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Clinical evaluation of Deep Brain Stimulation of Nucleus Accumbens for Opioid Relapse Prevention: protocol of a multi-centre, prospective and double-blinded study

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Abstract

Introduction： Deep brain stimulation (DBS) of the Nucleus Accumbens (NAc) is a potentially new surgical treatment for Opioid dependence. However, it is currently controversial on the implementing of NAc-DBS for patients due to the potentially risks. The aim of our study is mainly to investigate the therapeutic efficacy of bilateral NAc-DBS in patients with refractory substance dependence (RSD).

Methods and analysis： 60 patients with RSD will be enrolled in this multicentre, prospective, observational study, and will be followed up for 25 weeks (6 months) after surgery. Patients with RSD who meet the criteria for NAc-DBS surgery will be allocated to either the early stimulation group or the late stimulation group based on the randomized ID number. The primary outcome was defined as the abstinent rate at 25 weeks after DBS stimulation on, which will be confirmed by the opiate urine tests. The secondary outcomes include changes in visual analog scale (VAS) craving score for opioid drugs, body weight, psychological evaluation measured using Hamilton Depression Scale（HAMD-17), Hamilton Anxiety Scale (HAMA), Pittsburgh sleep quality index(PSQI), Fagerstrom Test Nicotine Dependence assessment (FTND), Social Disability Screening Schedule (SDSS), Activity of Daily Living Scale (ADL), 36-Item Short Form Health Survey (SF-36) and safety profiles of both groups.

Ethics and dissemination： The study received ethical approval from the Medical Ethical Committee of Tangdu Hospital, The Fourth Military Medical University. The results of this study will be published in peer-reviewed journals and presented at international conferences.

Trial registration number： NCT03424616; Pre-results

Keywords: *Deep Brain Stimulation, Nucleus Accumbens, Opioid Relapse Prevention*

INTRODUCTION

Background and rationale

Among various functional brain diseases, substance dependence is a behavioral pathology characterized by compulsive drug-seeking and taking with progressive loss of control over drug intake, which leads the addicted subjects to a number of adverse social and health consequences[1]. Heroin and other opiates act as the category for which The burden of substance dependence is the highest for ,when compared to any other illicit drugs[2], and the use of opiates has emerged as an international public health concern within the past decade[3]. The treatment of substance dependence still mainly relies on maintenance treatment with a controllable and less dangerous medical substitute. Deep brain stimulation is a potentially new treatment for opiates dependence and other substances abuse. Based on the knowledge of the importance of the nucleus accumbens in addiction, the idea of DBS of the NAc to treat alcohol and smoking addiction has been introduced since 2007[4-7]. The concept of treating addiction via NAc-DBS has recently been broadened to heroin addiction, and is supported by further evidence in animal models of DBS in addiction[8-12]. However, it is currently controversial on the implementing of DBS for patients with refractory substance dependence. Because of the potentially serious risks that are associated with surgery and neurostimulation, recommendations from experts in this field support the use of DBS only when patients have failure of at least three addiction treatments in hospital or compulsive rehabilitation. DBS has been considered earlier for therapeutic intervention with the aim of improving the quality of life in patients with this disease. Recent studies indicate that DBS would be similarly cost-effective in treating opiate addiction to methadone maintenance treatment, and a promising therapeutic method for the treatment of addiction[11 13 14]. Thus far, no multi-centre prospective and double-blinded study has been performed in the China to investigate the efficacy, safety and adverse effects of NAc-DBS as a therapeutic alternative for opiate dependence.

Objectives

Deep brain stimulation of Nucleus Accumbens for opioid relapse prevention

(NAc-DBSORP) study was initiated in 2018, and is anticipated to be concluded by 2020. The primary objective of this study is to demonstrate statistically significant difference in the abstinent rate between early stimulation group with late stimulation group from baseline to 25 weeks after DBS surgery. Additional objectives are to summarise or characterise the following: the total days of abstinence, the longest duration for sustained abstinence, visual analog scale (VAS) craving score for opioid drugs, body weight , Hamilton Depression Scale（HAMD-17), Hamilton Anxiety Scale (HAMA), Pittsburgh sleep quality index (PSQI), Fagerstrom Test Nicotine Dependence assessment (FTND), Social Disability Screening Schedule (SDSS), Activity of Daily Living Scale (ADL), 36-Item Short Form Health Survey (SF-36) and safety profiles for both groups based on severe adverse effects reported throughout the study.

METHODS AND ANALYSIS

Study design and setting

NAc-DBSORP is a Chinese, multicentre, double-blinded, prospective and observational study. Patients will be recruited by four centres in China, comprising (1) Tangdu Hospital of the Fourth Military Medical University (affiliation of the principal investigator; PI), Xi'an; (2) Ruijin Hospital of Shanghai Jiao Tong University, Shanghai; (3) West China Hospital of Sichuan University, Chengdu; (4) Nanfang Hospital of Southern Medical University, Guangzhou. The specified data centre: the first Affiliated Hospital of Peking University, Beijing. The work of statistical analysis will finish in the first Affiliated Hospital of Peking University.

Eligibility criteria

Inclusion criteria

Patients will be eligible for recruitment if they meet the following criteria: 1. 18 years old < Age < 50 years old; 2. Moderate to severe opiates abuse disorders (fulfilled diagnostic-criteria according to DSM-5): (1) History of opiates abuse no less than 3 years, (2) Failure of at least three addiction treatments or medication (Especially MMT and compulsive rehabilitation), (3) completion of detoxification (Negative

urine test for morphine, methamphetamine, ketamine and buprenorphine, no less than 10 days); 3. Patients who request for surgical treatment have normal cognitive status and ability to know the benefit and risk of the treatment. 4. The compliance of patient is well, and the relatives of patients can assist the researchers to complete the follow-up; 5. Complete informed consent forms.

Exclusion criteria

Patients with one of the following conditions will be excluded: (1) Clinical relevant psychiatric comorbidity (schizophrenic psychoses, bipolar affective diseases, severe personality disorder); (2) Contraindications of a MRI-examination, e.g. implanted cardiac pacemaker/heart defibrillator; (3) Abuse of other type of drugs; (4) Severe cognitive impairments; (5) Enrollment in other clinical trials; (6) Stereotactic respectively neurosurgical intervention in the past; (7) Contraindications of a stereotactic operation, e.g. increased bleeding-disposition, cerebrovascular diseases (e.g. arteriovenous malfunction, aneurysms, systemic vascular diseases); (8) Serious and instable organic diseases (e.g. instable coronal heart disease); (9) tested positively for HIV; (10) pregnancy and/or lactation; (11) Severe disorders for coagulation and liver function; (12) Epilepsy or other severe brain trauma or neurological impairments.

Procedures

Baseline assessment

Patients with RSD with an intention of undergoing bilateral NAc-DBS will be screened and recruited by neurologists in an outpatient clinic. When a patient decides to participate in the study, the informed consent form (ICF) will be signed and personally dated by the patient or legally authorized representative and the investigator. One copy of the signed ICF will be sent to the PI's institute and one will be kept in the patient's binder at the investigation site. After the recruitment, there will be at least a month for observation and preparation. During this period, patients will have to complete the process of detoxification (negative urine test for morphine, methamphetamine, ketamine and buprenorphine, no less than 10 days) for a period of two consecutive weeks. They will then be admitted to the neurology department for

preoperative evaluation, which includes (1) VAS craving score for opioid drugs; (2) Characteristics of the participants (such as gender, age, body weight and BMI); (3) Psychological evaluation including HAMD-17[15], HAMA[16 17], PSQI[18 19], FTND[20 21], SDSS[22], ADL[23] and SF-36[24]; (4) The evaluation of withdrawal symptoms; (5) The evaluation of MATRICS-test[25]; (6) The urine test. Those who meet the inclusion criteria will be admitted to the neurosurgery department for implantation of the DBS device. Patients who fail the inclusion criteria will be excluded from the study. Follow-ups will be scheduled for 25 weeks after surgery.

Surgery

All centres have the expertise to perform DBS surgery, with surgeons having more than 5 years of experience at the start of the trial. Surgical procedures between each centre may differ, but the following requirements will be met to guarantee an optimal approach: (1) DBS electrode placement was planned according to MRI findings by using a Leksell Surgical planning system (SurgiplanTM). The coordinates at the tip of the most ventral contact (contact 0) were 8–10.5 mm from the midline, 15.5–18.5 mm anterior to the midcommissural point, and 4.5–8.5 mm below the anterior commissure (AC)–posterior commissure (PC) line for NAc. (2) Electrode implantation can be done under general anaesthesia, and the electrode leads were then externalized to confirm the electrode locations and to perform a temporary stimulation test. (3) Leads will be secured at the burr hole site using the Stimloc system (SN1181, Scene Ray, Su Zhou, China). (4) The implantable pulse generator (IPG) (SN1510, Scene Ray, Su Zhou, China) will be implanted subcutaneously usually at the right subclavicular area, with in the same procedure for the electrodes.

Stimulation parameter programming

Two weeks after surgery, patients will visit the clinic in the "off" state for initial programming of electrical parameters for stimulation. The patients will fall into two groups by a randomized allocation system: early stimulation group and late stimulation group. Both of investigators and patients do not know the grouping situations until the data of study were unblended. In the following 25-weeks, the IPG of stimulus group will be turned on and all the contacts tested based on a standard

protocol. With the IPG as anode, the tested contact as cathode, pulse width of 180 μs and frequency of 145 Hz, the amplitude will be gradually increased to 2-4 V in increments of 0.2 V or until side effects are intolerable. The voltages of initial stimulation will be set at 2.5 V. And the IPG of late stimulus group will be not be turned on in this period. After the follow-up of 25-weeks, the IPG of each group will be turned on, and the grouping situations and the data of different groups will be collected and analyzed in the PI's centre. If the patient had relapse, the grouping information of patient would have to open. The patient should repeat the process of detoxification (no less than 10 days), and then the IPG will be turned on.

Sample size

Due to the high rate of failure of the follow-up for patients with opioid dependence of more than 3 years, we decide that nA, the size of the treatment group, should be twice nB, the size of the control group. Calculation of the sample size will be based on the primary outcome of the abstinent rate. Based on retrospective analysis of our previous data, the abstinent rate from baseline to 25 weeks after DBS surgery was 70% in 11 patients with opioid dependence, and previous study show the abstinent rate of patients with opioid dependence is about 30%. A two-sample test will be used to determine if the mean of the treatment group (μA) is different from that of the control group (μB). The hypotheses is: H0: μA−μB=0, H1: μA− μ B≠0. The sample size will be calculated using the PASS V.11 sample size calculation software. Based on tests for two means, with a two-sided significance level of 5% and statistical power at 80% and allowing for a 15% dropout rate, a sample size of 60 patients will be needed to test the hypothesis with the two-sided test. This will consists of 40 patients for the treatment group and 20 patients for the control group.

Outcome measurements

Primary outcome: the abstinent rate at 25 weeks after DBS stimulation on （Urine Tests）. If the participants or their families report no less than 2 times of the drug use in each of two consecutive weeks, or the consecutive 2 times of urine tests showed positive, or failure of follow-up, the case was defined as relapse.

Secondary outcomes will be measured based on: 1. The total days of abstinence for

participants; 2. The longest duration for sustained abstinence for participants; 3. VAS craving score for opioid drugs; 4. Body weight of the participants; 5. Psychological evaluation including HAMD-17, HAMA, PSQI, FTND, SDSS, ADL and SF-36; 6. The evaluation of withdrawal symptoms; 7. The evaluation of MATRICS-test; 8. The rate of positive urine test results (times of positive urine test/ total times of urine test.

Data collection methods

Assessment of safety

Safety data will be inclusive of all adverse effects (AEs), from the point of subject enrolment to the final follow-up visit or discontinuation, whichever comes first. Reports of AEs will minimally include the following information; date of event; diagnosis or description of the event; assessment of the seriousness; treatment; outcome and date.

Collection of data

Before the start of the study, investigators from each centre will be trained on proper data recording. Data collected from each patient will be transcribed in case report form (CRF) with the print version and sent to the specified data centre (the first Affiliated Hospital of Peking University, Beijing.) every two months. A copy of the CRF will be placed in the subject's binder at the investigation site. Three monitors will audit the contents of the CRF before being entered into the database. Personal data will be coded and made anonymous.

Statistical methods

The work of statistical analysis will finish in the first Affiliated Hospital of Peking University. The parameters of interest will be mean changes of the observed values from baseline to 25 weeks follow-up. The primary analysis will be a complete case analysis (ie, using only cases with complete data), supported by sensitivity analysis, where missing data will be filled in using the multiple imputation method. The number, timing, pattern and reason for missing data or dropout will be reported, as well as their possible implications in efficacy and safety assessments. Statistical analysis of the primary and secondary endpoints will be performed within the framework of the generalised linear model with baseline adjustment. The scores of

instrument scalings will be introduced into the linear model. Summaries of continuous variables will be presented as means (±SD) for normally distributed data and as medians with interquartile ranges for skewed data; categorical variables will be presented as frequencies (percentages). Statistical analysis will be performed using the SPSS V.19.0. All statistical tests will be two-tailed, and a *p* value of less than 0.05 is considered to indicate statistical significance.

ETHICS AND DISSEMINATION

Any amendments to the study will be submitted to the local ethics committee for review. Signed informed consent forms will be required for each patient enrolled. Final study results and conclusions will be presented at international conferences and publications in peer-reviewed journals.

Contributors

XL Wang, J Shi, SN Ge and L. Qu contributed the conception and design of the study. W. Wang, P. Wu, N. Li and K. Yang provided their area of expertise for protocol development. N. Li and XL Wang arranged the meetings and took the minutes. L. Qu and XL Wang drafted the manuscript. All authors revised the manuscript and provided feedback and comments.

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Competing interests None declared.

Ethics approval

The Medical Ethical Committee of Tangdu Hospital, Fourth Military Medical University, 27 December 2017. Registered in ClinicalTrial.gov (number: NCT03424616).

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Clinical evaluation of Deep Brain Stimulation of Nucleus Accumbens/Anterior Limb of Internal Capsule for Opioid Relapse Prevention: protocol of a multi-centre, prospective and double-blinded study

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Conflict of interest: The authors have no conflict of interest.

Abstract

Introduction： Deep brain stimulation (DBS) is a new potential surgical treatment for opioid dependence. However, the implement of DBS treatment in addicted patients is currently controversial due to the significant associated risks. The aim of this study was mainly to investigate the therapeutic efficacy of bilateral DBS of nucleus accumbens and the anterior limb of the internal capsule (NAc/ALIC-DBS) in patients with refractory opioid dependence (ROD).

Methods and analysis： 60 patients with ROD will be enrolled in this multicentre, prospective, double-blinded study, and will be followed up for 25 weeks (6 months) after surgery. Patients with ROD (semi-synthetic opioids) who meet the criteria for NAc/ALIC-DBS surgery will be allocated to either the early stimulation group or the late stimulation group (control group) based on the randomized ID number. The primary outcome was defined as the abstinence rate at 25 weeks after DBS stimulation on, which will be confirmed by an opiate urine tests. The secondary outcomes include changes in the visual analog scale (VAS) score for craving for opioid drugs, body weight, as well as psychological evaluation measured using the Hamilton depression scale (HAMD-17), the Hamilton anxiety scale (HAM-A), the Pittsburgh sleep quality index (PSQI), Fagerstrom test nicotine dependence assessment (FTND), social disability screening schedule (SDSS), the activity of daily living scale (ADL), the 36-item short form health survey (SF-36) and safety profiles of both groups.

Ethics and dissemination： The study received ethical approval from the medical ethical committee of Tangdu Hospital, The Fourth Military Medical University, Xi'an, China. The results of this study will be published in a peer-reviewed journal and presented at international conferences.

Trial registration number： NCT03424616; Pre-results

Keywords: *Deep Brain Stimulation, Nucleus Accumbens, Opioid Relapse Prevention*

Strengths and limitations of this study

- This study is the first multi-centre research protocol for evaluating the therapeutic

efficacy of bilateral NAc-DBS in patients with refractory substance dependence.

- There is a risk of recruiting patients with severe opiate abuse disorders despite our strict inclusion criteria.
- Another limitation of this study protocol is the extensive burden of monitoring required of patients, and outpatient follow-up for 4 weeks, 12 weeks, and 25 weeks after DBS stimulation requires the consent of patients.

INTRODUCTION

Background and rationale

Substance dependence is a functional brain disease characterized by behavioral pathology involving compulsive drug-seeking and consumption with progressive loss of control over drug intake, which leads to a number of adverse social and health consequences for the addicted subjects [1]. Heroin and other opiates are the drug category with the highest burden of substance dependence is the more severe than any other group of illicit drugs [2]. Moreover, the abuse of opiates has emerged as a major international public health concern within the past decade [3]. The treatment of substance dependence still mainly relies on maintenance treatment with a controllable and less dangerous medical substitute [4 5]. Deep brain stimulation (DBS) is often advocated as a reversible alternative to neurosurgery, and it is a potentially new treatment for opiates dependence and other substances abuse [6]. Based on the knowledge of the importance of the nucleus accumbens in addiction, the idea of DBS of the NAc (NAc-DBS) to treat alcohol and smoking addiction has been pursued since 2007 [7-12]. The concept of treating addiction via NAc-DBS has recently been broadened to heroin addiction, and is supported by evidence from animal models [13-17]. The anterior limb of the internal capsule (ALIC), which contains supero-lateral part of the medial forebrain bundle (MFB) carrying dopaminergic projections from ventral tegmental area (VTA) to forebrain limbic structures, underlie the pathophysiology of several psychiatric disorders including addiction as well [18-20], making ALIC to be another possible targets for addiction treatment. Though the implementation of DBS in patients with refractory substance dependence is currently still controversial [7 12 21], the reversible feature and less invasion to the brain tissue still make DBS to be a possible choice for addiction therapy, considering its superior to other conventional methods for relapse prevention according to other and our previous reports [22-24]. Some recommendations from experts in this field support the use of DBS only in patients in which at least three addiction treatments in the hospital or compulsive rehabilitation have failed. NAc-DBS has been considered as an early therapeutic intervention with the aim of improving the quality of life and

giving patients who have failed rehabilitation more than three times a chance to undergo a possible therapeutic treatment for opioid addiction [22 25-28]. Recent studies indicate that DBS would be similarly cost-effective in treating opiate addiction to methadone maintenance treatment, which makes it a promising therapeutic method for the treatment of addiction [6 16 28]. Thus far, no multi-centre prospective and double-blinded study has been performed in China to investigate the efficacy, safety and adverse effects of NAc-DBS as an alternative treatment for opiate dependence.

Objectives

The study termed Deep brain stimulation of Nucleus Accumbens and the anterior limb of the internal capsule for opioid relapse prevention (NAc-DBSORP) was initiated in May 2018, and is anticipated to be concluded by July 2020. The primary objective of this study is to demonstrate a statistically significant difference in the abstinence rate between the early stimulation group and the late stimulation group (control group) from baseline to 25 weeks after DBS surgery. Additional objectives are to summarize or characterize: the total days of opioid relapse prevention, the longest duration of prevented opioid relapse , the visual analog scale (VAS) craving score for opioid drugs, body weight, the Hamilton depression scale (HAMD-17), the Hamilton anxiety scale (HAM-A), the Pittsburgh sleep quality index (PSQI), the Fagerstrom test for nicotine dependence assessment (FTND), the social disability screening schedule (SDSS), the activity of daily living scale (ADL), the 36-item short form health survey (SF-36) and the safety profiles for both groups based on severe adverse effects reported throughout the study.

METHODS AND ANALYSIS

Patient and public involvement

The study was consulted and reviewed by patient representatives during the protocol development. And two patients have been invited to join the project advisory group (PAG). They were asked to offer a proposal about recruitment strategy, visit schedule and benefits of the study participants. Investigators asked about their experience of assisted conception, the things they liked and disliked, and the potential difficulties or

barriers to attending for treatment, randomized allocation and how this might affect recruitment. During 25 weeks follow-up, the burden of the intervention for patients will be assessed by investigators and consulted by family members of patients. On completion of the trial, the results will be summarised in both plain Chinese and English, and distributed to participants and patient support groups with the assistance of collaborators in our study.

Study design and setting

NAc-DBSORP is a Chinese, multicentre, prospective and double-blinded study. Patients will be recruited by four centers in China, comprising (1) Tangdu Hospital of the Fourth Military Medical University (affiliation of the principal investigator), Xi'an; (2) Ruijin Hospital of Shanghai Jiao Tong University, Shanghai; (3) West China Hospital of Sichuan University, Chengdu; (4) Nanfang Hospital of Southern Medical University, Guangzhou. The specified data centre is the First Affiliated Hospital of Peking University, Beijing. The statistical analysis will be conducted at the First Affiliated Hospital of Peking University.

All the patients voluntarily came to our institution and chose to receive the surgery independently after they were given the recruitment information, after which they signed informed consent forms. As shown in **Figure 1**, all recruited participants will be allocated to either the early stimulation group (study group) or the late stimulation group (control group) based on the randomized ID number after the 2-3 recruitment. Then both groups of patients will undergo the DBS surgery. Four weeks after surgery, all patients will visit the clinic with the probes in the "off" state for initial programming of electrical parameters for stimulation. The patients will then be assigned to one of two groups, i.e. the early stimulation group and late stimulation group, by a randomized allocation system (Scene Ray, Su Zhou, China) integrated into the programmer according to the randomization plan completed preoperatively.

For the early stimulation group, the electrical stimulation will be actually "turned on" immediately after the initial programming, while for the late stimulation group, the electrical stimulation will be actually off after the initial programming. The randomized allocation system integrated into the programmer will guarantee that both

investigators and patients do not know the grouping situations. The initial programming procedures and parameters were fixed for all patients and the initial programming procedure was completely the same just according to the operation interface of the programmer (achieved by the randomized allocation system integrated into the programmer), so that both the investigators and patients will be blinded to the actual status of the stimulation after the programming, i.e. if DBS was initially on or off. The stimulation status will remain unchanged for both groups until 25 weeks after the initial programming, when the grouping of the study will be unblinded and all data will be collected. However, according to the ethical principles of clinical trials, if a relapse occurs for either groups of patients during the 25-week study period, the grouping status for the relapsed cases should be unblinded and theses patients should immediately receive proper treatment after relapse. All such patients should repeat the process of detoxification (no less than 10 days), after which the IPG will be actually turned on for patients either from the early stimulation group (study group) or the late stimulation group (control group). It should be noted that these conditions will not affect the primary endpoint measurement when the 25-week study period ends. When the 25-week study period ends, the stimulation will be kept turned on for all patients. Especially, for the patients in the late stimulation group who remain abstinent until this timepoint, the stimulation will be turned on as well. After the study has ended, follow-up for the patients will be continued, the frequency and methods of which will be decided by investigators themselves.

Eligibility criteria

Inclusion criteria

Patients will be eligible for recruitment if they meet the following criteria: 1. Aged 18 to 50 years old; 2. Severe abuse disorders involving semi-synthetic opiates (fulfilling the diagnostic-criteria according to DSM-5): (1) History of opiate abuse no less than 3 years, (2) Failure of at least three addiction treatments or medication (especially MMT and compulsive rehabilitation), (3) completion of detoxification (negative urine test for morphine, methamphetamine, ketamine and buprenorphine, no less than

10 days); 3. The patients who request surgical treatment have normal cognitive status and ability to understand the benefit and risk of the treatment. 4. The patient shows good compliance, and the relatives of the patient can assist the researchers to complete the follow-up; 5. Complete informed consent forms.

Exclusion criteria

Patients with one of the following conditions will be excluded: (1) Clinically relevant psychiatric comorbidity (schizophrenic psychoses, bipolar affective diseases, severe personality disorder); (2) Contraindications for an MRI-examination, e.g. implanted cardiac pacemaker/heart defibrillator; (3) Abuse of other types of drugs; (4) Severe cognitive impairments; (5) Enrollment in other clinical trials; (6) Stereotactic or orther neurosurgical intervention in the past; (7) Contraindications against a stereotactic operation, e.g. increased bleeding-disposition, cerebrovascular diseases (e.g. arteriovenous malfunction, aneurysms, systemic vascular diseases); (8) Serious and unstable organic diseases (e.g. unstable coronal heart disease); (9) tested positively for HIV; (10) pregnancy and/or lactation; (11) Severe disorders of coagulation and liver function; (12) Epilepsy or other severe brain trauma or neurological impairment.

Procedures

Instruments

The visual analog scale (VAS) is used for patients by self reporting the degree of craving for drugs, with “0” indicting “no craving” and “10” indicting “extreme craving” [24].

The 17-item Hamilton depression rating scale (HAMD-17) is a multiple-item questionnaire used by clinicians to provide an indication of depression, with higher total HAMD scores indicting higher severity of depression for patients [29].

The Hamilton anxiety rating scale (HAM-A) is a psychological questionnaire used by clinicians to rate the severity of a patient's anxiety, with higher total HAM-A scores indicting higher severity of anxiety for patients [30 31];

The Pittsburgh sleep quality index (PSQI) is a self-reporting questionnaire that assesses sleep quality for patients over a 1-month time period, consisting of 19

individual items, creating 7 components that produce one global score, with lower scores denoting a healthier sleep quality [32 33].

The Fagerstrom test for nicotine dependence (FTND) is a self-reporting tool for assessing nicotine addiction by conceptualizing dependence through physiological and behavioral symptoms. A higher total DTND score indicates more intense physical dependence on nicotine [34 35].

The social disability screening schedule (SDSS) is part of the disability assessment schedule edited by the WHO, which is a self-reporting tool for indicating social disability of patients, with higher scores denoting more social disability [36].

The activities of daily living (ADL) scale is a questionnaire used by clinicians to assess the ability of patients to independently perform the activities of daily living. The scores for ADL range from 14 to 56, with a score of 14 indicating completely normal activities of daily living and a score ≥ 20 indicating significant inability to perform the daily activities without assistance [37]

The 36-item short-form survey (SF-36) is a patient-reported survey of patient health. The SF-36 consists of eight scaled scores which represent the weighted sums of the questions in the respective sections, with lower scores denoting greater disability [38].

The MATRICS consensus cognitive battery (MCCB), which is a package of 10 tests, provides a relatively brief evaluation of key cognitive domains relevant to schizophrenia and related disorders [39].

All these instruments have been validated in Chinese, and the Chinese version of each instrument will be used in the present trial. In addition, the evaluation of withdrawal symptoms was done using the self-rating scale of protracted withdrawal symptoms for opiate dependence developed by Chen et al., which consists of 33 items [40].

Baseline assessment

Patients with ROD with an intention of undergoing bilateral NAc-DBS will be screened and recruited by neurologists in an outpatient clinic. When a patient decides to participate in the study, the informed consent form (ICF) will be signed and personally dated by the patient or legally authorized representative and the

investigator. One copy of the signed ICF will be sent to the PI's institute and one will be kept in the patient's folder at the investigation site. After the recruitment, there will be at least a month for observation and preparation. During this period, the patients will have to complete the process of detoxification (negative urine test for morphine, methamphetamine, ketamine and buprenorphine, no less than 10 days) for a period of two consecutive weeks. They will then be admitted to the neurology department for preoperative evaluation, which includes (1) VAS craving score for opioid drugs; (2) demographic characteristics of the participants (such as gender, age, body weight and BMI); (3) psychological evaluation including HAMD-17, HAM-A, PSQI, FTND, SDSS, ADL and SF-36 (4) evaluation of withdrawal symptoms; (5) MATRICS-test (MCCB); (6) urine test. Those who meet the inclusion criteria will be admitted to the neurosurgery department for implantation of the DBS device. Patients who do not meet the inclusion criteria will be excluded from the study. Follow-ups will be scheduled for 25 weeks after surgery.

Surgery

All centres have the expertise to perform DBS surgery, with surgeons having more than 5 years of experience at the start of the trial. Surgical procedures between each centre may differ, but the following requirements will be met to guarantee an optimal approach: (1) DBS electrode placement was planned according to MRI findings using a Leksell Surgical planning system (SurgiplanTM, Elekta, Sweden). The coordinates at the tip of the most ventral contact (contact 0) will be placed were 8–10.5 mm from the midline, 15.5–18.5 mm anterior to the midcommissural point, and 4.5–8.5 mm below the anterior commissure (AC)–posterior commissure (PC) line for NAc. (2) Electrode implantation can be done under general anesthesia, and the electrode leads will be externalized to confirm the electrode locations and to perform a temporary stimulation test. (3) Leads will be secured at the burr hole site using the Stimloc system (SN1181, Scene Ray, Su Zhou, China). (4) The implantable pulse generator (IPG) (SN1510, Scene Ray, Su Zhou, China) will be implanted subcutaneously, usually at the right subclavicular area, during the same procedure as the electrodes.

The initial stimulation parameter programming

With the help of randomized allocation system integrated into the programmer, two measures were additionally performed to guarantee both the investigators and patients were blinded: (1) The procedure to titrate the simulation parameters in both groups were omitted ; and thus (2) As shown in **Figure 2,** the simulation parameters were fixed for all patients, with the two active contacts selected as one ALIC-ventral contact and one NAc-dorsal contact by postoperatively MRI (thus for most cases were the two middle contacts of the electrodes) , and the stimulation parameters was fixed at voltage of 3.0 V , pulse width of 210 μs and frequency of 165 Hz for ALIC-ventral active contact and voltage of 3.0 V , pulse width of 210 μs and frequency of 145 Hz for NAc-dorsal active contact. Of note, these stimulation parameters were according to the experience from the previous studies and our single-centred preliminary study[22 24 41].

Sample size

In order that more patients can be allocated into the early stimulation group (receiving “true” but not “sham” intervention), which make trial representing more ethical considerations and make recruitment more easier (patients were informed that they have more chance to be allocated into the early stimulation group), the statistical experts decided the sample ratio to be 2:1 for treatment group：control group，which has been applied for most previous similar trials. Calculation of the sample size were further done by statistical experts designated by CFDA (Chinese food and drug administration that was in charge of the quality control and approval for clinical trials), based on the primary outcome of the abstinence rate reported by previous literatures [24 42]. Based on retrospective analysis of our previous data, the abstinence rate from baseline to 25 weeks after DBS surgery was 70% in 11 patients with opioid dependence, and previous studies showed that the abstinence rate of patients with opioid dependence who do not receive any treatment is around 30%[4 5]. A two-sample test will be used to determine if the mean of the treatment group (μA) is different from that of the control group (μB). The hypotheses is: H0: μA−μB=0, H1: μA−μB≠0. The sample size will be calculated using the PASS V.11 sample size calculation software (NCSS, United States). Based on tests for two means, with a

two-sided significance level of 5% and statistical power at 80%, allowing for a 15% dropout rate, a sample size of 60 patients will be needed to test the hypothesis with the two-sided test. This will consists of 40 patients for the treatment group and 20 patients for the control group.

Outcome measurements

Primary outcome: the abstinence rate which was defined as non-relapsed cases/ total participants × 100%, at 25 weeks after DBS stimulation has been turned on.

The definition of non-relapsed cases: If the participants or their families report the drug use at the frequency of ≥ 2 times per week in two consecutive weeks, or the urine tests remain positive in two consecutive weeks, or failure of follow-up, the case was defined as relapse, otherwise, the cases will be defined as non-relapsed. These definitions will be applied for the consecutive follow-up period from turning the DBS stimulation on to 25 weeks afterwards.

The frequency of urine tests is planned as follows: firstly, the urine tests will be done once per week at a fixed time, then two randomized urine tests will be done every month, then this urine test plan will guarantee the power to find the relapsed cases as defined above.

Secondary outcomes will be measured based on: 1. the total days of opioid relapse prevention for participants (the entire time after DBS stimulation has been turned on); 2. The longest duration of opioid relapse prevention for participants (the entire time after DBS stimulation has been turned on); 3. VAS craving score for opioid drugs (time frame): baseline (preoperative), 4 weeks, 12 weeks, 25 weeks after DBS stimulation has been turned on; 4. body weight of the participants (time frame): baseline (preoperative), 4 weeks, 12 weeks, 25 weeks after DBS stimulation has been turned on; 5. psychological evaluation including HAMD-17, HAM-A, PSQI, FTND, SDSS, ADL and SF-36 (time frame): baseline (preoperative), 4 weeks, 12 weeks, 25 weeks after DBS stimulation has been turned on; 6. the evaluation of withdrawal symptoms (time frame): baseline (preoperative), 4 weeks, 12 weeks, 25 weeks after DBS stimulation has been turned on; 7. MATRICS-test (time frame): baseline (preoperative), 4 weeks, 12 weeks, 25 weeks after DBS stimulation has been turned

on; 8. the rate of positive urine test results (times of urine test was positive / total times of urine test (time frame): 25 weeks after DBS stimulation has been turned on.

Data collection methods

Assessment of safety

Safety data will include all adverse effects (AEs), from the point of subject enrolment to the final follow-up visit or discontinuation, whichever comes first. Reports of AEs will minimally include the following information: date of event; diagnosis or description of the event; assessment of the seriousness; treatment; outcome and date.

Collection of data

Before the start of the study, investigators from each centre will be trained on proper data recording. Data collected from each patient will be transcribed in case report form (CRF) with a printed version and sent to the specified data centre (First Affiliated Hospital of Peking University, Beijing.) every two months. A copy of the CRF will be placed in the subject's folder at the investigation site. Three monitors will audit the contents of the CRF before the data are entered into the database. Personal data will be coded and made anonymous.

Statistical methods

Statistical analysis will be conducted in the First Affiliated Hospital of Peking University. The parameters of interest will be mean changes of the observed values from baseline to the 25-week follow-up. The primary analysis will be a complete case analysis (i.e., using only cases with complete data), supported by sensitivity analysis, where missing data will be filled in using the multiple imputation method. The number, timing, pattern and reason for missing data or dropout will be reported, as well as their possible implications for efficacy and safety assessments. Statistical analysis of the primary and secondary endpoints will be performed within the framework of the generalized linear model with baseline adjustment. The scores of instrument scales will be introduced into the linear model. Summaries of continuous variables will be presented as means ±SD for normally distributed data and as medians with interquartile ranges for skewed data. Categorical variables will be presented as frequencies (percentages). Statistical analysis will be performed using

SPSS V.19.0 (IBM Corp., USA). All statistical tests will be two-tailed, and a *p* value of less than 0.05 is considered to indicate statistical significance.

ETHICS AND DISSEMINATION

Informed consent will be obtained from all individual participants included in this study or their legal representatives. The analysis and usage of patient information for this study was approved by the ethics committee of Tangdu Hospital. This randomized control trial was registered with the clinical trial registry under the registration number NCT03424616. Any amendments to the study will be submitted to the ethical committee of Tangdu Hospital for review. The final study results and conclusions will be presented at international conferences and published in a peer-reviewed journal.

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Contributors

XL Wang, J Shi, SN Ge and L. Qu contributed the conception and design of the study. W. Wang, P. Wu, N. Li and K. Yang provided their area of expertise for protocol development. N. Li and XL Wang arranged the meetings and took the minutes. L. Qu and XL Wang drafted the manuscript. All authors revised the manuscript and provided feedback and comments.

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Competing interests None declared.

Ethics approval

The medical ethical committee of Tangdu Hospital, Fourth Military Medical University, 27 December 2017. Registered in ClinicalTrial.gov (number: NCT03424616).

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Figure Legend

Figure 1. Study design and setting.

Figure 2. Simulated diagram for the initial stimulation parameter programming. The simulation parameters were fixed for all patients with the two active contacts selected as one ALIC-ventral contact and one NAc-dorsal contact (red dot).

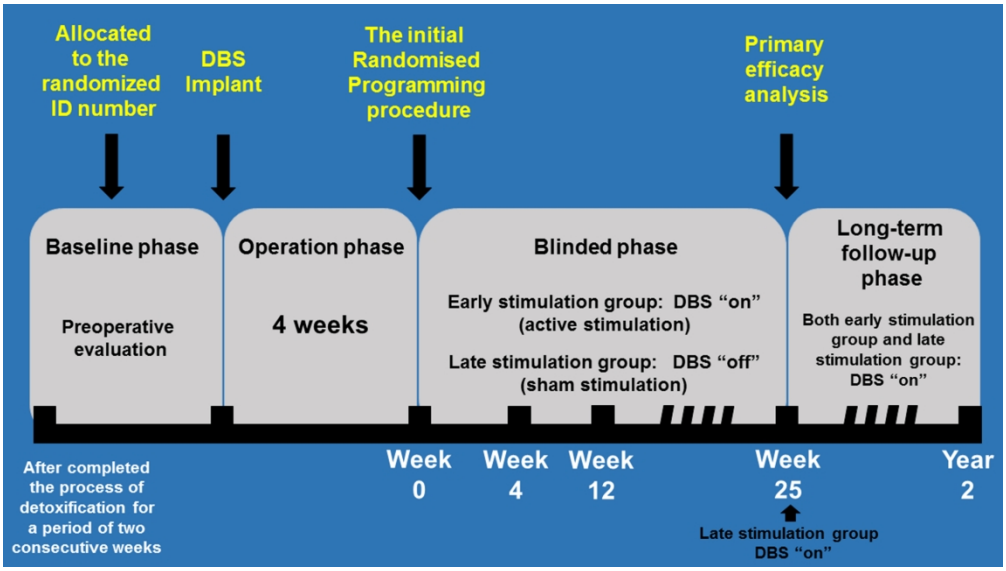

Figure 1. Study design and setting

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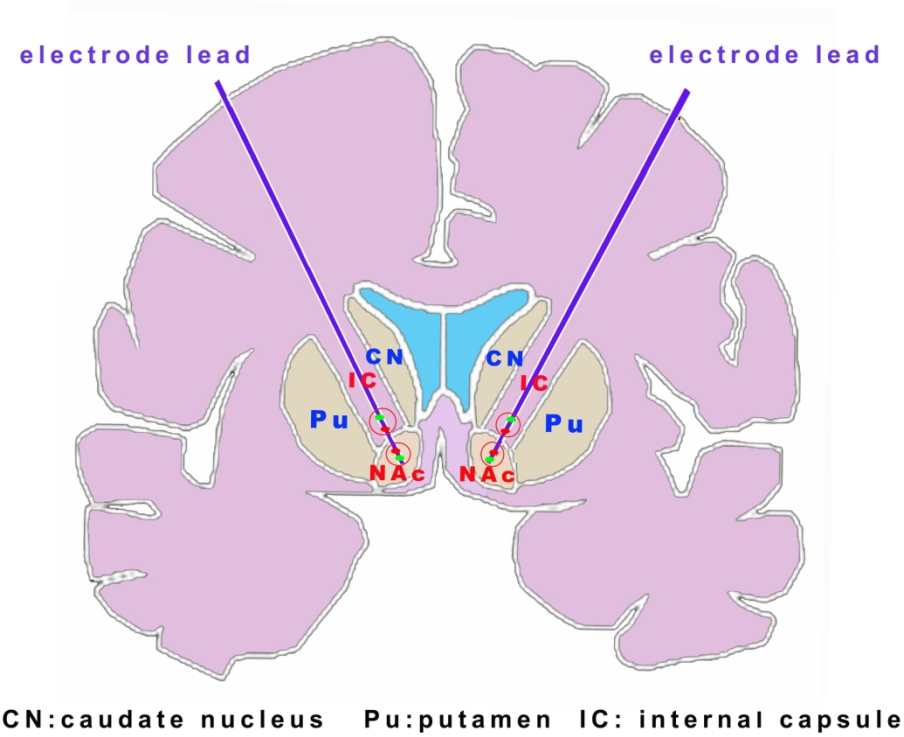

Figure 2. Simulated diagram for the initial stimulation parameter programming. The simulation parameters were fixed for all patients with the two active contacts selected as one ALIC-ventral contact and one NAc-dorsal contact (red dot).

159x127mm (300 x 300 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Page Number on which item is reported
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	P1 Title
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	P2 para 4; P12 para 2
	2b	All items from the World Health Organization Trial Registration Data Set	
Protocol version	3	Date and version identifier	P4 para 2
Funding	4	Sources and types of financial, material, and other support	P13 para 3
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	P13 para 2
	5b	Name and contact information for the trial sponsor	P1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	P13 para 2
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	P4 last para
Introduction			

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	P3 para 1
	6b	Explanation for choice of comparators	P3 para 1
Objectives	7	Specific objectives or hypotheses	P4 para 2
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	P4
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	P4 last para
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	P6 para 2-3; P5 para 2-3
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	P5 para 2-3
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	P5 para 2-3
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	P5 para 2-3
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	P5 para 2-3
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	P10 para 2

Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	P10 para 2
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	P9 last para; P10 para 1
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	P8 para 3
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	P5 para 2-3; P9 para 2
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	P5 para 2-3; P9 para 2
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	P5 para 2-3
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	P5 para 2
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	P5 para 3
Methods: Data collection, management, and analysis			

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	P11 last para
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	P11 last para
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	P12 para 1
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	P12 para 1
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	P12 para 1
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	P12 para 1
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	P12 para 1
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	P12 para 1

Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	P12 para 1
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	P12 para 1
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	P12 para 2
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	P12 para 2
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	P12 para 2
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	P12 para 2
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	P12 para 2
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	P13 para 3
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	P12 last para
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	P12 para 2

	31b	Authorship eligibility guidelines and any intended use of professional writers	P12 para 2
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	P12 para 2
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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Clinical evaluation of Deep Brain Stimulation of Nucleus Accumbens/Anterior Limb of Internal Capsule for Opioid Relapse Prevention: protocol of a multi-centre, prospective and double-blinded study

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Clinical evaluation of Deep Brain Stimulation of Nucleus Accumbens/Anterior Limb of Internal Capsule for Opioid Relapse Prevention: protocol of a multi-centre, prospective and double-blinded study

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Conflict of interest: The authors have no conflict of interest.

Abstract

Introduction： Deep brain stimulation (DBS) is a new potential surgical treatment for opioid dependence. However, the implement of DBS treatment in addicted patients is currently controversial due to the significant associated risks. The aim of this study was mainly to investigate the therapeutic efficacy and safety of bilateral DBS of nucleus accumbens and the anterior limb of the internal capsule (NAc/ALIC-DBS) in patients with refractory opioid dependence (ROD).

Methods and analysis： 60 patients with ROD will be enrolled in this multicentre, prospective, double-blinded study, and will be followed up for 25 weeks (6 months) after surgery. Patients with ROD (semi-synthetic opioids) who meet the criteria for NAc/ALIC-DBS surgery will be allocated to either the early stimulation group or the late stimulation group (control group) based on the randomized ID number. The primary outcome was defined as the abstinence rate at 25 weeks after DBS stimulation on, which will be confirmed by an opiate urine tests. The secondary outcomes include changes in the visual analog scale (VAS) score for craving for opioid drugs, body weight, as well as psychological evaluation measured using the Hamilton depression scale (HAMD-17), the Hamilton anxiety scale (HAM-A), the Pittsburgh sleep quality index (PSQI), Fagerstrom test nicotine dependence assessment (FTND), social disability screening schedule (SDSS), the activity of daily living scale (ADL), the 36-item short form health survey (SF-36) and safety profiles of both groups.

Ethics and dissemination： The study received ethical approval from the medical ethical committee of Tangdu Hospital, The Fourth Military Medical University, Xi'an, China. The results of this study will be published in a peer-reviewed journal and presented at international conferences.

Trial registration number： NCT03424616; Pre-results

Keywords: *Deep Brain Stimulation, Nucleus Accumbens, Opioid Relapse Prevention*

Strengths and limitations of this study

- This study is the first multi-centre research protocol for evaluating the therapeutic

efficacy of bilateral NAc-DBS in patients with refractory substance dependence.

- There is a risk of recruiting patients with severe opiate abuse disorders despite our strict inclusion criteria.
- Another limitation of this study protocol is the extensive burden of monitoring required of patients, and outpatient follow-up for 4 weeks, 12 weeks, and 25 weeks after DBS stimulation requires the consent of patients.

INTRODUCTION

Background and rationale

Substance dependence is a functional brain disease characterized by behavioral pathology involving compulsive drug-seeking and consumption with progressive loss of control over drug intake, which leads to a number of adverse social and health consequences for the addicted subjects [1]. Heroin and other opiates are the drug category with the highest burden of substance dependence is the more severe than any other group of illicit drugs [2]. Moreover, the abuse of opiates has emerged as a major international public health concern within the past decade [3]. The medical treatment of substance dependence still mainly relies on maintenance treatment with a controllable and less dangerous medical substitute [4 5]. Deep brain stimulation (DBS) is often advocated as a reversible alternative to neurosurgery, and it is a potentially new treatment for opiates dependence and other substances abuse [6]. Based on the knowledge of the importance of the nucleus accumbens in addiction, the idea of DBS of the NAc (NAc-DBS) to treat alcohol and smoking addiction has been pursued since 2007 [7-12]. The concept of treating addiction via NAc-DBS has recently been broadened to heroin addiction, and is supported by evidence from animal models [13-17]. The anterior limb of the internal capsule (ALIC), which contains supero-lateral part of the medial forebrain bundle (MFB) carrying dopaminergic projections from ventral tegmental area (VTA) to forebrain limbic structures, underlie the pathophysiology of several psychiatric disorders including addiction as well [18-20], making ALIC to be another possible targets for addiction treatment. Though the implementation of DBS in patients with refractory substance dependence is currently still controversial [7 12 21], the reversible feature and less invasion to the brain tissue still make DBS to be a possible choice for addiction therapy, considering its superior to other conventional methods for relapse prevention according to other and our previous reports [22-24]. Some recommendations from experts in this field support the use of DBS only in patients in which at least three addiction treatments in the hospital or compulsive rehabilitation have failed. NAc-DBS has been considered as an early therapeutic intervention with the aim of improving the quality of life and giving patients

who have failed rehabilitation more than three times a chance to undergo a possible therapeutic treatment for opioid addiction [22 25-28]. Recent studies indicate that DBS would be similarly cost-effective in treating opiate addiction to methadone maintenance treatment, which makes it a promising therapeutic method for the treatment of addiction [6 16 28]. Thus far, no multi-centre prospective and double-blinded study has been performed in China to investigate the efficacy, safety and adverse effects of NAc-DBS as an alternative treatment for opiate dependence.

Objectives

The study termed Deep brain stimulation of Nucleus Accumbens and the anterior limb of the internal capsule for opioid relapse prevention (NAc-DBSORP) was initiated in May 2018, and is anticipated to be concluded by July 2020. The primary objective of this study is to demonstrate a statistically significant difference in the abstinence rate between the early stimulation group and the late stimulation group (control group) from baseline to 25 weeks after DBS surgery. Additional objectives are to summarize or characterize: the total days of opioid relapse prevention, the longest duration of prevented opioid relapse , the visual analog scale (VAS) craving score for opioid drugs, body weight, the Hamilton depression scale (HAMD-17), the Hamilton anxiety scale (HAM-A), the Pittsburgh sleep quality index (PSQI), the Fagerstrom test for nicotine dependence assessment (FTND), the social disability screening schedule (SDSS), the activity of daily living scale (ADL), the 36-item short form health survey (SF-36) and the safety profiles for both groups based on severe adverse effects reported throughout the study.

METHODS AND ANALYSIS

Patient and public involvement

The study was consulted and reviewed by patient representatives during the protocol development. And two patients have been invited to join the project advisory group (PAG). They were asked to offer a proposal about recruitment strategy, visit schedule and benefits of the study participants. Investigators asked about their experience of assisted conception, the things they liked and disliked, and the potential difficulties or

barriers to attending for treatment, randomized allocation and how this might affect recruitment. During 25 weeks follow-up, the burden of the intervention for patients will be assessed by investigators and consulted by family members of patients. On completion of the trial, the results will be summarised in both plain Chinese and English, and distributed to participants and patient support groups with the assistance of collaborators in our study.

Study design and setting

NAc-DBSORP is a Chinese, multicentre, prospective and double-blinded study. Patients will be recruited by four centers in China, comprising (1) Tangdu Hospital of the Fourth Military Medical University (affiliation of the principal investigator), Xi'an; (2) Ruijin Hospital of Shanghai Jiao Tong University, Shanghai; (3) West China Hospital of Sichuan University, Chengdu; (4) Nanfang Hospital of Southern Medical University, Guangzhou. The specified data centre is the First Affiliated Hospital of Peking University, Beijing. The statistical analysis will be conducted at the First Affiliated Hospital of Peking University.

All the patients voluntarily came to our institution and chose to receive the surgery independently after they were given the recruitment information, after which they signed informed consent forms. As shown in **Figure 1**, all recruited participants will be allocated to either the early stimulation group (study group) or the late stimulation group (control group) based on the randomized ID number after the 2-3 recruitment. Then both groups of patients will undergo the DBS surgery. Four weeks after surgery, all patients will visit the clinic with the probes in the “off” state for initial programming of electrical parameters for stimulation. The patients will then be assigned to one of two groups, i.e. the early stimulation group and late stimulation group, by a randomized allocation system (Scene Ray, Su Zhou, China) integrated into the programmer according to the randomization plan completed preoperatively.

For the early stimulation group, the electrical stimulation will be actually “turned on” immediately after the initial programming, while for the late stimulation group, the electrical stimulation will be actually off after the initial programming. The randomized allocation system integrated into the programmer will guarantee that both investigators

and patients do not know the grouping situations. The initial programming procedures and parameters were fixed for all patients and the initial programming procedure was completely the same just according to the operation interface of the programmer (achieved by the randomized allocation system integrated into the programmer), so that both the investigators and patients will be blinded to the actual status of the stimulation after the programming, i.e. if DBS was initially on or off. The stimulation status will remain unchanged for both groups until 25 weeks after the initial programming, when the grouping of the study will be unblinded and all data will be collected. However, according to the ethical principles of clinical trials, if a relapse occurs for either groups of patients during the 25-week study period, the grouping status for the relapsed cases should be unblinded and these patients should immediately receive proper treatment after relapse. All such patients should repeat the process of detoxification (no less than 10 days), after which the IPG will be actually turned on for patients either from the early stimulation group (study group) or the late stimulation group (control group). It should be noted that these conditions will not affect the primary endpoint measurement when the 25-week study period ends. When the 25-week study period ends, the stimulation will be kept turned on for all patients. Especially, for the patients in the late stimulation group who remain abstinent until this timepoint, the stimulation will be turned on as well. After the study has ended, follow-up for the patients will be continued, the frequency and methods of which will be decided by investigators themselves.

Eligibility criteria

Inclusion criteria

Patients will be eligible for recruitment if they meet the following criteria: 1. Aged 18 to 50 years old; 2. Severe abuse disorders involving semi-synthetic opiates (fulfilling the diagnostic-criteria according to DSM-5): (1) History of opiate abuse no less than 3 years, (2) Failure of at least three addiction treatments or medication (especially MMT and compulsive rehabilitation), (3) completion of detoxification (negative urine test for morphine, methamphetamine, ketamine and buprenorphine, no less than 10 days); 3. The patients who request surgical treatment have normal cognitive status and ability to

understand the benefit and risk of the treatment. 4. The patient shows good compliance, and the relatives of the patient can assist the researchers to complete the follow-up; 5. Complete informed consent forms.

Exclusion criteria

Patients with one of the following conditions will be excluded: (1) Clinically relevant psychiatric comorbidity (schizophrenic psychoses, bipolar affective diseases, severe personality disorder); (2) Contraindications for an MRI-examination, e.g. implanted cardiac pacemaker/heart defibrillator; (3) Abuse of other types of drugs; (4) Severe cognitive impairments; (5) Enrollment in other clinical trials; (6) Stereotactic or orther neurosurgical intervention in the past; (7) Contraindications against a stereotactic operation, e.g. increased bleeding-disposition, cerebrovascular diseases (e.g. arteriovenous malfunction, aneurysms, systemic vascular diseases); (8) Serious and unstable organic diseases (e.g. unstable coronal heart disease); (9) tested positively for HIV; (10) pregnancy and/or lactation; (11) Severe disorders of coagulation and liver function; (12) Epilepsy or other severe brain trauma or neurological impairment.

Procedures

Instruments

The visual analog scale (VAS) is used for patients by self reporting the degree of craving for drugs, with “0” indicting “no craving” and “10” indicting “extreme craving” [24].

The 17-item Hamilton depression rating scale (HAMD-17) is a multiple-item questionnaire used by clinicians to provide an indication of depression, with higher total HAMD scores indicting higher severity of depression for patients [29].

The Hamilton anxiety rating scale (HAM-A) is a psychological questionnaire used by clinicians to rate the severity of a patient's anxiety, with higher total HAM-A scores indicting higher severity of anxiety for patients [30 31];

The Pittsburgh sleep quality index (PSQI) is a self-reporting questionnaire that assesses sleep quality for patients over a 1-month time period, consisting of 19 individual items, creating 7 components that produce one global score, with lower scores denoting a healthier sleep quality [32 33].

The Fagerstrom test for nicotine dependence (FTND) is a self-reporting tool for assessing nicotine addiction by conceptualizing dependence through physiological and behavioral symptoms. A higher total DTND score indicates more intense physical dependence on nicotine [34 35].

The social disability screening schedule (SDSS) is part of the disability assessment schedule edited by the WHO, which is a self-reporting tool for indicating social disability of patients, with higher scores denoting more social disability [36].

The activities of daily living (ADL) scale is a questionnaire used by clinicians to assess the ability of patients to independently perform the activities of daily living. The scores for ADL range from 14 to 56, with a score of 14 indicating completely normal activities of daily living and a score ≥ 20 indicating significant inability to perform the daily activities without assistance [37]

The 36-item short-form survey (SF-36) is a patient-reported survey of patient health. The SF-36 consists of eight scaled scores which represent the weighted sums of the questions in the respective sections, with lower scores denoting greater disability [38].

The MATRICS consensus cognitive battery (MCCB), which is a package of 10 tests, provides a relatively brief evaluation of key cognitive domains relevant to schizophrenia and related disorders [39].

All these instruments have been validated in Chinese, and the Chinese version of each instrument will be used in the present trial. In addition, the evaluation of withdrawal symptoms was done using the self-rating scale of protracted withdrawal symptoms for opiate dependence developed by Chen et al., which consists of 33 items [40].

Baseline assessment

Patients with ROD with an intention of undergoing bilateral NAc-DBS will be screened and recruited by neurologists in an outpatient clinic. When a patient decides to participate in the study, the informed consent form (ICF) will be signed and personally dated by the patient or legally authorized representative and the investigator. One copy of the signed ICF will be sent to the PI's institute and one will be kept in the patient's folder at the investigation site. After the recruitment, there will be at least a month for

observation and preparation. During this period, the patients will have to complete the process of detoxification (negative urine test for morphine, methamphetamine, ketamine and buprenorphine, no less than 10 days) for a period of two consecutive weeks. They will then be admitted to the neurology department for preoperative evaluation, which includes (1) VAS craving score for opioid drugs; (2) demographic characteristics of the participants (such as gender, age, body weight and BMI); (3) psychological evaluation including HAMD-17, HAM-A, PSQI, FTND, SDSS, ADL and SF-36 (4) evaluation of withdrawal symptoms; (5) MATRICS-test (MCCB); (6) urine test. Those who meet the inclusion criteria will be admitted to the neurosurgery department for implantation of the DBS device. Patients who do not meet the inclusion criteria will be excluded from the study. Follow-ups will be scheduled for 25 weeks after surgery.

Surgery

All centres have the expertise to perform DBS surgery, with surgeons having more than 5 years of experience at the start of the trial. Surgical procedures between each centre may differ, but the following requirements will be met to guarantee an optimal approach: (1) DBS electrode placement was planned according to MRI findings using a Leksell Surgical planning system (SurgiplanTM, Elekta, Sweden). The coordinates at the tip of the most ventral contact (contact 0) will be placed were 8–10.5 mm from the midline, 15.5–18.5 mm anterior to the midcommissural point, and 4.5–8.5 mm below the anterior commissure (AC)–posterior commissure (PC) line for NAc. (2) Electrode implantation can be done under general anesthesia, and the electrode leads will be externalized to confirm the electrode locations and to perform a temporary stimulation test. (3) Leads will be secured at the burr hole site using the Stimloc system (SN1710, Scene Ray, Su Zhou, China). (4) The implantable pulse generator (IPG) (SN1181, Scene Ray, Su Zhou, China) will be implanted subcutaneously, usually at the right subclavicular area, during the same procedure as the electrodes.

The initial stimulation parameter programming

With the help of randomized allocation system integrated into the programmer, two measures were additionally performed to guarantee both the investigators and patients

were blinded: (1) The procedure to titrate the simulation parameters in both groups were omitted ; and thus (2) As shown in **Figure 2,** the simulation parameters were fixed for all patients, with the two active contacts selected as one ALIC-ventral contact and one NAc-dorsal contact by postoperatively MRI (thus for most cases were the two middle contacts of the electrodes) , and the stimulation parameters was fixed at voltage of 3.0 V , pulse width of 210 μs and frequency of 165 Hz for ALIC-ventral active contact and voltage of 3.0 V , pulse width of 210 μs and frequency of 145 Hz for NAc-dorsal active contact. Of note, these stimulation parameters were according to the experience from the previous studies and our single-centred preliminary study[22 24 41].

Sample size

In order that more patients can be allocated into the early stimulation group (receiving "true" but not "sham" intervention), which make trial representing more ethical considerations and make recruitment more easier (patients were informed that they have more chance to be allocated into the early stimulation group), the statistical experts decided the sample ratio to be 2:1 for treatment group：control group，which has been applied for most previous similar trials. Calculation of the sample size were further done by statistical experts designated by CFDA (Chinese food and drug administration that was in charge of the quality control and approval for clinical trials), based on the primary outcome of the abstinence rate reported by previous literatures [24 42]. Based on retrospective analysis of our previous data, the abstinence rate from baseline to 25 weeks after DBS surgery was 70% in 11 patients with opioid dependence, and previous studies showed that the abstinence rate of patients with opioid dependence who do not receive any treatment is around 30%[4 5]. A two-sample test will be used to determine if the mean of the treatment group (μA) is different from that of the control group (μB). The hypotheses is: H0: μA−μB=0, H1: μA−μB≠0. The sample size will be calculated using the PASS V.11 sample size calculation software (NCSS, United States). Based on tests for two means, with a two-sided significance level of 5% and statistical power at 80%, allowing for a 15% dropout rate, a sample size of 60 patients will be needed to test the hypothesis with the two-sided test. This will consists of 40 patients for the treatment group and 20 patients for the control group.

Outcome measurements

Primary outcome: the abstinence rate which was defined as non-relapsed cases/ total participants × 100%, at 25 weeks after DBS stimulation has been turned on.

The definition of non-relapsed cases: If the participants or their families report the drug use at the frequency of ≥ 2 times per week in two consecutive weeks, or the urine tests remain positive in two consecutive weeks, or failure of follow-up, the case was defined as relapse, otherwise, the cases will be defined as non-relapsed. These definitions will be applied for the consecutive follow-up period from turning the DBS stimulation on to 25 weeks afterwards.

The frequency of urine tests is planned as follows: firstly, the urine tests will be done once per week at a fixed time, then two randomized urine tests will be done every month, then this urine test plan will guarantee the power to find the relapsed cases as defined above.

Secondary outcomes will be measured based on: 1. the total days of opioid relapse prevention for participants (the entire time after DBS stimulation has been turned on); 2. The longest duration of opioid relapse prevention for participants (the entire time after DBS stimulation has been turned on); 3. VAS craving score for opioid drugs (time frame): baseline (preoperative), 4 weeks, 12 weeks, 25 weeks after DBS stimulation has been turned on; 4. body weight of the participants (time frame): baseline (preoperative), 4 weeks, 12 weeks, 25 weeks after DBS stimulation has been turned on; 5. psychological evaluation including HAMD-17, HAM-A, PSQI, FTND, SDSS, ADL and SF-36 (time frame): baseline (preoperative), 4 weeks, 12 weeks, 25 weeks after DBS stimulation has been turned on; 6. the evaluation of withdrawal symptoms (time frame): baseline (preoperative), 4 weeks, 12 weeks, 25 weeks after DBS stimulation has been turned on; 7. MATRICS-test (time frame): baseline (preoperative), 4 weeks, 12 weeks, 25 weeks after DBS stimulation has been turned on; 8. the rate of positive urine test results (times of urine test was positive / total times of urine test (time frame): 25 weeks after DBS stimulation has been turned on.

Data collection methods

Assessment of safety

Safety data will include all adverse effects (AEs), from the point of subject enrolment to the final follow-up visit or discontinuation, whichever comes first. Reports of AEs will minimally include the following information: date of event; diagnosis or description of the event; assessment of the seriousness; treatment; outcome and date.

Collection of data

Before the start of the study, investigators from each centre will be trained on proper data recording. Data collected from each patient will be transcribed in case report form (CRF) with a printed version and sent to the specified data centre (First Affiliated Hospital of Peking University, Beijing.) every two months. A copy of the CRF will be placed in the subject's folder at the investigation site. Three monitors will audit the contents of the CRF before the data are entered into the database. Personal data will be coded and made anonymous.

Statistical methods

Statistical analysis will be conducted in the First Affiliated Hospital of Peking University. The parameters of interest will be mean changes of the observed values from baseline to the 25-week follow-up. The primary analysis will be a complete case analysis (i.e., using only cases with complete data), supported by sensitivity analysis, where missing data will be filled in using the multiple imputation method. The number, timing, pattern and reason for missing data or dropout will be reported, as well as their possible implications for efficacy and safety assessments. Statistical analysis of the primary and secondary endpoints will be performed within the framework of the generalized linear model with baseline adjustment. The scores of instrument scales will be introduced into the linear model. Summaries of continuous variables will be presented as means ±SD for normally distributed data and as medians with interquartile ranges for skewed data. Categorical variables will be presented as frequencies (percentages). Statistical analysis will be performed using SPSS V.19.0 (IBM Corp., USA). All statistical tests will be two-tailed, and a p value of less than 0.05 is considered to indicate statistical significance.

ETHICS AND DISSEMINATION

Informed consent will be obtained from all individual participants included in this study

or their legal representatives. The analysis and usage of patient information for this study was approved by the ethics committee of Tangdu Hospital. This randomized control trial was registered with the clinical trial registry under the registration number NCT03424616. Any amendments to the study will be submitted to the ethical committee of Tangdu Hospital for review. The final study results and conclusions will be presented at international conferences and published in a peer-reviewed journal.

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Contributors

XL Wang, J Shi, SN Ge and L. Qu contributed the conception and design of the study. W. Wang, P. Wu, N. Li and K. Yang provided their area of expertise for protocol development. N. Li and XL Wang arranged the meetings and took the minutes. L. Qu and XL Wang drafted the manuscript. All authors revised the manuscript and provided feedback and comments.

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Competing interests None declared.

Ethics approval

The medical ethical committee of Tangdu Hospital, Fourth Military Medical University, 27 December 2017. Registered in ClinicalTrial.gov (number: NCT03424616).

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Figure Legend

Figure 1. Study design and setting.

Figure 2. Simulated diagram for the initial stimulation parameter programming. The simulation parameters were fixed for all patients with the two active contacts selected as one ALIC-ventral contact and one NAc-dorsal contact (red dot).

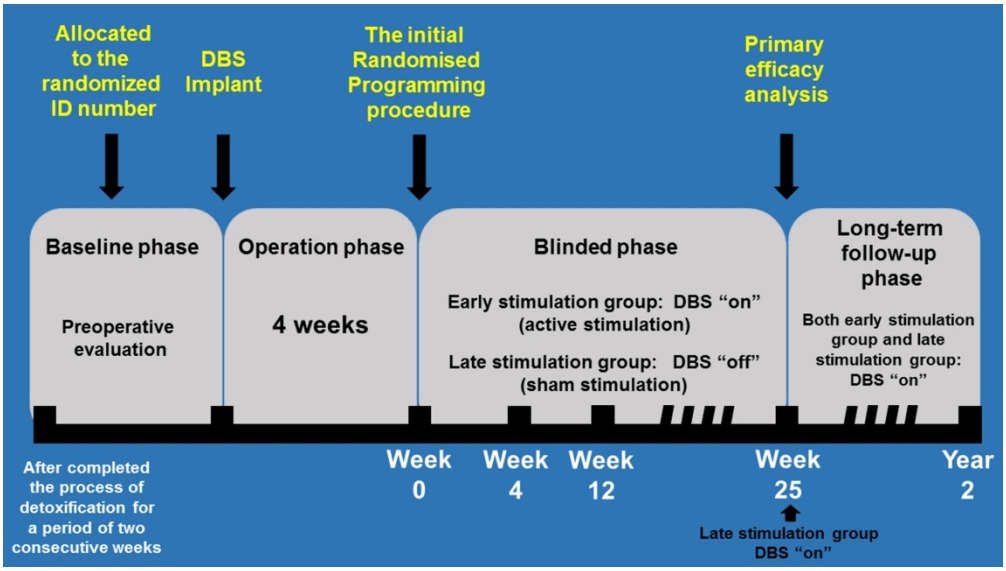

Figure 1. Study design and setting

190x107mm (300 x 300 DPI)

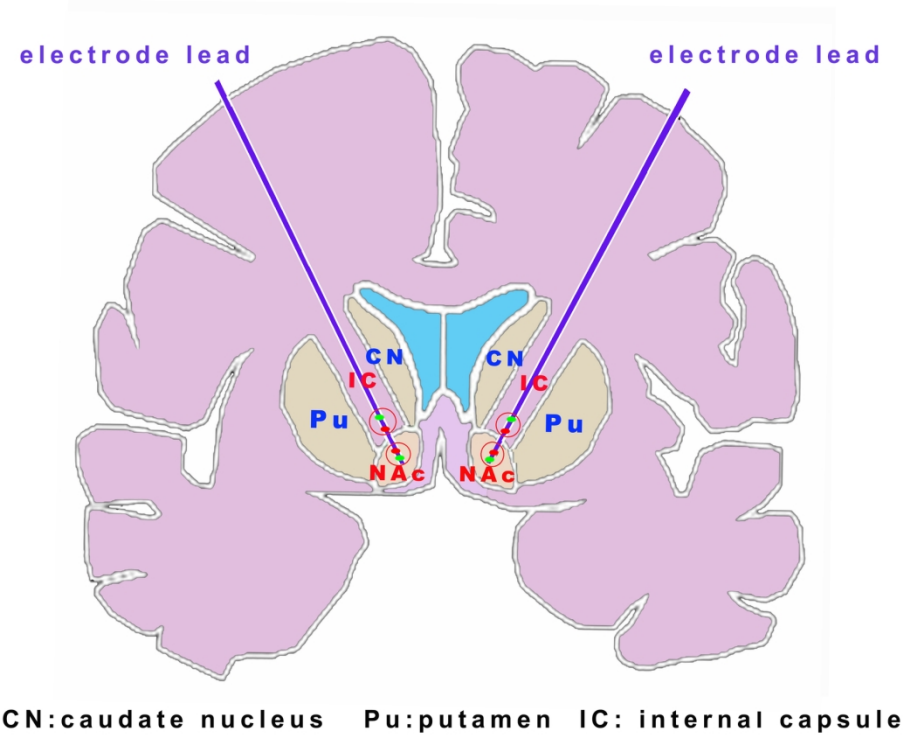

Figure 2. Simulated diagram for the initial stimulation parameter programming. The simulation parameters were fixed for all patients with the two active contacts selected as one ALIC-ventral contact and one NAc-dorsal contact (red dot).

159x127mm (300 x 300 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Page Number on which item is reported
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	P1 Title
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	P2 para 4; P12 para 2
	2b	All items from the World Health Organization Trial Registration Data Set	
Protocol version	3	Date and version identifier	P4 para 2
Funding	4	Sources and types of financial, material, and other support	P13 para 3
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	P13 para 2
	5b	Name and contact information for the trial sponsor	P1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	P13 para 2
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	P4 last para
Introduction			

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	P3 para 1
	6b	Explanation for choice of comparators	P3 para 1
Objectives	7	Specific objectives or hypotheses	P4 para 2
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	P4
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	P4 last para
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	P6 para 2-3; P5 para 2-3
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	P5 para 2-3
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	P5 para 2-3
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	P5 para 2-3
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	P5 para 2-3
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	P10 para 2

Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	P10 para 2
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	P9 last para; P10 para 1
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	P8 para 3
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	P5 para 2-3; P9 para 2
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	P5 para 2-3; P9 para 2
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	P5 para 2-3
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	P5 para 2
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	P5 para 3
Methods: Data collection, management, and analysis			

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	P11 last para
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	P11 last para
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	P12 para 1
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	P12 para 1
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	P12 para 1
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	P12 para 1
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	P12 para 1
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	P12 para 1

Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	P12 para 1
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	P12 para 1
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	P12 para 2
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	P12 para 2
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	P12 para 2
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	P12 para 2
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	P12 para 2
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	P13 para 3
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	P12 last para
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	P12 para 2

	31b	Authorship eligibility guidelines and any intended use of professional writers	P12 para 2
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	P12 para 2
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.