.8 ± 3.1 and did not differ from baseline.

Side effects during VNS therapy are shown in Table 2. We found no significant differences in the frequency of side effects between the patients with and without narcolepsy.

Discussion

To the best of our knowledge, this is the first study on neurostimulation in narcolepsy and the first study investigating the effects of VNS on the symptoms of this disease. Our findings evidenced a significant improvement in the daytime sleepiness, as measured by the ESS, after three and six months of the VNS therapy as compared to baseline. The entire study population consisted of patients who were implanted with VNS because of depression or epilepsy. The only difference between index patients and controls was the presence of comorbid narcolepsy. Interestingly, the effect on ESS was specific for the patients with narcolepsy, since no statistically significant changes were observed in patients without narcolepsy. The attested improvement in daytime sleepiness was independent from the antidepressant effect of VNS. It is worth to mention that the positive effects of VNS on daytime sleepiness in patients with

narcolepsy were more notable with increased duration of VNS. The ESS-change between the time points three and six months can be explained either by the well-known fact that the therapeutic effect of neurostimulation is increasing with the duration of stimulation [22, 23] or by the minimal fluctuations of ESS related to the small sample size. The difference between ESS values at three and six months was small and below the minimal important difference of 2.5 points. The longitudinal effect of VNS in narcolepsy should be investigated in multicenter randomized controlled studies with larger study populations. They also would help to answer the question, if there is effect of VNS on cataplexies. In our study there was only a trend to improvement.

We intentionally compared patients with narcolepsy and patients without narcolepsy experiencing daily sleepiness in this study in order to detect the possible disease-specific effect of VNS in narcolepsy. Comparison of VNS with the best medical treatment in narcolepsy was out of the scope of our study. All the mechanisms mentioned in the introduction and depicted in Figure 1 support our finding and the assumption of an alerting effect and the possible positive influence of the VNS on excessive daytime sleepiness in patients with narcolepsy. However, the exact mechanisms are still not completely understood and the influence of VNS on the symptoms of narcolepsy requires further investigation.

We registered an improvement of ESS by 39.6% at six months compared to baseline, which is higher than recommended clinically important difference for this measure (≥25%)[8]. Also, the absolute difference of 6.3 points on ESS between baseline and follow up at six months was higher than the minimal important difference of 2.5 points[9]. And the absolute difference of 3.6 points on ESS between narcolepsy patients and controls was also above this value. Therefore, our findings confirm the need to conduct a randomized sham-controlled trial of VNS in narcolepsy. Neurostimulation as an innovative approach to treat EDS in narcolepsy has a potential to significantly improve the management of this disease. It would prevent polytherapy in drug-resistant cases and improve adherence. Considering the data on refractory cases and poor adherence, approximately 30% of patients could be possible candidates for neurostimulation. In addition, teratogenic effects of medication could be avoided by the use of

neurostimulation in pregnancy. Further investigation of neurostimulation in narcolepsy could provide new ways to treat this disease and to search for synergistic effects of medication in combination with neurostimulation as it is already being done in epilepsy[24].

We evaluated a special population of patients with chronic diseases (epilepsy, depression), that is why the baseline level of depression and ESS were higher than in the overall population of patients with these diseases. Because of the small size of our study population, comorbidities were precisely evaluated and were not different between study groups. Patients with sleep apnea, which is a prevalent condition in narcolepsy, were sufficiently treated. In a larger study, the influence of the comorbidities can be stronger and especially the influence of sleep apnea. Therefore, we suggest a screening for sleep apnea for all candidates of future studies.

Our study has several limitations. The data collection was not blinded and we did not include a sham-controlled group in our study. However, the comparison to patients with depression and epilepsy experiencing daily sleepiness without narcolepsy revealed a possible specific effect of VNS in narcolepsy, which we tried to explain theoretically in discussion. This was only an open-label study without a sham stimulation and therefore provides only the class III evidence. As long as VNS is only approved for the treatment of epilepsy and depression, it is a challenge to select patients with narcolepsy and these two conditions, where VNS treatment is indicated. To our knowledge, this is the first study that could successfully recruit these patients. The number of patients included was not enough to perform subgroup analyses for NT1 and NT2.

In conclusion, VNS could be a safe complementary treatment option for patients with narcolepsy who did not respond to drug treatment. Our data suggest a positive effect of VNS on daytime sleepiness in patients with narcolepsy of both types. Our open-label study should motivate future randomized sham-controlled studies on VNS in narcolepsy.

Data sharing statement

Data will be provided to any researcher by the corresponding author upon reasonable request.

Author contributions

YW: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Data Curation, Writing - Review & Editing, Visualization, Supervision, Project administration; KS: Conceptualization, Validation, Investigation, Resources, Writing - Original Draft, Writing - Review & Editing; CB: Writing - Review & Editing; MG: Resources, Writing - Review & Editing; DC: Visualization, Writing - Review & Editing; AZ: Resources, Writing - Review & Editing; AK: Resources, Writing - Review & Editing; AS: Resources, Writing - Review & Editing; JK: Resources, Writing - Review & Editing; FR: Resources, Writing - Review & Editing; SG: Conceptualization, Writing - Review & Editing, Supervision, Project administration.

Declaration of Interests

YW reports honoraria for educational presentations and consultations from Angelini Pharma, Arvelle Therapeutics, Bayer AG, BIAL, Bioprojet, Eisai, Idorsia Pharmaceuticals, JAZZ Pharmaceuticals, LivaNova, Novartis and UCB Pharma. SG received compensation for professional services from Abbott, Abbvie, Bial, Medtronic, UCB and Zambon; research grants from Abbott, Boston Scientific, MagVenture, German Research Council and German Ministry of Education and Health. CB, KS, MG, DC, AZ, AK and AS declare no conflict of interest. JK performed consultations for Medtronic and Boston Scientific. FR is a consultant for Stryker, Brainlab, Icotec and Spineart and receives royalties from Spineart.

References

[1] Scammell TE. Narcolepsy. N Engl J Med 2015;373(27):2654-62.

[2] Bassetti CLA, Adamantidis A, Burdakov D, Han F, Gay S, Kallweit U, et al. Narcolepsy - clinical spectrum, aetiopathophysiology, diagnosis and treatment. Nat Rev Neurol 2019;15(9):519-39.

[3] Bassetti CLA, Kallweit U, Vignatelli L, Plazzi G, Lecendreux M, Baldin E, et al. European guideline and expert statements on the management of narcolepsy in adults and children. J Sleep Res 2021;30(6):e13387.

[4] Winter Y, Mayer G, Kotterba S, Benes H, Burghaus L, Koch A, et al. Solriamfetol real world experience study (SURWEY): Initiation, titration, safety, effectiveness, and experience during follow-up for patients with narcolepsy from Germany. Sleep Med 2023;103:138-43.

[5] Pérez-Carbonell L, Lyons E, Gnoni V, Higgins S, Otaiku AI, Leschziner GD, et al. Adherence to wakefulness promoting medication in patients with narcolepsy. Sleep Med 2020;70:50-4.

[6] Winter Y, Lang C, Kallweit U, Apel D, Fleischer V, Ellwardt E, et al. Pitolisant-supported bridging during drug holidays to deal with tolerance to modafinil in patients with narcolepsy. Sleep Med 2023;112:116-21.

[7] Cohen A, Mandrekar J, St Louis EK, Silber MH, Kotagal S. Comorbidities in a community sample of narcolepsy. Sleep Med 2018;43:14-8.

[8] Scrima L, Emsellem HA, Becker PM, Ruoff C, Lankford A, Bream G, et al. Identifying clinically important difference on the Epworth Sleepiness Scale: results from a narcolepsy clinical trial of JZP-110. Sleep Med 2017;38:108-12.

[9] Johansen PM, Trujillo FA, Hagerty V, Harland T, Davis G, Pilitsis JG. Establishing Minimal Clinically Important Difference in Sleep Outcomes after Spinal Cord Stimulation in Patients with Chronic Pain Disorders. Stereotact Funct Neurosurg 2023;101(1):41-6.

[10] Malow BA, Edwards J, Marzec M, Sagher O, Ross D, Fromes G. Vagus nerve stimulation reduces daytime sleepiness in epilepsy patients. Neurology 2001;57(5):879-84.

[11] Cao J, Lu KH, Powley TL, Liu Z. Vagal nerve stimulation triggers widespread responses and alters large-scale functional connectivity in the rat brain. PLoS One 2017;12(12):e0189518.

[12] Collins L, Boddington L, Steffan PJ, McCormick D. Vagus nerve stimulation induces widespread cortical and behavioral activation. Curr Biol 2021;31(10):2088-98.e3.

[13] Dong XY, Feng Z. Wake-promoting effects of vagus nerve stimulation after traumatic brain injury: upregulation of orexin-A and orexin receptor type 1 expression in the prefrontal cortex. Neural Regen Res 2018;13(2):244-51.

[14] Mahoney CE, Cogswell A, Koralnik IJ, Scammell TE. The neurobiological basis of narcolepsy. Nat Rev Neurosci 2019;20(2):83-93.

[15] Hays SA. Enhancing Rehabilitative Therapies with Vagus Nerve Stimulation. Neurotherapeutics 2016;13(2):382-94.

[16] Hulsey DR, Riley JR, Loerwald KW, Rennaker RL, 2nd, Kilgard MP, Hays SA. Parametric characterization of neural activity in the locus coeruleus in response to vagus nerve stimulation. Exp Neurol 2017;289:21-30.

[17] Van Bockstaele EJ, Peoples J, Telegan P. Efferent projections of the nucleus of the solitary tract to peri-locus coeruleus dendrites in rat brain: evidence for a monosynaptic pathway. J Comp Neurol 1999;412(3):410-28.

[18] Conway CR, Sheline YI, Chibnall JT, Bucholz RD, Price JL, Gangwani S, et al. Brain blood-flow change with acute vagus nerve stimulation in treatment-refractory major depressive disorder. Brain Stimul 2012;5(2):163-71.

[19] Kosel M, Brockmann H, Frick C, Zobel A, Schlaepfer TE. Chronic vagus nerve stimulation for treatment-resistant depression increases regional cerebral blood flow in the dorsolateral prefrontal cortex. Psychiatry Res 2011;191(3):153-9.

[20] Valdés-Cruz A, Magdaleno-Madrigal VM, Martínez-Vargas D, Fernández-Mas R, Almazán-Alvarado S. Long-term changes in sleep and electroencephalographic activity by chronic vagus nerve stimulation in cats. Prog Neuropsychopharmacol Biol Psychiatry 2008;32(3):828-34.

[21] Sateia MJ. International classification of sleep disorders-third edition: highlights and modifications. Chest 2014;146(5):1387-94.

[22] Elliott RE, Morsi A, Tanweer O, Grobelny B, Geller E, Carlson C, et al. Efficacy of vagus nerve stimulation over time: review of 65 consecutive patients with treatment-resistant epilepsy treated with VNS > 10 years. Epilepsy Behav 2011;20(3):478-83.

[23] Schulze-Bonhage A, Hirsch M, Knake S, Kaufmann E, Kegele J, Rademacher M, et al. Focal Cortex Stimulation With a Novel Implantable Device and Antiseizure Outcomes in 2 Prospective Multicenter Single-Arm Trials. JAMA Neurol 2023.

[24] Winter Y, Sandner K, Glaser M, Ciolac D, Sauer V, Ziebart A, et al. Synergistic effects of vagus nerve stimulation and antiseizure medication. J Neurol 2023.

Table 1. Demographics and clinical characteristics of patients

	All patients	Narcolepsy	Controls
	N = 36	N = 18	N = 18
Age, years			
mean (± SD)	31.5 (± 8.2)	31.1 (± 8.6)*	32 (± 8.0)*
median (range)	29 (22 - 56)	28.5 (22 - 56)	29.5 (24 - 54)
Gender, n (%)			
male	16 (44.4)	8 (44.4)*	8 (44.4)*
female	20 (55.6)	10 (55.6)	10 (55.6)
Duration of depression (years)			
mean (± SD)	7.3 (± 5.5)	7.0 (± 6.9)*	7.4 (± 6.0)*
Duration of epilepsy (years)			
mean (± SD)	8.7 (± 4.8)	8.9 (± 6.5)*	8.5 (± 5.7)*
Number of ASM at baseline			
mean (± SD)	2.1 (± 1.9)	1.9 (± 2.4)*	2.3 (± 4.1)*
Number of antidepressants at baseline			
mean (± SD)	1.5 (± 1.7)	1.4 (± 2.3)*	1.7 (± 3.0)*
Number of failed ASM prior to baseline			
mean (± SD)	5.2 (± 4.1)	5.9 (± 7.0)*	5.0 (± 6.4)*
Number of failed antidepressants prior to baseline			
mean (± SD)	3.3 (± 5.1)	3.0 (± 6.3)*	3.4 (± 5.9)*
ESS baseline			
mean (± SD)	15.4 (± 3.3)	15.9 (± 2.5)*	14.9 (± 3.9)*
median (range)	15 (8 - 20)	15 (12 - 20)	15.5 (8 - 20)
BDI-II baseline			
mean (± SD)	9.2 (± 10.2)	9.9 (± 11.5)*	8.4 (± 9.0)*
median (range)	4.5 (0 - 28)	3.5 (0 - 28)	7.5 (0 - 27)
BDI-II after 3 months			

mean (± SD)	8.4 (± 9)**	8.6 (± 9.8)**	8.2 (± 8.4)**
median (range)	4 (0 - 24)	3.5 (0 - 28)	7 (0 - 24)
BDI-II after 6 months			
mean (± SD)	8.4 (± 8.5)**	8.6 (± 8.9)**	8.2 (± 8.4)**
median (range)	5.5 (0 - 25)	4.5 (0 - 22)	7 (0 - 25)
Monthly seizure frequency baseline			
mean (± SD)	3.1 (± 2.5)	2.9 (± 5.9)	3.3 (± 6.2)
median (range)	3 (1 - 7)	3 (1 -6)	3 (1 - 7)
Monthly seizure frequency after 6 months			
mean (± SD)	2.5 (± 2.8)***	2.6 (± 6.4)***	2.3 (± 6.9)***
median (range)	3 (1 - 5)	3 (1 -5)	3 (1 - 4)
Comorbidities			
obstructive sleep apnea, n (%)	7 (19.4%)	4 (22.2%)	3 (16.7%)
arterial hypertension, n (%)	5 (13.9%)	2 (11.1%)	3 (16.7%)
hyperlipidemia, n (%)	3 (8.3%)	2 (11.1%)	1 (5.6%)
diabetes mellitus, n (%)	4 (11.1%)	2 (11.1%)	2 (11.1%)
obesity, n (%)	9 (25.0%)	5 (27.8%)	4 (22.2%)

* No statistically significant differences of age, gender, disease duration, number of medications prior and at baseline as well as baseline ESS and BDI-II between the patients with narcolepsy and controls, all $p > 0.05$.

** No statistically significant differences in BDI-II scores between three and six month follow ups and baseline

*** No statistically significant differences monthly seizure frequency between six month follow up and baseline

Abbreviations: ASM, antiseizure medication, BDI-II, Beck Depression Inventory II; ESS, Epworth Sleepiness Scale; SD, standard deviation; VNS, vagus nerve stimulation.

Table 2. Adverse side effects during vagus nerve stimulation

Adverse side effects*	**Narcolepsy**, n (%)	**Controls**, n (%)
No adverse side effects	12 (66.7)	11 (61.1)
Hoarseness	3 (16.7)	4 (22.2)
Coughing	2 (11.1)	2 (11.1)
Post-surgery pain	2 (11.1)	3 (16.7)
Panic attacks	1 (5.6)	0 (0)

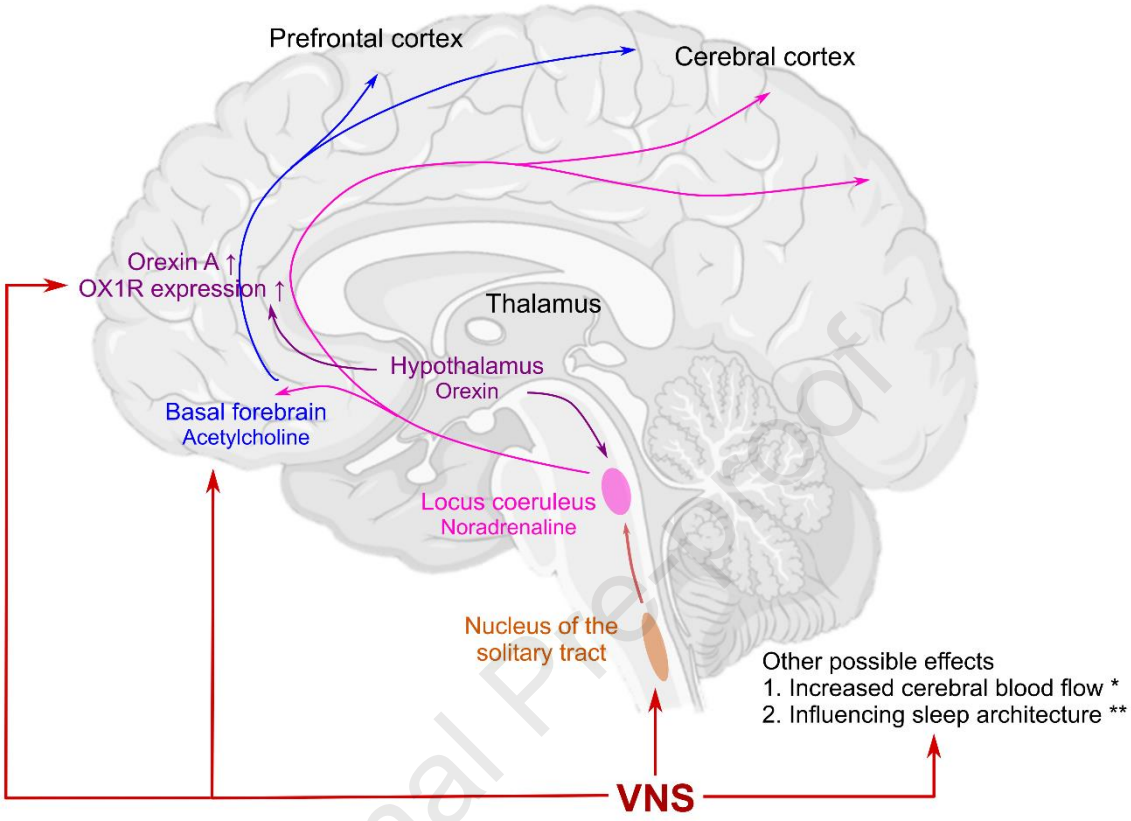
* No statistically significant differences in the frequency of adverse effects between the patients with narcolepsy and controls, all $p > 0.05$

Table 3. Multiple regression analysis factors influencing daily sleepiness on ESS at six months follow-up

	B	**95% CI**	**p-value**
Age	-0.09	-0.23; 0.06	0.22
Female gender	0.87	-1.52; 3.27	0.46
BDI-II at baseline	0.24	-0.27; 0.74	0.35
BDI-II at 6 months	-0.25	-0.85; 0.34	0.39
VNS therapy	-3.97	-6.21; -1.72	0.01
Constant	14.78		<0.001

Abbreviations: BDI-II, Beck Depression Inventory II; ESS, Epworth Sleepiness Scale; VNS, vagus nerve stimulation; B, regression coefficient; CI, confidence interval

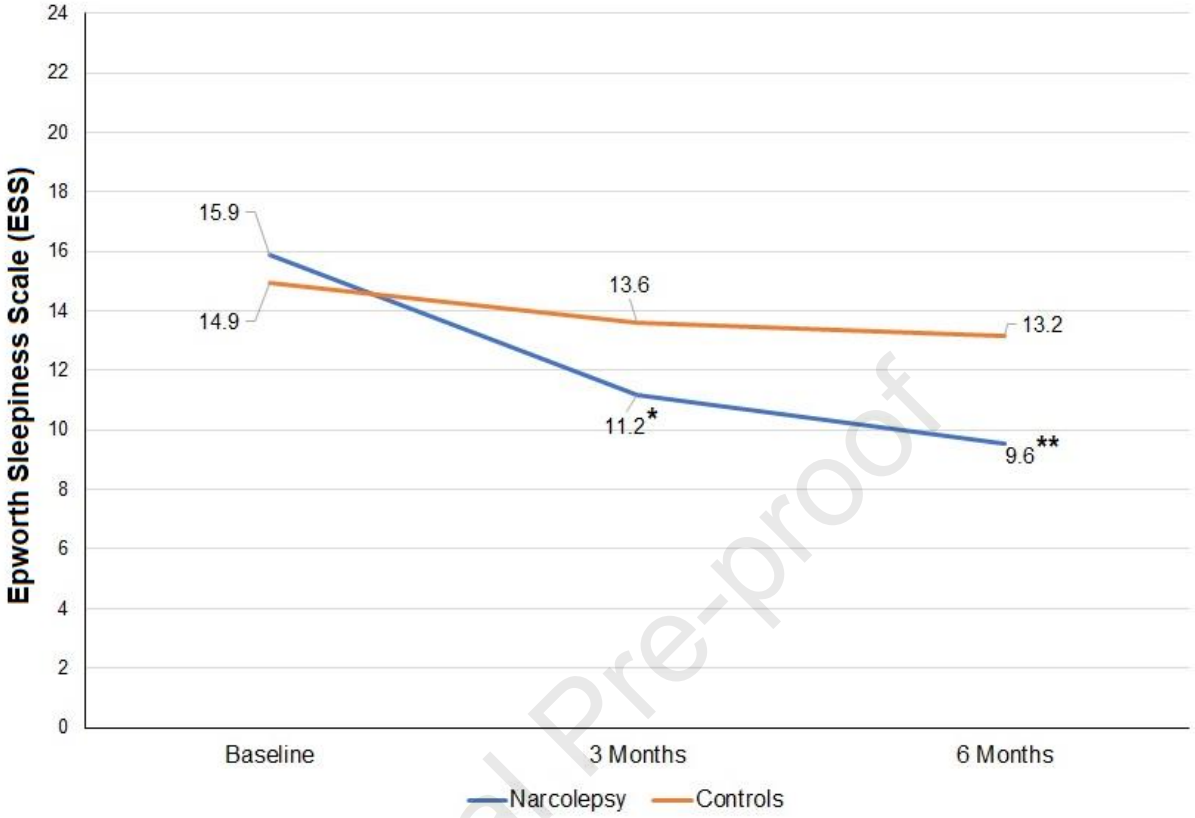
Figure 1. Mechanisms of possible wakefulness- and alertness-promoting effects of vagus nerve stimulation.



***** VNS increases cerebral blood flow in the left posterior limb of internal capsule/medial putamen, the right dorsal anterior cingulate, the right superior temporal gyrus, the left cerebellum and the left dorsolateral prefrontal cortex[18, 19].

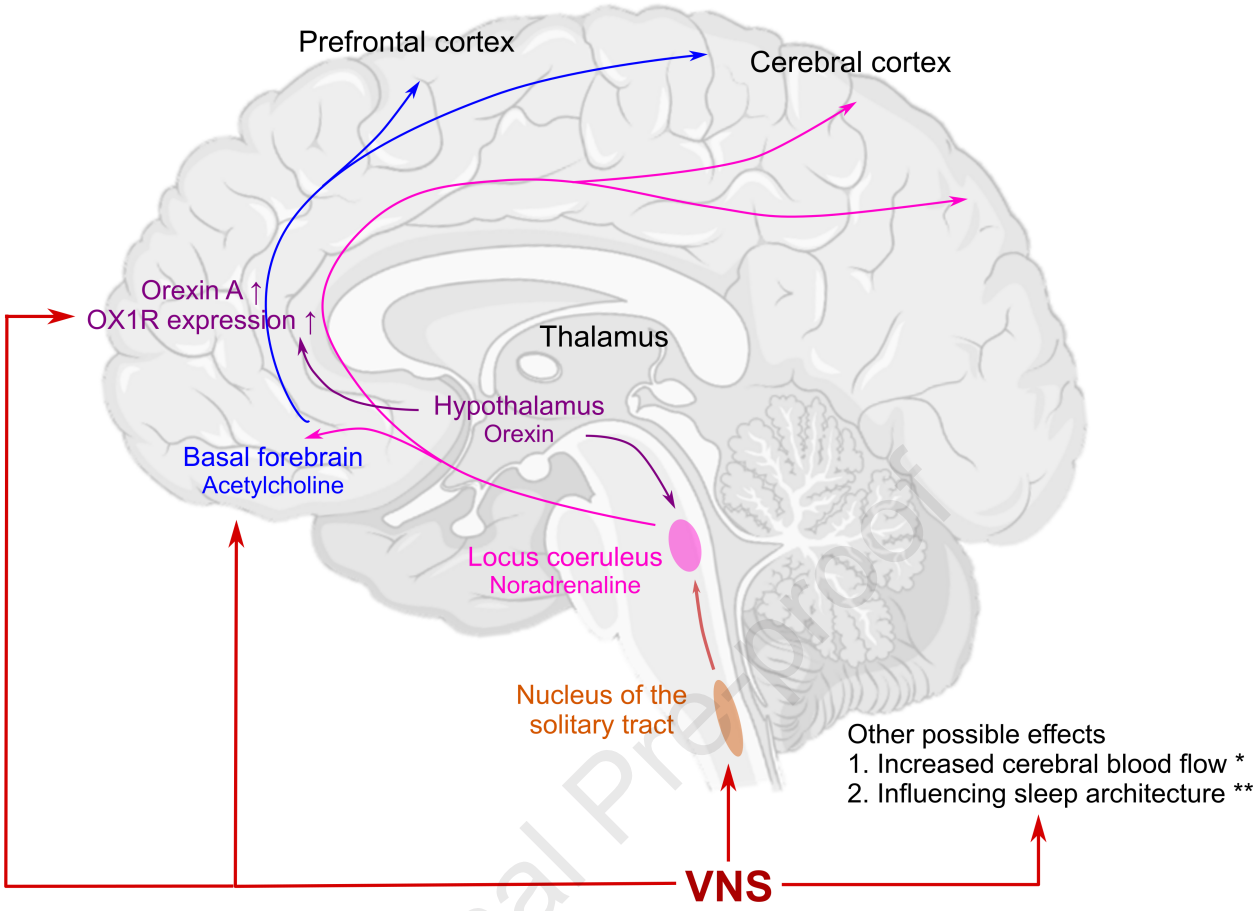
** VNS increases the slow-wave sleep and upregulates the sleep spindles, delta activity and ponto-geniculo-occipital waves in cats[20].

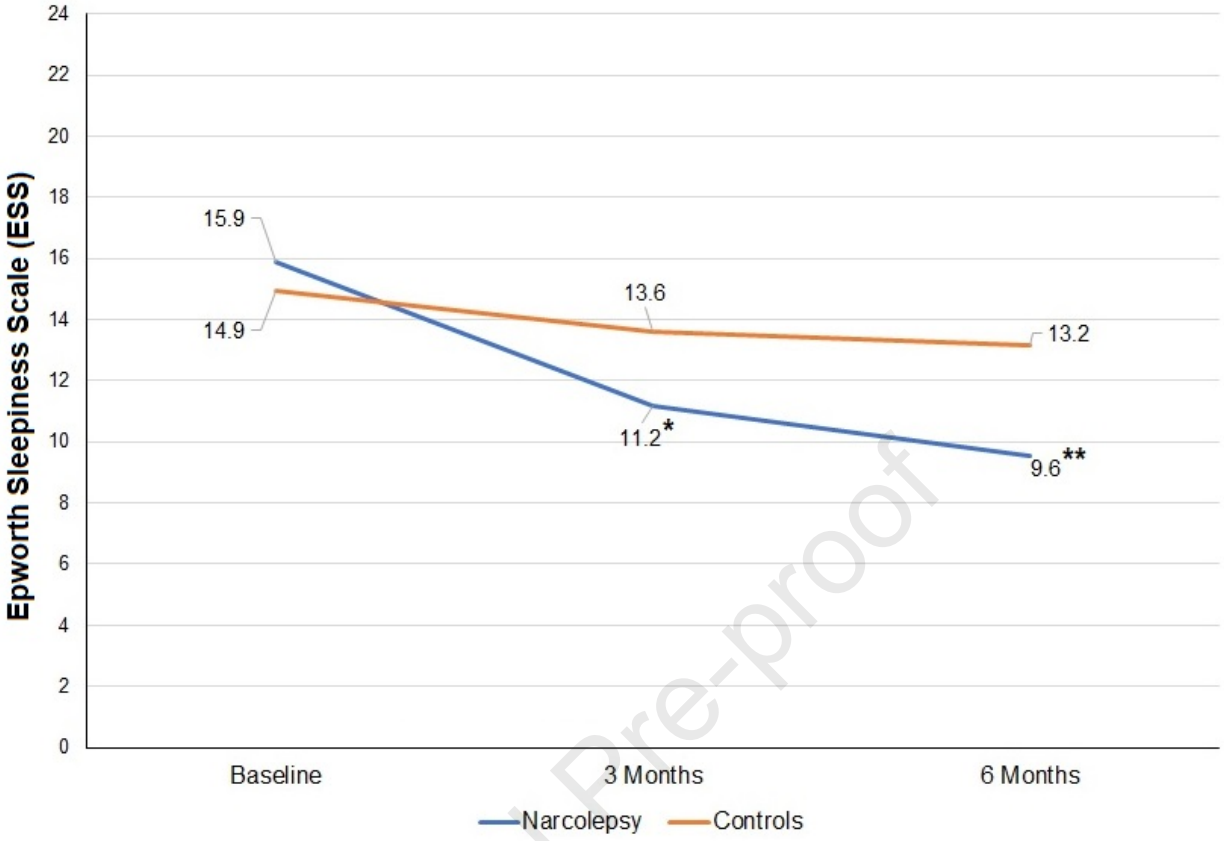
Figure 2. Daytime sleepiness in patients with narcolepsy on vagus nerve stimulation



* statistically significant at $p < 0.05$ compared to baseline

** statistically significant at $p < 0.01$ compared to baseline





Highlights

Vagus nerve stimulation (VNS) shows wake-promoting effects in epilepsy and depression

VNS in the treatment of narcolepsy was not evaluated until now

This first VNS-study in narcolepsy showed significant improvement of daily sleepiness

Neurostimulation could be a promising non-medical treatment in narcolepsy

Declaration of interests

☐ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☒The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

YW reports honoraria for educational presentations and consultations from Angelini Pharma, Arvelle Therapeutics, Bayer AG, BIAL, Bioprojet, Eisai, Idorsia Pharmaceuticals, JAZZ Pharmaceuticals, LivaNova, Novartis and UCB Pharma. SG received compensation for professional services from Abbott, Abbvie, Bial, Medtronic, UCB and Zambon; research grants from Abbott, Boston Scientific, MagVenture, German Research Council and German Ministry of Education and Health. CB, KS, MG, DC, AZ, AK and AS declare no conflict of interest. JK performed consultations for Medtronic and Boston Scientific. FR is a consultant for Stryker, Brainlab, Icotec and Spineart and receives royalties from Spineart.