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Improving neural control of gait in Parkinson's disease

Submission date	Recruitment status	[X] Prospectively registered
09/07/2021	No longer recruiting	[X] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
23/08/2021	Completed	[_] Results
Last Edited	**Condition category**	[_] Individual participant data
28/09/2023	Nervous System Diseases	[_] Record updated in last year

Plain English summary of protocol

Background and study aims
Problems with walking and thinking are common in people with Parkinson's disease. Research has shown that there is a loss of chemicals other than dopamine in the brain in people with Parkinson's such as acetylcholine. Acetylcholine is a special chemical in the brain and the body that for example controls muscles and has been shown to play an important role in memory, thinking and walking. This is important as changes in the way people with Parkinson's walk can increase the risk of falling. Researchers are interested in a new treatment known as non-invasive vagus nerve stimulation (nVNS). The vagus nerve is a nerve located in the neck and is an important player in transferring information between the brain and the body. nVNS uses a small handheld device placed on the neck to stimulate the vagus nerve. Stimulating the vagus nerve may increase the amount of acetylcholine available in the brain. A recent study showed that a single dose of nVNS may improve walking in people with Parkinson's. Researchers are now looking to verify these findings and to check that this treatment is acceptable to people with Parkinson's. The aims of this study are to increase the amount of acetylcholine in the brain by using nVNS to boost the cholinergic function and in turn improve walking, thinking and memory in people with Parkinson's.

Who can participate?
Patients with Parkinson's disease who can walk unassisted for at least 2 minutes, are on stable medication for the preceding month and anticipated over the next 3 months and are aged less than 75 years.

What does the study involve?
Participants undergo memory tests, a walking test and other assessments. Participants will be randomly split to receive either the 'active' or 'placebo' treatment. The participant (and their carer if they will accompany the participant) will be shown how to use the nVNS device and asked to self-administer two stimulations to the neck for 2 minutes with 1-5 minutes between stimulations, and asked to use the device twice a day for 2 minutes (total 8 minutes of stimulation per day) for 12 weeks. At 12 weeks the researchers will repeat the measurements including walking, thinking and memory assessments and compare the active and placebo

groups. They will also ask the people with Parkinson's about their experience of using the device. The researchers will repeat most of the assessments again at 24 weeks after participants have stopped using the device to see if there are any carry-over effects of the intervention.

What are the possible benefits and risks of participating?
The potential benefits of participating may include improvement in walking, thinking and memory in those participants in the active treatment group, but those on the placebo treatment will not receive the treatment. The risks of taking part are low and the researchers will carefully monitor any serious side effects that may come up from using the device but none were reported in the initial small single-dose study. The nVNS treatment device has been used worldwide on over 2500 patients with no serious side effects reported. The device has received a CE mark (CE 571753) from the British Standards Institute. Mild side effects have been reported by a small number of participants (1-3%) including burning/tingling sensations, muscle discomfort, pain at the stimulation site and skin irritation/inflammation (from the gel used with the device). Given the extensive and excellent safety record of the nVNS device and vagus nerve stimulation in general, the researchers believe that the risks are very small and much less than reported with drug treatments. The inclusion and exclusion criteria are in accordance with safety data and participants reported by the device manufacturer ElectroCore.

Where is the study run from?
Newcastle University (UK)

When is the study starting and how long is it expected to run for?
December 2019 to August 2024

Who is funding the study?
1. Parkinson's UK (UK)
2. Dunhill Medical Trust (UK)

Who is the main contact?
1. Dr Hilmar P. Sigurdsson, hilmar.sigurdsson@newcastle.ac.uk
2. Mrs Heather Hunter, heather.hunter1@newcastle.ac.uk
3. Dr Alison J. Yarnall, alison.yarnall@newcastle.ac.uk

Study website
https://bam-ncl.co.uk/

Contact information

Type(s)
Scientific

Contact name
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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
292216

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
CPMS 49595, IRAS 292216

Study information

Scientific Title
Adjunctive vagus nerve stimulation for improving neural control of gait in Parkinson’s disease

Acronym
AdVaNSING-PD

Study objectives
The primary aim of this study is to generate clinical, digital and laboratory data to assess the safety, tolerability, feasibility and potential effectiveness of two doses of non-invasive vagus nerve stimulation (nVNS) for 12 weeks in people with Parkinson’s. This pilot study will determine whether a larger definitive future study of nVNS would be safe, justified and feasible. The study will also explore the effects of multi-dose nVNS treatment on gait as proof of concept and to estimate standard deviations to enable sample size calculations for a future trial. Further explorations of the effect of nVNS on cognition, heart-rate variability and other non-motor symptoms will be completed.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 05/08/2021, East Midlands - Derby Research Ethics Committee (The Old Chapel, Royal Standard Place, Research Ethics Office, NG1 6FS; +44 (0)207 104 8211; derby.rec@hra.nhs.uk), REC ref: 21/EM/0177

Study design
Randomized; Interventional; Design type: Treatment, Device

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details to request a participant information sheet

Health condition(s) or problem(s) studied
Parkinson’s disease

Interventions
Participants will be asked to visit the research gait laboratory on three occasions separated by 12 weeks (for a total duration study duration of 24 weeks). All assessments will take place at the Clinical Ageing Research Unit (CARU), Newcastle Upon Tyne.

During the first study visit (baseline) participants will provide written informed consent. A screening interview will be completed to assess disease severity (MDS-UPDRS-III), concomitant medication and global cognition (Montreal Cognitive Assessment). A medical examination will be performed to confirm exclusion criteria. Following baseline assessments including motor, cognitive and autonomic functioning in addition to venous blood samples, participants will be allocated at random (using a balanced randomisation process) to one of two intervention arms to receive either active or sham nVNS or sham nVNS. Participants in the active group will receive non-invasive transcutaneous cervical Vagus Nerve Stimulation (nVNS) using the gammaCore® (electroCore, Basking Ridge, NJ, USA) handheld nVNS device. The device emits a low-voltage 5 kHz sine wave electrical signal burst that repeat once every 40 milliseconds (25 Hz frequency, maximum voltage: 24V, maximum intensity: 60 mA). Participants in the sham group will receive a device that is identical to the active nVNS device including appearance, user interface, weight, and audible feedback but delivers an electrical stimulus that causes a buzzing sensation to the skin but does not stimulate the vagus nerve. For the intervention, the two stimulation surfaces will be coated with conducting gel before being applied to the neck. The correct treatment site will be located, the stimulation surface placed on one side of the neck (left) and the stimulus applied twice for 120 seconds with 1-5 minutes between dosages. Two doses of active and sham stimulation will be self-administered twice a day for 12 weeks in the morning and afternoon. Participants in both arms will be shown how to deliver the intervention in CARU by a member of the research team who will be unblinded and will be followed up with phone calls to check progress.

All assessments will be repeated following the 12-week intervention period. Participants will additionally be asked to complete a questionnaire on nVNS device tolerability. The third visit (24

weeks) will assess any possible carry-over effects. Clinical, gait and cognitive assessments will be repeated. No post-assessment intervention will be carried out. No venous blood samples will be collected.

Adverse events will be recorded throughout the study period. During the 12-week intervention period, participants' ambulatory activity and gait will be measured using small, lightweight, body-worn sensors worn on the lower back. The sensors will be worn for 7 days. Falls will be recorded prospectively using standardised falls diaries, sent out on a monthly basis with a pre-paid envelope. A member of the study team will conduct regular telephone interviews to verify the information. Both participants and experimenters are blinded to the intervention.

In addition to receiving active or sham stimulation, samples of blood serum and plasma will be collected from all participants by venepuncture.

Intervention Type
Device

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
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Primary outcome measure
1. Intervention safety measured by recording adverse events using self-reports and clinical judgment of the Chief investigator with interim phone calls at 4 and 8 weeks and at 12 weeks.
2. Process indicators of the study: recruitment and randomisation rates defined by:
2.1. Proportion of eligible patients who consent to participate in the trial at baseline
2.2. Proportion of enrolled patients who successfully complete follow-up at 12 and 24 weeks
3. Acceptability of study design including attendance rates, completion of nVNS, experience of intervention, retention and reasons for drop-outs, suitability of the intervention package, as assessed by questionnaires at 12 weeks
4. Tolerability of multi-dose nVNS measured using self-reported compliance with interim phone calls at 4 and 8 weeks and at 12 weeks

Secondary outcome measures
1. Change in gait measured using an instrumented walkway and body-worn sensors at 12 and 24 weeks
2. Change in macrostructural gait characteristics including volume, variability, pattern of walking bouts and steps measured using body-worn sensors and 7-day free-living monitoring at 12 and 24 weeks
3. Change in attention and fluctuating attention measured using the simple reaction time (SRT), choice reaction time (CRT) and digit vigilance (DV) tasks (fluctuating attention is determined by the coefficient of variance of the three tasks) at 12 and 24 weeks
4. Change in executive function measured using the One Touch Stockings of Cambridge (OTS) from the Cambridge Neuropsychological Test Automated Battery (CANTAB) computerised battery at 12 and 24 weeks
5. Change in memory measured using the Paired Associates Learning (PAL) from CANTAB at 12 and 24 weeks
6. The number of falls, fall rate and time to first fall measured prospectively using standardised falls diaries during the 12-week intervention period

7. Change in autonomic function and heart-rate variability components measured using a cardiac monitor at 12 and 24 weeks

Overall study start date
19/12/2019

Completion date
31/08/2024

Eligibility

Key inclusion criteria
1. Diagnosis of Parkinson's disease, as defined by the UK Brain Bank Criteria
2. Hoehn and Yahr stage I – III
3. Stable medication for preceding one month and anticipated over next 3 months
4. Able to walk independently without aid for a minimum of 2 minutes without rest
5. Able to provide informed consent
6. Aged <75 years

Participant type(s)
Patient

Age group
Adult

Upper age limit
75 Years

Sex
Both

Target number of participants
Planned Sample Size: 40; UK Sample Size: 40

Key exclusion criteria
1. Parkinson's disease dementia or significant cognitive impairment (Montreal Cognitive Assessment (MoCA) score <21)
2. History of stroke, traumatic brain injury, intracranial aneurysm, intracranial haemorrhage, brain tumour or atypical parkinsonian disorder
3. Unstable medical condition in the last 6 months, or planned surgeries that may involve implants within the next 6 months
4. Prescribed centrally acting anticholinergics (e.g., amitriptyline) and cholinesterase inhibitors
5. Severe orthopaedic or neurological (excluding Parkinson's disease) pathology that will adversely affect gait
6. Pain at the nVNS treatment site (e.g. dysaesthesia, neuralgia, cervicalgia)
7. Previous use of nVNS stimulator device, including previous participation in nVNS research
8. Women of child-bearing potential or who are pregnant
9. Active participation in another interventional trial or exposure to an experimental drug or intervention
10. Has a lesion (including lymphadenopathy), previous surgery (including carotid

endarterectomy or vascular neck surgery) or abnormal anatomy at the treatment site (open wound, rash, infection, swelling, cut, sore, drug patch, surgical scar[s])
11. Has known or suspected severe atherosclerotic cardiovascular disease, severe carotid artery disease (e.g. bruits or history of TIA or stroke), congestive heart failure (CHF), known severe coronary artery disease or prior myocardial infarction
12. Abnormal baseline electrocardiogram (ECG) within the last year (e.g. second or third-degree heart block, prolonged QT interval, atrial fibrillation, atrial flutter, history of ventricular tachycardia or ventricular fibrillation, clinically significant premature ventricular contraction)
13. Uncontrolled high blood pressure (systolic >160 mmHg, diastolic >100 mmHg) after three measurements within 24 hours
14. Has had a previous unilateral or bilateral vagotomy
15. Has been implanted with metal cervical spine hardware, other metallic implants or implantable medical device (such as a deep brain stimulator, hearing aid implant, pacemaker, implantable cardioverter defibrillator, cranial aneurysm and/or cranial aneurysm clips, history of facial/orbital/metallic fragments, implanted electronic device, neurostimulator, valve replacements/stents, metallic implants/prostheses) near the stimulation site (such as stent, bone plate or bone screw)
16. History of syncope or seizures (within the last 2 years)
17. Patients with an active cancer or are in recent remission of cancer
18. Clinically significant hypotension, bradycardia or tachycardia
19. Known carotid atherosclerosis
20. Insufficient comprehension of the English language

Date of first enrolment
15/11/2021

Date of final enrolment
31/01/2024

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Freeman Hospital
Freeman Road
High Heaton
Newcastle upon Tyne
United Kingdom
NE7 7DN

Sponsor information

Organisation
Newcastle upon Tyne Hospitals NHS Foundation Trust

Sponsor details
Newcastle Joint Research Office
Regent Point
Newcastle-Upon-Tyne
England
United Kingdom
NE3 3HD
+44 (0)191 282 5490
Nuth.nuthsponsorship@nhs.net

Sponsor type
Hospital/treatment centre

Website
http://www.newcastle-hospitals.org.uk/

ROR
https://ror.org/05p40t847

Funder(s)

Funder type
Charity

Funder Name
Parkinson's UK; Grant Codes: G-1903

Alternative Name(s)

Funding Body Type
Private sector organisation

Funding Body Subtype
Associations and societies (private and public)

Location
United Kingdom

Funder Name
Dunhill Medical Trust; Grant Codes: RPGF1906\154

Alternative Name(s)

The Dunhill Medical Trust, DMT

Funding Body Type
Private sector organisation

Funding Body Subtype
Other non-profit organizations

Location
United Kingdom

Results and Publications

Publication and dissemination plan
1. The researchers aim to publish the protocol.
2. Planned publication in a high-impact peer-reviewed journal in 2024.

Intention to publish date
31/10/2024

Individual participant data (IPD) sharing plan
All data generated or analysed during this study will be included in the subsequent results publication.

IPD sharing plan summary
Other

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		03/02/2023	06/02/2023	Yes	No
HRA research summary			26/07/2023	No	No