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Transcutaneous Vagal Nerve Stimulation in Treatment-Resistant Depression: A Feasibility Study

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ABSTRACT

Background: Major depression (MD) contributes significantly to the global burden of disease with up to one-third of patients being treatment resistant. Therefore, the development of new treatment options for treatment-resistant depression (TRD) is needed. Vagus nerve stimulation (VNS) has shown mood improvements in patients with TRD. However, due to high costs related to the implantation and the invasive nature of VNS, an application with transcutaneous VNS (t-VNS) has been developed stimulating a vagal nerve branch in the earlobe (Arnold's nerve). A few studies with t-VNS in MD has shown a possible antidepressant effect, but feasibility is poorly described and patients with TRD have not been investigated.

Objectives: As the full antidepressant effect of t-VNS takes months we wanted to assess feasibility and side effects of daily treatments.

Materials and Methods: Single-arm feasibility trial assessing compliance, usability, side effects, cognitive speed, and depression in a four-week period with a recommended t-VNS stimulation duration of four hours per day in patients with TRD. The primary outcome was compliance with 80% of the recommended daily treatment time.

Results: Compliance threshold was reached for 80.0% of the 20 included participants. Usability was acceptable. Side effects were few, mild or moderate, mostly as local effects at the contact point in the ear. The device was difficult to use for some participants. A statistically significant reduction in depression severity and an increase in cognitive speed were seen with unchanged suicidal ideation and sleep.

Conclusions: We would recommend larger long-term randomized studies of t-VNS to access any antidepressant effect in TRD. The design of the device might be improved for higher usability.

Keywords: Psychiatric somatic therapies, treatment-resistant depression, vagus nerve stimulation

Conflict of Interest: None of the above authors has any conflicts of interest to report concerning this study.

INTRODUCTION

Major depression (MD) is a common and severe illness and a leading contributor to the global health burden and is predicted to become the second leading cause of disability worldwide by the year 2020 (1). Despite the use of antidepressant drugs and a variety of psychological and somatic therapies, treatment resistance develops in a substantial proportion of patients. When applying the most common definitions of treatment-resistant depression (TRD), approximately 13–31% of patients with MD meets the criteria for TRD (2). The burden of TRD is well documented and involves both personal suffering, direct costs such as medical treatment and therapy, and indirect costs, including unemployment and suicide (3). Treatment resistance highlights the importance of developing new treatment options for MD.

Within the neurostimulation field, a number of newer devices are used for TRD such as repetitive transmagnetic stimulation (rTMS), deep brain stimulation (DBS), transcranial applied pulsed electroMagnetic fields (t-PEMF), and implanted vagus nerve stimulation (VNS) (4-6).

The idea of using VNS for depression came from observations of improved mood when administering VNS therapy in epilepsy patients (7). These improvements were not significantly correlated with a reduction in seizure frequency, implying that the improvement was not solely caused by seizure reduction (8). During the last decade, some evidence has accumulated for an

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antidepressant effect in TRD of VNS even though the effect seems to be moderate and with an gradually increasing onset of effect after several months of therapy (9). Surgical intervention is needed to remove/replace the VNS battery, exposing patients to perioperative risks, infection, irritation of the skin, and cardiac events. The electrode implant may carry a risk of nerve damage during implantation or even more when it is removed. Thus, in summary, even though there is a growing evidence of an antidepressant effect of VNS treatment in TRD, the usability is limited due to the relative high costs related to the implantation and the possible damage from lead removal and the need and costs for battery replacement.

On this background, a noninvasive vagus stimulation method has been developed using stimulation of a vagus nerve branch in the skin of the outer ear canal. The stimulus is applied to the specific part of the conchae corresponding to the sensory area of the vagal nerve branch (Arnold's nerve).

Stimulation of the cutaneous branches of the vagus nerve in the ear leads to afferent stimulation of the brainstem (tractus nucleus solitarius) and further to higher brain regions through second (to thalamus) and third order neurons (to primary sensory cortex) within the brain (10). The t-VNS stimulation is believed to affect multiple physiological functions but not targeted at any specific function in the brain. These physiological functions include reduced firing in the central nucleus of amygdala, suppression of epileptiform activity, changes in resting electroencephalogram, increased intracortical inhibition, improvement of maladaptive neuronal plasticity, neuropeptide changes, and modulation of serotonergic and noradrenergic pathways linked to potential antianxiety and antidepressant effects (10).

The sensory innervation by this vagus branch is also associated with the well-known cough reflex (11), and stimulation of the right vagus nerve causes efferent stimulation of the sinoatrial node (12). Therefore, t-VNS is only used in the left ear to avoid bradycardia.

A systematic review and meta-analysis on effect of t-VNS in MD from 2018 (13), including one randomized controlled t-VNS trial from 2013 (14) and two non-randomized controlled t-VNS trials in patients with MD from 2016 and 2018 (15,16), concluded that t-VNS was an effective and safe method for treating MD.

One of the nonrandomized t-VNS studies from 2018 found in fMRI scans that the functional connectivity between the bilateral medial hypothalamus and rostral anterior cingulate cortex was significantly decreased during t-VNS but not during sham t-VNS (16) .

A randomized sham-controlled t-VNS study from 2016 (17) showed a significantly better outcome ($p < 0.05$) in the active t-VNS treatment group compared to a sham group on the HAM-D_{24} scale. This study also made some interesting findings regarding the mechanism of action as they found that the resting-state functional connectivity (rsFC) in the areas of the brain collectively called the default mode network (DMN) was significantly modulated by the active versus the sham t-VNS.

A review from 2019, describing different t-VNS devices, stimulation points, stimulation parameters, and side effects (18) concluded that the optimal type of device and stimulation parameters for t-VNS are still unknown. The review also refers to the great individual variation in nerve fiber types in the auricular branch of the vagal nerve that could account for individual responses to t-VNS (19). Stimulation parameters in the mentioned studies (14-17) varied with frequencies from 1.5 Hz to 25 Hz, and current strengths from 130 μA to 4–6 mA either fixed or patient-selected, and no data is given on what currents were actually used by the patients. The daily total duration of treatment varied from 15 min to 60 min per day.

A review from 2018, describing side effects of t-VNS, when used in a variety of conditions, concluded that t-VNS was well tolerated and safe with the most common side effects being skin irritation at the stimulus site and in less than 1% nasopharyngitis, headache, dizziness, nausea/vomiting, or facial drooping (20).

Even though there is some evidence for an antidepressant effect of t-VNS in MD with a seemingly good feasibility with home-based treatment, and mild side effects, no study has used t-VNS in TRD. We expect that patients with TRD might have more problems using self-administered daily stimulation methods and the aim of this study was accordingly to evaluate the feasibility of t-VNS treatment in patients with TRD by assessing compliance, self-evaluated usability, and side effects of the treatment to evaluate whether longer-term studies are possible in this patient group.

MATERIALS AND METHODS

Study Design

The study design was an interventional, single-arm, prospective feasibility trial. Study duration for each participant was four weeks. The overall duration of the study period was projected to six months. We planned to include 20 participants. Current antidepressant treatment was not allowed to be changed during the four weeks treatment and no other treatment modalities were to be initiated in the study period.

Study Population

We recruited participants from the Psychiatric Centre Copenhagen (PCC) and a psychiatrist's clinic in the private sector in Copenhagen. Participants included from PCC had recently been discharged from inpatients stay. Participants were assessed and followed at the PCC.

Inclusion and Exclusion Criteria

Inclusion criteria were: fulfilling the criteria of a major depressive episode in the M.I.N.I module A (21); a score of 18 or more on HAM-D_{17} (22); age over 18; treatment resistance score of more than 7 assessed by the Maudsley Staging Method (MSM) (23) for the actual depressive episode; willingness to comply with the scheduled trial plan and to use the device for four hours per day for four weeks; understanding the oral and written study information and willingness to sign an informed consent.

Exclusion criteria were: participants with a current addiction to drugs or alcohol; suicidal risk corresponding to a score of 2 or more on the Hamilton depression rating scale item 3; psychotic disorder; bipolar disorder; dementia; actual psychotic depressive episode; subjects with borderline personality disorder; participants under any kind of mandatory treatment; subjects currently enrolled in another investigational treatment study; subjects with significant heart and lung or chronic bowel condition; acute myocardial Infarction or variant angina pectoris or current diagnosis of an arrhythmic cardiac disease or unstable angina or acute coronary syndrome in the previous three months; cardiac pacemaker or ICD or other implantable stimulators (VNS or deep brain stimulator).

Medical Device

The study used the CE certificated t-VNS device NEMOS® (Cerbomed GmbH, Erlangen, Germany) (18). The system includes an external pulse generator, roughly the size and weight of a cellular telephone, and a cutaneous contact electrode that is placed in the auricular tract of the left ear. We have opted for the NEMOS device as the device is currently used by our study group to treat patients with epilepsy and because it has been shown to be well tolerated in a study with patients with tinnitus (24). The NEMOS device stimulates with a 25 Hz pulse with 30 sec on and 30 sec off. The current is adjustable according to tolerance from 0.1 mA to 5.0 mA.

Participants were instructed in the use of the device, and the therapy was done in participants' home.

In this study, participants were advised to titrate the current until a mild tingling sensation in the earlobe was felt and to try to increase the dosage but to stay at a level causing no painful sensation. This procedure was in agreement with the instructions in the user manual. We wanted patients to use the highest tolerable current level as we expected a dose–response effect of current on antidepressant effect. The recommended stimulation time was four hours daily.

Psychometrics

Diagnoses was assessed by the module A, ''Depressive Episode,'' of the M.I.N.I instrument (21), and depression severity was assessed by the HAM-D_{17} (22,25). Treatment resistance was assessed by the MSM (23). The maximum score for the MSM is 15, and the score is categorized into mild: 3–6, moderate: 7–10, and severe 11–15 (26). Usability was assessed by the System Usability Scale (SUS) (27). The participants were evaluated for inclusion/exclusion criteria and provided an informed consent before being enrolled in the study. Sleepiness before and after individual daily t-VNS treatment sessions were self-assessed by the Stanford sleepiness scale (SSS) (28). Participants filled in a daily sleep diary with sleep onset, sleep offset, naps, sleep quality (0–10, 10 = best), and awakenings. Sleep quality was assessed by the Pittsburgh Sleep Quality Index (PSQI) (29) at baseline and endpoint. The self-reported sleepiness and sleep diaries were checked with the participants at the weekly assessments to enhance compliance. Participants were also asked to log the mean electric current used for each day and the total daily stimulation time. Depression severity was assessed weekly with the interviewer-based HAM-D_{17} scale (22,25) by the primary investigator.

Side effects were assessed weekly by the UKU scale, including free text comments (30). Depression severity was also self-assessed with the Major Depression Inventory (MDI) (31), quality of life weekly by the WHO-well-being index (WHO-5) (32), and suicidal ideation weekly by the Suicidal Ideation Attributes Scale (SIDAS) (33). Cognitive and processing speed was measured weekly by the AQT (A quick test of Cognitive speed) (34,35). Adverse events were recorded at each visit. Medications were retrieved from participant case files, and sociodemographic were collected at the baseline visit and from interview.

Outcomes

The primary outcome was compliance with treatment. The predefined threshold for compliance was defined as a mean daily t-VNS stimulation time of more than 3.2 hours, corresponding to more than 80% of the recommended four-hours daily treatment during the four-week study period. Secondary outcomes were scores on the SUS and scores on the UKU side effect rating scale (30). Tertiary outcomes were reduction in blinded and investigator-assessed HAM-D_{17} scores. Explorative outcomes were reductions in scores on the MDI, WHO-5, sleep measures, PSQI, SIDAS, SSS, and AQT naming times.

Data Collection

Participants participated in an initial 1.5-hour interview at baseline and weekly one-hour interviews over a period of four weeks. All t-VNS treatments were self-administrated at the participant's home.

STATISTICS

The analysis of the weekly HAM-D_{17}, MDI, and WHO-5 scores was done within a repeated measure mixed model including visit and covariates for sub-analyses. Rater blinded HAM-D_{17} scores from baseline and endpoint were analyzed with a paired *t*-test. Statistical significance for rejection of the null hypothesis was set at a $p < 0.05$. All analyses were performed using the SAS 9.4 software.

Ethical Considerations

The study was approved by the Ethical Committee (journal number H-18000331, the Danish Data Protection Agency (journal number 2012-58-0004), the Danish Medicines Agency section for Medical Devices (journal number 2018010697), and Psychiatric Centre Copenhagen. The study was monitored by the Good Clinical Practice unit, which performed monitoring visitations during the study (36). Participants were allocated a consecutive trial number (001-020) and registered by initials in the paper Case Report Form. The Trial Master File, which contained the participant's civil registration number, was stored behind double-locked doors. Informed consent was obtained from all participants. While participating in the study, all the participants could continue their regular treatment. We assessed adverse events according to Good Clinical Practice rules.

RESULTS

In all, 20 participants were included in the study from March 2018 to January 2019 with four of the participants dropping out (two at week 4, one at week 2, and one at week 1). In all, 15 participants were included from PCC and five from a psychiatrist's clinic. The drop-out was caused by unwillingness to come to last visit ($n = 1$), being pressed for time ($n = 1$), worsening of depression and admittance to a psychiatric ward ($n = 1$), and difficulties placing the electrode in the earlobe ($n = 1$). The sociodemographic and the use of medication at inclusion are shown in Table 1. Participants had a mean age of 49.4 (SD = 11.2) years, only 5% ($n = 1$) were in full-time employment, and 50% of participants ($n = 10$) were on sick leave at inclusion. The median duration of the actual depressive episode was 31.5 month (IQR 24.0–78.0), 35% of participants had one or more lifetime suicide attempts, and 60% had been treated with ECT in the current episode. Participants were in treatment with a broad range of antidepressants, antipsychotics, mood stabilizers, and anxiolytics (see Table 1).

Table 1. Sociodemographics and Medication.

Sociodemographics	
Age, years, mean (SD) [range]	49.4 (11.2) [30–76]
Gender, female % (*n*)	65.0% (13)
Full-time employment % (*n*)	5.0% (1)
Part-time employment % (*n*)	20.0% (4)
Currently on sickleave % (*n*)	50.0% (10)
Duration of actual depressive episode, median (IQR)	31.5 (24.0–78.0)
Number of previous depressive episodes, median (IQR)	2.0 (0–3.0)
Suicide attempts, lifetime % (*n*)	35% (7)
Alcohol abuse % (*n*)	10% (2)
Smoking % (*n*)	30% (6)
Eliciting factor for depression % (*n*)	80% (16)
ECT in current episode % (*n*)	60% (12)
Drug therapy	
SSRI's % (*n*)	25% (4)
SNRI's % (*n*)	10% (2)
Antipsychotics % (*n*)	60% (12)
Lithium, % (*n*)	25% (4)
Tricyclics % (*n*)	10% (2)
Agomelatine % (*n*)	10% (2)
Benzodiazepines % (*n*)	45% (9)
Benzodiazepine class sleeping drugs % (*n*)	40% (8)
Mood stabilizers, antiepileptics % (*n*)	25% (5)
Mood stabilizers, lithium % (*n*)	20% (4)
MAO inhibitors % (*n*)	10% (2)
Antihistamine % (*n*)	5% (1)
Pregabalin % (*n*)	10% (2)
Mirtazapine % (*n*)	10% (2)
Melatonin % (*n*)	15% (3)
Vortioxetine % (*n*)	15% (3)

The MSM score was 11.7 (SD = 1.9, range 9–14) indicating severe treatment resistance (26).

In all, 18 participants reported stimulation parameters. The mean daily stimulation duration was 3.6 hours (SD = 0.9; range 0.0–5.0 hours), and 89% of participants (16/18) had a mean daily stimulation duration above the predefined threshold of 3.2 hours. The remaining two participants did not report any stimulation parameters but did use the device for 15 and 19 days. Thus, when applying an intension to treat method, 80.0% of participants fulfilled the compliance criteria (16/20). The mean daily stimulation strength of the 18 participants was 1.1 mA (SD = 0.9; range 0.3–5.0 mA).

One participant was admitted to a psychiatric ward due to an anxiety attach. This was categorized as a serious adverse reaction with a probable relation to treatment and reported to the authorities according to the regulatory rules.

In all, nine participants reported one or more adverse events or adverse reactions.

Probable Adverse Reactions

Feeling of depression and exhaustion (pt. 1), feeling of vibration reminding of side effect of earlier electroconvulsive treatment and crippling sensations, and flashbacks (pt. 1), tiredness and strange feelings in the body (pt. 3), pain in neck and pressure in the head and more appetite and anxiety of unusual kind, and headache (pt. 3), intense headache as stimulation strength was increased to 2.0 mA and improved as stimulation was reduced to 1,0 mA (pt. 12), feeling of flaccidness (pt. 14).

Certain Adverse Reactions (pt. 4, 6, 10)

Skin wound at electrode placement area (pt. 4), severe headache necessitating bed rest (pt. 6), redness of skin at electrode placement area (pt. 7), and stinging feeling in the ear (pt. 10).

Serious and Probable Adverse Reactions (pt. 15)

Anxiety and worsening and depression causing admittance to a psychiatric ward.

The mean SUS score was 80.0 (SD = 14.0; range 55–100) indicating acceptable usability of the Nemos system, however for the item 3 (“The system was easy to use”) only 58.8% had a score above 3, and for item 9 (“I felt in control while using the system”) only 76.5% had a score above 3 (both items scored on a modified Likert scale from 0 = quite disagree to 5 = quite agree).

Results from the UKU side effect scale showed a significant increase in the item “increased sleep length” ($p = 0.03$; $F = 5.1$) and “itching in the ear” ($p = 0.05$; $F = 3.9$) from baseline to endpoint. For all other UKU items, the change from baseline to endpoint was insignificant. For items regarding local side effects in the earlobe area, the frequency of visits where patients reported moderate/severe side effect was 13%/2% for itching, 8%/2% for pain, 9.7%/2% for other sensory disturbances, 2%/2% for redness of skin, zero/zero for pressure marks, and 4.5%/1.5% for skin wounds. The actual scores for items in the UKU scale are shown in Table 2.

Ham-D_{17} scores were obtained by a blinded rater for all participants at baseline, but due to unexpected unavailability of the rater only ten participants were assessed blindly at endpoint. These results are therefore not considered valid and are not analyzed.

Mean scores from the HAM-D_{17} scale, assessed weekly by the primary investigator, and from the weekly self-assessed MDI and WHO-5 scales are shown in Figures 1–3. The score changes in these scales, analyzed with data from all five visits, were statistically significant for HAM-D_{17} ($p = 0.03$; $F = 5.5$), HAM-D_6 ($p = 0.002$; $F = 11.3$), MDI (p = 0.0003, $F = 20.2$), and WHO-5 (p = 0.02, $F = 6.1$). The score change on the SIDAS scale was insignificant.

The baseline AQT naming times were within the expected range for patients with TRD, including a low overhead (35). There was a statistically significant decrease in naming times for tables AQT1 ($p = 0.03$, F-test = 5.1), AQT2 ($p = 0.0002$, F-test = 14.8), and AQT3 (p = 0.02, F-test = 10.7) indicating an improvement in cognitive speed (see Fig. 4).

Results from the sleep diaries showed statistically insignificant changes from baseline to endpoint for of all sleep parameters.

Sleepiness assessed before and after each daily t-VNS stimulation, using the Stanford Sleepiness Scale, was 3.7 (SD = 1.0) before stimulation and 3.9 (SD = 1.2) after stimulation ($p = 0.01$, $t = 2.6$) indicating a minor increase in sleepiness.

Sleep quality assessed with the PSQI was very low at baseline with a PSQI global score of 12.2 (SD = 4.3) and a small insignificant decrease (improvement) at endpoint with a score of 11.1 (SD = 4.4; $p = 0.32$).

Table 2. Mean and SD of Adverse Events Scores for Patients in t-VNS Treatment (Score Range From: Score 0 = None, Score 1 = Mild, Score 2 = Moderate, and Score 3 = Severe).

Adverse events scores, mean and (SE)	Baseline	Week 1	Week 2	Week 3	Week 4
Concentration	1.9 (0.6)	1.5 (0.8)	1.6 (0.6)	1.8 (0.7)	1.6 (0.8)
Sleepiness	1.2 (0.9)	1.4 (0.9)	1.1 (0.7)	1.1 (0.7)	0.9 (0.8)
Memory disturbance	1.7 (0.7)	1.8 (0.6)	1.6 (0.5)	1.8 (0.8)	1.5 (0.8)
Depression	2.1 (0.5)	2.0 (0.5)	1.9 (0.5)	1.9 (0.6)	2.1 (0.6)
Anxiety	1.6 (1.0)	1.5 (1.0)	1.3 (1.1)	1.2 (1.2)	1.3 (1.1)
Increased sleep length	0.3 (0.6)	0.5 (0.7)	0.6 (0.8)	0.5 (0.9)	0.7 (0.9)
Reduced sleep length	1.4 (1.1)	1.1 (1.0)	0.6 (0.8)	1.2 (0.9)	1.0 (1.0)
Awakenings	1.4 (0.8)	1.3 (0.2)	1.3 (0.7)	1.7 (0.8)	1.3 (0.7)
Increased dreaming	1.2 (0.9)	1.3 (1.1)	1.5 (0.9)	1.6 (0.9)	1.1 (0.7)
Emotional blunting	0.9 (0.8)	1.0 (0.9)	0.9 (0.5)	1.2 (0.7)	1.1 (0.7)
Nausea	0.3 (0.6)	0.3 (0.6)	0.2 (0.4)	0.6 (0.9)	0.0 (0.0)
Dizziness	0.7 (0.7)	0.2 (0.4)	0.4 (0.7)	0.6 (0.9)	0.3 (0.6)
Itching in ear	0.1 (0.2)	0.1 (0.3)	0.2 (0.6)	0.2 (0.4)	0.3 (0.5)
Pain in ear	0.0 (0.0)	0.2 (0.4)	0.2 (0.6)	0.0 (0.0)	0.1 (0.3)
Other sensory disturbance in ear	0.0 (0.0)	0.1 (0.4)	0.4 (0.7)	0.0 (0.0)	0.1 (0.4)
Redness of ear skin	0.0 (0.0)	0.1 (0.3)	0.3 (0.9)	0.2 (0.6)	0.1 (0.3)
Pressure marks in ear skin	0.0 (0.0)	0.0 (0.0)	0.1 (0.3)	0.1 (0.3)	0.1 (0.3)
Skin wound in ear	0.0 (0.0)	0.0 (0.0)	0.3 (0.9)	0.1 (0.4)	0.0 (0.0)
Headache	0.6 (0.8)	0.6 (0.8)	0.3 (0.6)	0.5 (0.9)	0.3 (0.6)

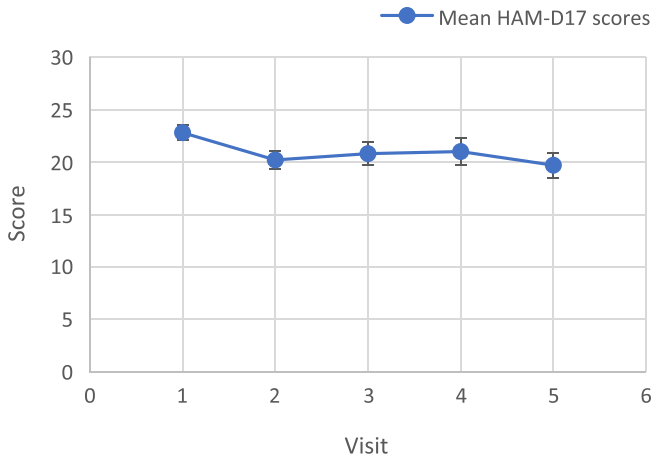

Figure 1. HAM-D17 scores per visit with error bars. [Color figure can be viewed at wileyonlinelibrary.com]

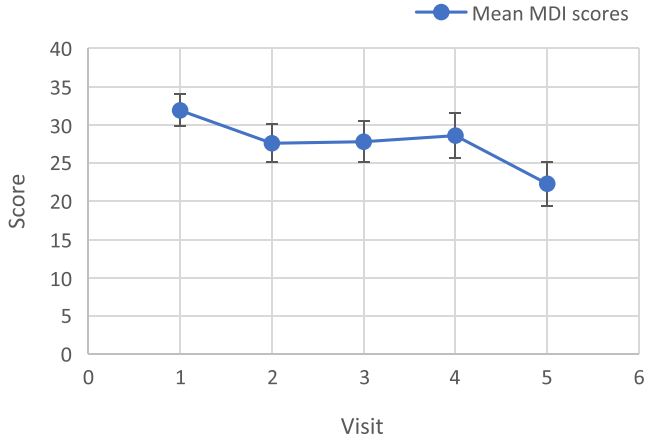

Figure 2. MDI scores per visit with error bars. [Color figure can be viewed at wileyonlinelibrary.com]

DISCUSSION

A number of newer neurostimulation methods such as DBS, rTMS, and t-PEMF have been used in TRD. The evidence base for DBS is still limited and the method requires surgical implantation. The evidence for an effect of rTMS is better established but requires patients to come to the hospital for daily treatments. T-PEMF can be administered at home, but the device is relatively costly and so far only a few and small t-PEMF studies have been carried out in TRD (37,38). The use of VNS is limited due to the need for a neurosurgical procedure and battery replacement (4,5). Thus, the development of a wearable neurostimulation device such as the t-VNS has the propensity to be used on a larger scale in TRD provided that the feasibility is good enough to allow use for extended periods and if an antidepressant effects can be established. In this feasibility trial, we found that the predefined compliance goal was reached in a high number of participants, and side effects were infrequent and mostly mild. There was some local irritation at the ear stimulation point for a few participants. Some participants found it difficult to establish adequate electrical contact in the earlobe, causing the device to make repeated alarms. The total SUS score indicated acceptable usability, but two items indicated that the device was difficult to use for some participants. The drop-out of 20% was rather high, considering the short study duration. The drop-out rate might be reduced by a more patient-friendly device and by including a more stable patient group. The majority of participants included in this study had recently been discharged from inpatient wards and perhaps for some of them the stress of having to use t-VNS

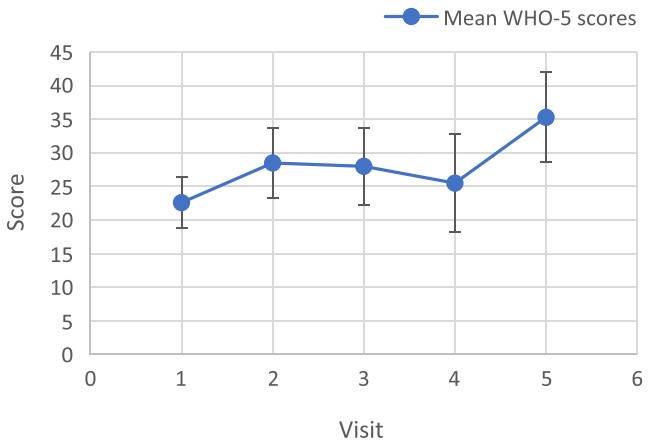

Figure 3. WHO-5 scores per visit with error bars. [Color figure can be viewed at wileyonlinelibrary.com]

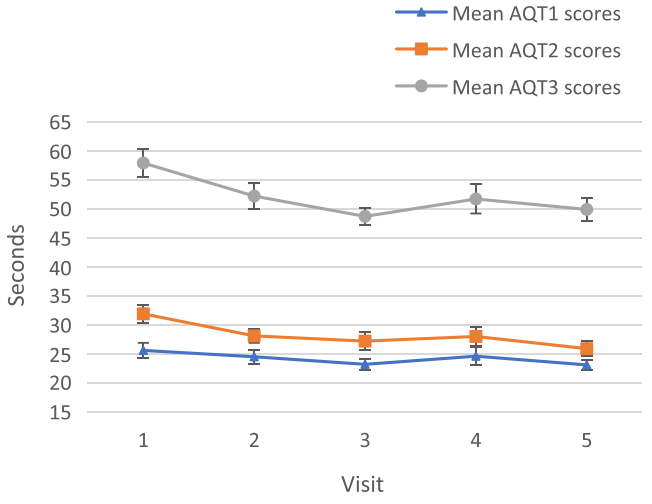

Figure 4. AQT naming times per visit with error bars. [Color figure can be viewed at wileyonlinelibrary.com]

with the current device, and having to come for extra visits, made them drop-out.

The psychometric outcomes showed a statistically significant effect of treatment on several depression outcomes. Since the antidepressant effect of VNS takes months to appear, this effect in t-VNS might be mediated by another mechanism such as a placebo response or perhaps caused by sensorial diversion of attention.

There was no indication of any effect on sleep timing or sleep quality. Specifically, no indication of worsening of suicidal ideation was found.

The cognitive speed measured with the AQT was within the expected range for TRD and a significant reduction was found for all three tables, indicating a possible improvement in cognitive speed, and the found reduction in naming times is probably not caused by a learning effect as this has not been found for this test (35).

The strength of this study is the rigorous design with predefined outcomes, comprehensible assessment of adherence, side effects, stimulation parameters and psychometrics. Main limitations are the low number of participants that increases the risk for type II errors and the short treatment duration that does not allow us to predict whether the treatment will also be tolerated for extended periods.

We opted not to use the built-in adherence reports from the device as we deemed this too difficult for participants to readout and note down. Therefore, we relied on self-report adherence, and there might be some uncertainty in these data. Further development of t-VNS devices might provide easier way to monitor adherence using automatic data capture.

The stimulus parameters used in this study differs somewhat from previous studies where most used a twice-daily stimulation and with shorter stimulation duration. None of the previous t-VNS studies reported mean self-selected current levels but probably some of the studies have used somewhat higher levels (around 4–6 mA) than the ones used in our study.

The relatively high rate of participants fulfilling the compliance criteria might have been inflated by the weekly visits where investigators encouraged patients to use the device according to instructions. Thus, lower rates might be expected in real-life settings, especially when of longer duration.

We need to consider that the observed reduction in depression scores is quite small and that paired analyses can give significant results even with small reductions as there is no between-subject variation in contrast to analyses of randomized trials. Furthermore, this small reduction could easily be a placebo effect even though placebo responses in TRD is usually of a small magnitude, and especially in short-term studies like the current.

CONCLUSION

In conclusion, the results show good compliance, good tolerability, and acceptable usability and there were possible indications of an antidepressant effect and improvement in cognitive speed and quality of life. Based on this pilot study, we would recommend that larger long-term studies are carried out in patients with TRD to access any antidepressant effect. The design of the device might be improved to allow for an easier administration.

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Authorship Statements

Dr. Kristin Evensen and Dr. Klaus Martiny were responsible for obtaining regulatory approvals, patient recruitment and data collection. Dr. Kristin Evensen and Dr. Klaus Martiny prepared the manuscript draft with important intellectual input from Dr. Anne Sabers and Dr. Martin Balslev Jørgensen. All authors contributed to the design of the study, data collection and analysis and the writing and acceptance of the manuscript. All authors had complete access to the study data.

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COMMENTS

This study, although few patients, could provide a rationale for using a non-invasive form of VNS for resistant depression. As reported by the authors, adverse reactions are frequent and in patients with depression can lead to cessation of external stimulation. It is necessary to improve the technique for this reason (1).

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Evensen et al. report a trial of transcutaneous vagus nerve stimulation (t-VNS) in a small cohort of treatment-resistant patients, with at-home use of the device and weekly check-ins. They demonstrate feasibility of the trial design (80% retention) and possibly an early antidepressant effect. They also identify some cutaneous side effects that would need to be managed in a larger trial design, and hint at a possibility for cognitive improvement. These results are far from definitive, given the relatively small sample size, the minimally blinded design, and the potential for non-specific therapeutic effects. Nevertheless, this represents the most treatment-resistant population ever treated with t-VNS. Moreover, it establishes the feasibility of at-home

treatment and the types of adherence issues one might expect in a more formal trial. This will be important groundwork as we continue to expand the neurostimulation options for patients with depression.

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