Spinal cord stimulation therapy for patients with Parkinson’s disease and gait problems (STEP-PD): study protocol for an exploratory, double-blind, randomised, placebo-controlled feasibility trial

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ABSTRACT

Introduction Gait difficulties are common in Parkinson’s disease (PD) and cause significant disability. These symptoms are often resistant to treatment. Spinal cord stimulation (SCS) has been found to improve gait, including freezing of gait, in a small number of patients with PD. The mechanism of action is unclear, and some patients are non-responders. With this double-blind, placebo-controlled efficacy and feasibility clinical and imaging study, we aim to shed light on the mechanism of action of SCS and collect data to inform development of a scientifically sound clinical trial protocol. We also aim to identify clinical and imaging biomarkers at baseline that could be predictive of a favourable or a negative outcome of SCS and improve patient selection.

Methods and analysis A total of 14 patients will be assessed with clinical rating scales and gait evaluations at baseline, and at 6 and 12 months after SCS implantation. They will also receive serial 18F-deoxyglucose and 18F-FITC PET scans to assess the effects of SCS on cortical/subcortical activity and brain cholinergic function. The first two patients will be included in an open pilot study while the rest will be randomised to receive active treatment or placebo (no stimulation) for 6 months. From this point, the entire cohort will enter an open label active treatment phase for a subsequent 6 months.

Ethics and dissemination This study was reviewed and approved by the Committee on Health Research Ethics, Central Denmark RM. It is funded by the Danish Council for Independent Research. Independent of outcome, the results will be published in peer-reviewed journals and presented at national and international conferences.

Trial registration number NCT05110053; ClinicalTrials.gov Identifier.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Several studies on spinal cord stimulation (SCS) have shown promising improvements in the affected gait of patients with Parkinson’s disease (PD). However, they have been limited by unblinding, lack of randomisation and/or true placebo control. Furthermore, the manner of action in the positive outcomes seen with SCS has yet to be elucidated.

WHAT THIS STUDY ADDS

⇒ This is to our knowledge the first placebo-controlled, randomised, double-blinded trial with imaging designed to investigate SCS as treatment of gait problems in patients with PD. The clinical assessments of gait problems in participants include both testing at hospital visits and a longer monitoring in patients’ home settings with a triaxial, wearable device. This trial includes 18F-FDG-PET and 18F-FITC-PET imaging in order to investigate mechanisms of actions of SCS and possible imaging outcome measures in future trials.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE AND/OR POLICY

⇒ The spinal cord stimulation therapy for patients with Parkinson’s disease trial is a feasibility study aimed to obtain pivotal information on recruitment of participants, tolerability (including adverse events), sample size requirements and clarification of outcome measurements in order to plan and conduct a large, multicentred trial. The imaging analyses of this study may allow us to define a subgroup of patients with PD who benefit from the SCS treatment and thereby avoid unnecessary interventions.

INTRODUCTION

Parkinson’s disease (PD) is a chronic neurodegenerative disorder affecting more
Spinal cord stimulation (SCS) is a surgical treatment used as a treatment for chronic neuropathic pain not responding to other conventional treatments. Several studies have shown an improvement in gait function in patients with PD following SCS for back pain. More recently, a small number of patients with PD with gait dysfunction (without back pain) were treated with encouraging initial results on gait function and with few adverse events.

The Spinal cord stimulation therapy for patients with Parkinson’s disease (STEP-PD) trial aims to assess the safety and feasibility of burst SCS as treatment of gait disorder in PD, such as FoG. The protocol is presented here according to the Standard Protocol Items: Recommendations for Interventional Trials checklist. Furthermore, this trial will investigate possible changes following SCS in the cholinergic activity and glucose metabolic patterns of cortex and associative cortical-subcortical loops with positron emission tomography (PET).

**STUDY OBJECTIVES**

**Primary, exploratory clinical end points**

1. To establish proof of concept by changes in Postural Instability and Gait Difficulty (PIGD) subscore of the Movement Disorder Society Unified Parkinson’s Disease Rating Scale (MDS-UPDRS). This subscore is the sum of 2.12 (Walking and balance), 2.13 (Freezing), 3.10 (Gait), 3.11 (Freezing of gait) and 3.12 (Postural stability).

2. Evaluation of the safety and tolerability of SCS treatment in patients with PD.

**Secondary, exploratory clinical end points**

1. Objective changes in gait assessments with stride length measurement, timed up and go test (TUG), TUG test with dual task (TUG-DT), 20m walking test, 20m walking test with obstacles, step length (ratio between the average number of steps and distance during the 20m test) as well as the figure of 8 test.

2. Objective changes in postural stability and balance by Berg’s Balance Scale.

3. Objective changes in gait function at home using biometric data collected by a waist-worn triaxial accelerometer over 6 days.

4. Overall changes in symptoms of PD, assessed by the four subscales of the MDS-UPDRS.

5. Subjective changes in symptom severity and improvements in quality of life as measured by Activity-specific Balance Confidence Scale (ABC), New Freezing of Gait Questionnaire (NFOGQ), 36-Item Short Form Survey (SF-36) and Parkinson’s disease questionnaire.


7. Assessment of clinical features/clinical phenotypes at baseline that may be predictive of favourable or negative outcome of SCS.

**Imaging end points**

1. The extent and the time course of changes in resting metabolic brain networks (measured with serial 18F-deoxyglucose (18F-FDG) PET scans) following SCS in patients with PD and gait problems and to determine the relationship of these changes to clinical responses.

2. The extent and the time course of changes in cholinergic function (measured with serial 18F-FOBV PET scans) following SCS in patients with PD and gait problems and to determine the relationship of these changes to clinical responses.

3. Specific changes in brain structural or functional connectivity and/or levels of abnormal cholinergic function at baseline that may be predictive of favourable or negative outcome of SCS.

**METHODS**

**Design**

This trial is comprised of an open-label, pilot study and a prospective, double-blind, randomised, placebo-controlled trial followed by a 6-month open extension. All patients will receive implantation of a complete SCS system (see below). The pilot arm of the study will include two patients who will receive the active treatment and neither they nor the investigators will be blinded. This is to gain proficiency with the required techniques along with facilitating an estimate of effect size in the main study group.

Subsequently, 12 patients will be randomised by sealed envelopes to either active SCS treatment or placebo in a double-blind procedure. Placebo in this case refers to operative implantation of an SCS.
Surgical implantation of an SCS device

The surgical implantation of an SCS device is a standardised procedure, done under local anaesthesia, in which an electrode is implanted in the epidural space of the spinal canal. The SCS implantations will be performed by an experienced implantor (author JCHS, KM or ANG) under light sedation and local anaesthesia. All patients will be implanted with a linear 3–6 70 cm 8-contact wide-spaced SCS lead (Boston Scientific, Marlborough).

The lead will be implanted via a percutaneous approach with a lumbar entry to the epidural space and fluoroscopy-guided rostral advancement of the lead. The lead tip will be placed in the midline at vertebral level Th8-10. Placement of the lead will be tested intraoperatively by a specialist nurse with conventional square-wave stimulation pattern, frequency 40–100 Hz, pulse width 300–500 µs. The stimulation should elicit paraesthesia in the back of both thighs; if this is not attainable, the lead will be repositioned until the intended paraesthesia are achieved.

When intended paraesthesia coverage is achieved, the lead will be fixated to the erector spinae fascia and subcutaneously connected to an implanted pulse generator (WaveWriter Alpha Prime 16 IPG, Boston Scientific), which serves as both the battery and pulse generator for the electrical field.

The procedure will be performed under antibiotic prophylaxis (single shot 1500 mg cefuroxime). Fourteen days after surgery, the patients will be randomised to the active stimulation or placebo group. The surgeons or responsible nurse will in both cases use the Bluetooth remote controller in a similar fashion, so the patient cannot tell whether the implanted pulse generator (IPG) is turned off or started on a non-paraesthetic burst stimulation setting of 6 microburst pulses with an interburst frequency of 40 Hz and an intraburst frequency of 450 Hz. For each patient, stimulation settings are progressively increased with tonic stimulation until the occurrence of paraesthesias. Once the lowest threshold of paraesthesias is established, the amplitude is reduced by 50% and the paradigm switched to burst stimulation. The investigators responsible for the clinical evaluation and imaging analyses will likewise be blinded to this. Three months after randomisation, all patients will visit the non-blinded staff for a check-up of the IPG device settings to ensure no accidental turn-off in the active stimulation group as well as adjustment of stimulation settings, using the same algorithm as described above, at 50% of the paraesthesia threshold. Double blinding is maintained as the procedure will be the same for all patients, and the blinded investigators will not be present.

Clinical examinations

Clinical examinations of possible improvements will be performed as described below at baseline, 6 months and 12 months. The MDS UPDRS, Berg’s Balance Scale, New Freezing of Gait Questionnaire (NFOGQ), ABC-scale, and MoCA will be used to assess the severity of PD and gait

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Box 1 Inclusion and exclusion criteria of the STEP-PD study

**Inclusion criteria**

1. Idiopathic PD diagnosed according to the MDS clinical diagnostic criteria by a movement disorders neurologist.
2. Presence of gait functional impairment, defined as the presence of Freezing of Gait in the medication ON-state, despite optimal medical management.
3. Optimal medical management, defined as being stable in PD medication at least 1 month prior to surgery and not expected to need any changes during the first 6 months of participation.
4. Able to walk independently without an aid for a minimum of twenty metres without rest.
5. Absence of secondary causes of gait problems.
6. Able to understand study requirements—able to provide consent.
7. Above 50 years of age.

**Exclusion criteria**

1. The presence of another significant neurological/psychiatric disorder or significant disease including contraindications to SCS surgery.
2. Presence of cognitive impairment, either previously diagnosed or as a score of <23 on the Montreal Cognitive Assessment (MoCA).
4. History of stroke or structural lesions on CT/MRI that could interfere with image analysis or could be responsible for the patients’ symptoms.
5. History of chronic pain and severe degenerative spine disease with or without chronic pain.
6. History of drug addiction or dependency.
7. Previous DBS surgery for PD.
8. Pregnancy or breast-feeding.

DBS, deep brain stimulation; MDS, Movement Disorder Society; SCS, spinal cord stimulation; STEP-PD, spinal cord stimulation therapy for patients with Parkinson’s disease.

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A device that will not be switched on. At the end of the study period, patients in the placebo group will have the option of a 6-month extension of active treatment. Patients will be recruited according to inclusion and exclusion criteria as listed in box 1. The pilot patients will receive the same examinations as the patients enrolled in the placebo-controlled phase.

For the purposes of this study, FoG is defined according to the first question of the NFOGQ, as a transient feeling of the patients’ feet being nailed to the floor despite the intention to walk. Furthermore, verification by the consultant neurologist and the occurrence of at least an episode of FoG in ON state during the screening assessment are required.

Patients who regularly use an aid such as a cane or walker are eligible for inclusion, so long as they are able to perform the gait assessment unaided and satisfy the criteria mentioned above. Prior to inclusion, all participants will be seen by a consultant neurologist and their medications reviewed. For patients who experience ‘wearing off’ fluctuation and FoG during OFF periods, medications will be adjusted in order to minimise these symptoms.
problems. Quality of life assessment will be done using the SF-36 and PDQ-39 questionnaires. Furthermore, patients’ gait will be assessed with TUG, TUG-DT, 20 min walking test, and 20 m walking test with obstacles, stride length and the figure of 8 test. The gait will be video recorded to illustrate any improvements to the patients. All these tests will be administered at the neurology clinic at Aarhus University Hospital (by authors MHT and VSH). All tests and functional assessments will be performed in the best medication ON state, as reported by the patients after the usual dose of their medication, in order to ensure that any measured effects on functional parameters of gait are not due to variations in medication status. Furthermore, we will assess gait function at home. For this, we use a waist-worn triaxial accelerometer (STATON, Sense4Care, Barcelona, Spain) for home detection of freezing of gait and other gait parameters, for example, stride length and falls over the course of 6 days prior to and the 6 days at each study visit (baseline, month 6, month 12).

**PET-CT and MRI imaging**

Imaging visits will also be at baseline, 6 months and 12 months. On each of these time points, changes in the brain cholinergic function and overall cortical metabolism will be assessed. $^{18}$F-fluoroethylbenzovesamicol ($^{18}$F-FEOBV) PET is an in vivo marker of the brain vesicular acetylcholine transporter (VACHT), which provides information of the functional integrity of the brain cholinergic neurotransmitter system. $^{18}$F-FDG PET is an in vivo marker of regional cerebral glucose metabolic rate (by the marker of synaptic activity, rCMRGlc). All PET scans will be performed on a Siemens Biograph Vision 600 scanner and coregistered to CT. Furthermore, at baseline only, patients will have T1 and T2 MRI scans for a detailed view of anatomical structures and neuromelanin sensitive sequences to assess the integrity of locus coeruleus on a 3 Tesla General Electric Company Signa MR PET scanner.

**Patient and public involvement**

Participants were recruited from the Movement Clinic of the Department of Neurology at Aarhus University Hospital and by public announcement in media, on social media and presentation at meetings hosted by the Danish Parkinson’s Foundation. Once the trial results have been published, participants will be informed by a study newsletter suitable for a non-specialist audience.

**Study setting and timeline**

This study will be conducted at the Departments of Neurosurgery, Neurology and Nuclear Medicine at Aarhus University Hospital in Denmark. Recruitment of patients started in the fall of 2021 and all patients are expected to be included before fall 2022. The study duration includes a 1-year follow-up and all examinations will be completed before the end of 2023.

**PET imaging data analysis**

Quantification of $^{18}$F-FDG PET scans will be performed using previously reported procedures. The optimal modelling approach for $^{18}$F-FEOBV PET is as previously referenced. Analysis of PET scans will be performed using both a region of interest (ROI) approach sampling hypothesised areas and exploratory statistical parametric mapping (SPM). For each subject, ROIs will be defined on the individual CT and copied onto coregistered PET images. ROIs will include putamen, caudate nuclei, ventral striatum, thalamus, red nucleus, amygdala, hypothalamus, locus coeruleus, median raphe and the ventral tegmental area. In addition, an anatomical probabilistic template that divides the entire brain into 62 cortical and subcortical volumes of interest, which has been defined on the Montreal Neurological Institute brain template, will be used to extract cortical data (eg, anterior cingulate, posterior cingulate). SPM will allow automated interrogation of parametric images across the whole brain volume at a voxel level to localise significant differences in tracer uptake without a priori selection of target regions.

The primary end points for the imaging analyses are the between-group differences in striatal and extrastriatal tracer uptake/binding.

**Statistics**

Between-group comparisons of clinical scores from baseline to follow-up will be analysed using difference between means.

We estimated a power of 96% for the sample size of 12 participants on the primary clinical end point, the PIGD subscore. An SD of normal progression over 1 year in patients with PD with gait problems (MDS-UPDRS Motor subscore Part III Gait score $\geq$ 1) was obtained using the Parkinson’s Progressive Markers Initiative database and a significant difference in scores set to 3 points. Between-group comparisons of PET findings will be performed using analysis of variance (ANOVA).

Based on the previous studies and previous experience with $^{18}$F-FEOBV PET, we estimate the mean values of uptake for the tracers within striatal and extrastriatal structures will have an SD of 20%. With this variance, the proposed sample size will provide us with 90% power to detect a 20% difference in mean update of $^{18}$F-FEOBV PET in extrastriatal ROIs ($p<0.01$) between groups.

Correlations between PET findings and clinical scores will be assessed with the Spearman non-parametric correlation statistic.

**Safety of SCS treatment in PD and reporting of adverse events**

The following definitions will be applied in the reporting of adverse events:

- **Adverse event (AE):** any untoward medical occurrence in a patient or clinical study subject.
- **Serious adverse event (SAE):** any untoward and unexpected medical occurrence or effect that:
  1. Results in death.
  2. Is life threatening—refers to an event in which the subject was at risk of death at the time of the event; it does
not refer to an event which hypothetically might have caused death if it was more severe.

3. Requires hospitalisation, or prolongation of existing inpatients’ hospitalisation.

4. Results in persistent or significant disability or incapacity.

5. Is a congenital anomaly or birth defect.

Medical judgement will be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, which will also be considered serious.

All adverse events will be reported. Depending on the nature of the event the reporting procedures below will be followed.

**Non-serious AEs**

All such events, whether expected or not, will be recorded.

**Serious AEs**

All SAEs will be collected and recorded whether they are:

- ‘Related’, that is, resulted from the administration of any of the research procedures.
- ‘Unexpected’, that is, an event that is not an expected occurrence.

**DISCUSSION**

The treatment refractory problem of the parkinsonian gait problems reflects our lack of knowledge concerning the pathologic mechanisms involved. Recent work has implicated cholinergic dysfunction in PD secondary to degeneration of brainstem locomotor regions such as the PPN, which is involved in the control of movement initiation and body equilibrium. However, so far, the response of postural and locomotor symptoms to interventions such as cholinesterase inhibitors or PPN DBS (that both enhance cholinergic neurotransmission) has been disappointing with a great deal of variability in reported responses among patients.

This variability in treatment response to therapy is probably related to the heterogeneity of mechanisms of postural and gait abnormalities across the PD population, suggesting the importance of phenotyping patients with PD with postural and gait problems when starting a therapeutic agent or recruiting patients in clinical studies to investigate new strategies for these problems.

SCS is based on stimulation of the spinal dorsal column by a weak electrical current delivered by implanted leads. The SCS leads come in different forms and in most cases have 8–16 electrodes, capable of producing a programmable and, thus, customisable electrical field. Until recently, most SCS protocols and stimulation paradigms used for treatment have relied on regularly spaced waves of stimulation at a frequency of typically 40–1000 Hz and pulse width of 100–400 ms, often termed tonic stimulation. One major drawback of this paradigm is that it produces slight paraesthesias, corresponding to the area of stimulation. For research purposes, this form of stimulation, thus, precludes a true double-blinded placebo-controlled design. Recently, however, several manufacturers of SCS devices have introduced burst stimulation paradigms. Under a burst stimulation paradigm, the stimulation is delivered as clusters, or bursts, of rapid action potentials followed by periods of dormancy. Therapeutic stimulation under this paradigm does not produce paraesthesias and is, thus, imperceptible to the patient. This allows for a double-blinded study design.

The trials performed on SCS treatment so far have left several unanswered questions that need to be addressed before this procedure can be used more widely in patients with PD with gait problems. First, all the published studies are either single-blinded or unblinded and carried out in small cohorts of patients with PD. Second, while these studies have shown that, overall, SCS seems to have a beneficial effect on gait in PD, they have also shown a heterogeneous outcome, as some patients had a poor response to treatment. Third, patient selection and gait characterisation in these studies were limited, and this lack of clinical phenotyping could have been responsible for the heterogeneous outcome of these studies. Fourth, mechanisms of actions of SCS are uncertain or unstudied in these papers.

Therefore, a prospective, double-blind clinical trial with a scientifically sound study protocol in larger cohort of well-characterised patients is required in order to provide clear Class I evidence whether SCS is effective in improving gait function in PD. The present placebo-controlled, feasibility study will provide crucial information that will allow us to design such a large, multicentred trial. In particular, it will help us:

1. Establish the following feasibility indicators: recruitment rate, consent rate and retention rate; participant adherence, burden and tolerability; adverse events.

2. Estimate SD of clinical effect of burst SCS to enable sample size calculations for the future trial.

3. Refine outcome measures for future studies by assessing the effects of burst SCS on several clinical and imaging measures.

The design of this trial includes several clinical end points to explore the assessment of parkinsonian gait and balance impairment. The PIGD subscore of MDS UPDRS is chosen as a primary, exploratory outcome as it includes both subjective and objective evaluation of gait. There is, to our knowledge, no consensus of a clinically significant difference in the PIGD subscore and we, therefore, suggest three points as a definite, significant change after intervention.

Additionally, the mechanisms of action of SCS in patients with PD with gait problems are uncertain, as they have not been fully investigated so far. Animal models of PD, including non-human primates, show that SCS improves locomotion by activating the dorsal column–medial lemniscal pathway that in turn desynchronises abnormal corticostral oscillations.

ascending lemniscal and extralemniscal pathways to the brainstem and thalamus that may modulate the supplementary motor area (SMA) are also highly connected to the cholinergic PPN in the brainstem. In turn, the SMA has corticofugal projections to PPN, as part of the circuit that controls anticipatory postural adjustments.  

Therefore, SCS might modulate the activity of SMA, globus pallidus and PPN that are impaired in patients with FoG. PET has been extensively used to assess the effects of pallidotomy on the brain cholinergic function and the motor and associative cortical-subcortical loops.  

PET can be used to assess in vivo changes induced by SCS on the brain cholinergic function and the motor and associative cortical-subcortical loops.  

Therefore, PET imaging with 18F-FEOBV and 18F-FDG PET before and after SCS treatment could significantly improve the understanding of the mechanisms of actions of SCS and its effects on brain cholinergic neurotransmission and resting metabolic brain networks. This knowledge may be helpful in selecting the right patient group for the procedure.

ETHICS AND DISSEMINATION

This study was reviewed and approved by the Committee on Health Research Ethics—Central Denmark Region and will be conducted according to the Danish Act on Data Protection (Registration number: 1-10-72-44-21). All participants give written informed consent and are free to withdraw without giving reason at any time without prejudicing further treatment. Any adverse events, related or unrelated to this trial, will be treated, and records will be kept for all participants. Adverse events will be reported to the authorities according to Danish law.

We intend to disseminate and publish the results of this study whether they are positive, negative or inconclusive. The results of the study will be published in high-impact, interdisciplinary journals and presented at international and national conferences. Furthermore, all results from the clinical trial (the two pilot-arm patients and the 12 participants in the main study) will be published at ClinicalTrials.gov.

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Acknowledgements We thank our study coordinator Rikke Van Damens (Department of Nuclear Medicine and PET Aarhus University Hospital and Aarhus University), neurosurgical nurse Anne Knudsen (Department of Neurosurgery, Aarhus University Hospital), and the Danish Parkinson’s Association for distributing our call for participants. We used the SPIRIT checklist when writing our report (11).

Contributors MHT, VSH and NP have drafted the first version of this paper. The remaining authors, who have contributed to the study design and will be involved in the conduction of the trial, have revised it and provided criticisms and suggestions.

Funding This work is supported by the Danish Council for Independent Research, grant number 0134-00305B.

Competing interests None declared.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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