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Multi-centre trial of cannabidiol (CBD) for the treatment of Parkinson's disease psychosis

Submission date	Recruitment status	[X] Prospectively registered
02/03/2020	No longer recruiting	[ ] Protocol
Registration date	**Overall study status**	[ ] Statistical analysis plan
16/09/2020	Completed	[ ] Results
Last Edited	**Condition category**	[ ] Individual participant data
18/12/2025	Mental and Behavioural Disorders	[X] Record updated in last year

Plain English summary of protocol

Background and study aims

People with Parkinson’s disease often suffer from unusual experiences such as hallucinations (e. g. seeing things or hearing voices that are not there) or develop delusions (i.e. false beliefs, for example, that someone may be trying to harm them) as part of their illness. These experiences are also known as psychotic symptoms and are distressing both to patients and those caring for them.

More than half of all patients withParkinson's eventually develop these symptoms over the course of their disorder. These problems can be difficult to manage and can impact quality of life. Currently, existing medications to treat these symptoms are either not very effective or have significant side effects.

The aim of this study is to test a new treatment called cannabidiol (CBD). CBD is a non-addictive substance present in the extract from the cannabis plant that is not responsible for the effects typically produced by cannabis, such as ‘feeling high’. Previous studies not only suggest that CBD may be useful in treating symptoms of psychosis, they also suggest that it is safe to use in older adults.

Although CBD may be a promising treatment for symptoms of psychosis, it is not known whether this treatment will be tolerated well in patients with Parkinson’s-related psychosis, whether it will provide relief from psychotic symptoms, and what doses may work best for people with Parkinson’s-related psychosis. The aim of this study is to address all of these questions.

Who can participate?

Patients aged 40 or older with Parkinson’s disease who are experiencing symptoms of psychosis (such as hallucinations e.g. seeing things or hearing voices that are not there or delusions e.g. false beliefs, for example, that someone may be trying to harm them) for at least 1 month before the first study visit

What does the study involve?

The study will be carried out in two parts. In Part I, the researchers want to know whether cannabidiol is safe for people with Parkinson’s-related psychosis and find the dose that may work best. For this, groups of participants (three participants per group) will receive different doses of CBD for 6 weeks, starting with a small dose i.e., 200 mg per day of CBD, to determine if

that dose is safe and tolerated well. If the treatment that the first three participants receive does not cause side effects, the dose of CBD will slowly be increased to the next dose i.e., 400 mg per day, as the researchers enrol the rest of the participants into the study. A minimum of three and a maximum of 24 participants will be treated with CBD in this part of the study to find the best-tolerated dose.
In the second part of the study, the researchers will assess the usefulness of CBD on symptoms of Parkinson's-related psychosis. For this, they will study 120 eligible and willing participants. Half of the participants will receive CBD and the other half will receive a placebo (an inactive substance) in addition to their regular treatment. Participants will have a 50/50 chance of receiving either CBD or placebo (dummy) capsules. Neither the participants nor researchers will know which treatment is being given to each individual. The researchers will monitor participants as in the first stage and compare CBD's effects with that of placebo. Participants will be asked to take the study medicine for 12 weeks (84 days).
There will also be an opportunity to take part in an optional sub-study that aims to understand how CBD may work. For this, a smaller group of participants from part II of the study will have two brain scans using functional magnetic resonance imaging (MRI). One brain scan will take place before they start treatment and the second scan after they complete treatment with the study medicine.
In each part of the study, participants will be expected to attend between five and six study visits of varying length (two of the visits will be about 1 to 2 hours, one visit will be 2 to 3 hours and two visits will be 3 to 5 hours), where the researchers will carry out the following assessments. Not all of the assessments will be carried out at every visit.
The researchers will explain the study procedures and obtain the participant's consent to take part in the study, ask about any relevant past medical history and current medications, and collect general information such as the participant's age, gender, and education. They will carry out a physical examination (blood pressure, heart rate, temperature, heart trace (ECG) and neurological examination), take a blood sample to test for underlying medical problems and measure levels of medications and collect a urine sample to test for pregnancy (where appropriate). The researchers will use paper-pencil questionnaires to assess a range of neurological (e.g. motor symptoms of Parkinson's disease) and psychological symptoms (e.g. non-motor symptoms of Parkinson's disease such as psychosis, sleep, mood), quality of life, memory and the burden on caregivers. They will check for any side effects that participants may be experiencing and give participants study medication to take home and also check how many capsules they have taken or may have missed during follow-up visits. Where possible, the researchers will conduct assessments and questionnaires remotely (i.e. over the telephone, video call or email). For study procedures that need to be carried out in person, i.e. blood samples and psychical examinations, there will be an option for these visits to take place at the participant's home.

What are the possible benefits and risks of participating?
Participants may or may not receive any benefits from taking CBD as part of the study. CBD might improve some of the symptoms of Parkinson's disease psychosis. The information obtained in this study may help doctors to treat Parkinson's disease patients with psychosis more effectively in the future, reducing both patient and caregiver distress. Previous research has shown that the effects of CBD are very subtle. Nevertheless, like all medicines, the active medication may cause side effects in some people, including mild sleepiness or tiredness, gastrointestinal (digestive) problems, headache or nausea. The physical risks and discomforts of giving the blood samples are the same as those for any other blood sample taken from a vein. There may be minor bruising or irritation. Some of the questionnaires and rating scales may involve the participants answering questions that are sensitive and of a personal nature. MRI scans can sometimes feel uncomfortable because of the noise and may cause temporary dizziness. People who are claustrophobic or have any metallic foreign bodies in the body or eyes

or metal implants in the body, such as intra-cranial aneurysm clips, pacemakers or defibrillators, cannot take part in this study.

Where is the study run from?
King's College London and South London and Maudsley NHS Foundation Trust (UK)

When is the study starting and how long is it expected to run for?
January 2019 to December 2025

Who is funding the study?
Parkinson's UK

Who is the main contact?
CAN-PDP Trial Manager
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Contact information

Type(s)
Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
2019-003623-37

Integrated Research Application System (IRAS)
271052

Central Portfolio Management System (CPMS)
43972

Study information

Scientific Title
CANnabidiol for Parkinson's Disease Psychosis (CAN-PDP)

Acronym
CAN-PDP

Study objectives
For Part I of the proposed study, it is predicted that:
1. Cannabidiol at doses between 200-800 mg/day will be safe for short-term (6 weeks) use as a treatment in patients with Parkinson's disease psychosis
2. A dose of 800 mg/day of cannabidiol will be the maximum tolerated dose in patients with Parkinson's disease psychosis
3. There will be a minimal effect of short-term (6 weeks) cannabidiol treatment (at doses between 200 to 800 mg/day) on levels of medications such as quetiapine and donepezil in peripheral blood (drug-drug interaction)

Based on the results of Part I, the researchers will identify a safe and tolerated dose of cannabidiol to test in Part II of the study.

For Part II of the proposed study, it is predicted that:
1. The dose of cannabidiol chosen based on Part I of the study will be safe over a 12-week period of treatment in patients with Parkinson's disease psychosis
2. The dose of cannabidiol chosen based on Part I of the study will show evidence of activity on measures of psychosis in patients with Parkinson's disease psychosis (pharmacodynamic signal)

For the mechanistic sub-study, it is predicted that:
1. Presence of psychosis in Parkinson's disease patients would be associated with altered brain function in the striatum and medial temporal, prefrontal and visual cortices and functional connectivity between those regions as measured using MRI
2. 12-week treatment with cannabidiol would normalise those brain functional and connectivity alterations present at baseline (pre-treatment) in Parkinson's disease patients with psychosis

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 20/01/2020, London - Hampstead Research Ethics Committee (Barlow House, 3rd Floor, 4 Minshull Street, Manchester, M1 3DZ, UK; +44 (0)207 104 8104, +44 (0)207 104 8134; hampstead.rec@hra.nhs.uk), REC ref: 19/LO/1967

Primary study design
Interventional

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

Study type(s)
Treatment

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

Interventions
The first phase is a multi-centre, open-label, safety, tolerability and dose-finding study of cannabidiol (CBD). CBD will be given orally, once per day for 6 weeks in different doses as per dosing protocol in up to 24 participants. To identify the maximum tolerated dose (MTD) of orally administered CBD, the researchers will employ a variation of the traditional 3+3 design, with subjects assigned in groups of 3 to each dose. For the purposes of this study, MTD will be determined by toxicity and defined as the highest dose at which 2 or more out of 6 patients at a specified dose level experience a drug-related dose-limiting toxicity.

The second phase is a multi-centre, randomised, double-blind, placebo-controlled trial of CBD versus placebo. Up to 120 eligible patients will be randomly assigned at the baseline visit to receive CBD or matching placebo capsules for 12 weeks. Within the CBD arm, a single daily dose of CBD (dosage as identified from Phase I study) given in capsule form to be taken orally.

For both phases of the study, CBD or placebo will be added as an adjunct to treatment as usual (TAU). TAU corresponds to the typical package of care offered to PDP patients and may include antiparkinsonian medications, quetiapine or cholinesterase inhibitors (rivastigmine/ donepezil) in line with existing clinical practice.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Cannabidiol (CBD)

Primary outcome(s)
Part I:
1. Maximum tolerated dose of CBD determined by the number of dose-limiting toxicities

occurring throughout the study
2. Safety and tolerability of CBD assessed by evaluating treatment-emergent adverse events, UKU side effect rating scale for psychotropic drugs, physical examination (vital signs, ECG and neurological assessment) and laboratory tests at every visit

Part II:
Safety and tolerability of CBD assessed by evaluating treatment-emergent adverse events, UKU side effect rating scale for psychotropic drugs, physical examination (vital signs, ECG and neurological assessment) and laboratory tests at every visit

Key secondary outcome(s)

Part I:
1. Drug-drug interaction with any of the safe and tolerated doses of CBD, assessed by measuring the change in CBD and quetiapine and its metabolite and/ or donepezil levels in the blood at baseline (pre-treatment) and weeks 2 and 6
2. Evidence of neuropsychiatric drug activity (pharmacodynamic signal) measured using Parkinson's disease-adapted scale for assessment of positive symptoms of psychosis (SAPS-PD) and Neuropsychiatric Inventory (NPI) at baseline (pre-treatment) and week 6
3. Non-motor symptoms of Parkinson's Disease measured using the non-motor assessment scale for PD (NMSS) at baseline (pre-treatment) and week 6
4. Quality of life measured using the Parkinson's disease questionnaire-39 (PDQ-39) at baseline (pre-treatment) and week 6
5. Sleep measured using SCOPA-Sleep at baseline (pre-treatment) and week 6
6. Cognition measured using SCOPA-COG and MoCA at baseline (pre-treatment) and week 6
7. Global improvement/change measured using the Clinical Global Impression of Change at baseline (pre-treatment) and week 6
8. Caregiver burden measured using the Zarit Burden Interview at baseline (pre-treatment) and week 6
9. Motor symptoms of Parkinson's disease measured using the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) at baseline (pre-treatment) and week 6.

Part II:
1. Drug-drug interaction with any of the safe and tolerated doses of CBD, assessed by measuring the change in CBD and quetiapine and its metabolite and/or donepezil levels in the blood at baseline (pre-treatment) and weeks 2, 6 and 12
2. Evidence of neuropsychiatric drug activity (pharmacodynamic signal) measured using Parkinson's disease-adapted scale for assessment of positive symptoms of psychosis (SAPS-PD) and Neuropsychiatric Inventory (NPI) at baseline (pre-treatment) and week 12
3. Non-motor symptoms of Parkinson's Disease measured using the non-motor assessment scale for PD (NMSS) at baseline (pre-treatment) and week 12
4. Quality of life measured using the Parkinson's disease questionnaire-39 (PDQ-39) at baseline (pre-treatment) and week 12
5. Sleep measured using SCOPA-Sleep at baseline (pre-treatment) and week 12
6. Cognition measured using SCOPA-COG and MoCA at baseline (pre-treatment) and week 12
7. Global improvement/change measured using the Clinical Global Impression of Change at baseline (pre-treatment) and week 12
8. Caregiver burden measured using the Zarit Burden Interview at baseline (pre-treatment) and week 12
9. Motor symptoms of Parkinson's disease measured using the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) at baseline (pre-treatment) and week 12

Mechanistic sub-study:
Neurophysiological mechanisms underlying the antipsychotic effects of CBD in PDP measured using:
1. Within-subject change in medial temporal, prefrontal, and striatal activation (as estimated from the blood oxygen level-dependent haemodynamic response signal measured using fMRI; BOLD signal) in the MRI scanner at baseline (pre-treatment) and week 12
2. Within-subject change in functional connectivity between the medial temporal, prefrontal, striatal and visual cortical regions of interest (as estimated from the BOLD signal) and between these regions and the rest of the brain using both resting state and task-based fMRI data in the MRI scanner at baseline (pre-treatment) and week 12

Completion date
19/12/2025

Eligibility

Key inclusion criteria
1. Satisfy established diagnostic criteria (NINDS-NIMH criteria for the diagnosis of Parkinson's disease psychosis) and UK Brian Bank criteria for idiopathic Parkinson's disease
2. Age 40 years or older
3. For psychotic symptoms, they should have developed after the PD diagnosis and should have been present for at least 1 month, occurring at least weekly over the month before screening and should have a combined score of at least 6 or an individual score of at least 4 on the neuropsychiatric inventory (NPI) A (delusions) and/or B (hallucinations) subscale in the month before screening
4. Parkinson's disease dementia would not be an exclusion criterion
5. Participants with score greater than 18 on the Montreal Cognitive Assessment scale
6. Treatment as usual will include patients on quetiapine and/ or cholinesterase inhibitors (rivastigmine/ donepezil) as well as standard antiparkinsonian treatments with dosage stable for at least 1 month
7. At least 6 months post stereotaxic surgery (deep brain stimulation) and stimulator settings stable for at least 1 month prior to baseline and must remain stable during the trial
8. Ability to participate in study evaluation and ingest oral medication
9. Reliable informant/caregiver
10. Written informed consent to participate

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
40 Years

Upper age limit
99 Years

Sex
All

Total final enrolment
100

Key exclusion criteria
1. Insufficient understanding of trial
2. History of significant psychotic disorders prior to or concomitantly with the diagnosis of Parkinson’s disease including, but not limited to, schizophrenia or bipolar disorder
3. Psychotic symptoms secondary to other toxic or metabolic disorders
4. Psychosis onset after ablative stereotaxic surgery
5. Diagnosis of dementia made concurrent with or prior to a PD diagnosis
6. Patients on clozapine due to the requirement of special safety monitoring required for clozapine, which will unblind the safety
7. Patients taking part in another intervention trial concurrently. However, those withdrawn from another study or who have recently completed another intervention study will be eligible for inclusion if they satisfy study inclusion/ exclusion criteria. For pharmacological intervention, they will be eligible only after a sufficient period of washout (~ 5 times half-life of other study drug)
8. Participant no longer able to report symptoms as a result of cognitive impairment
9. Presence of depressive symptoms would not be an exclusion criterion. However, we would exclude those participants who may have severe depression
10. Participants who answer "yes" on the C-SSRS Suicidal Ideation Item 4 or Item 5 (Active Suicidal Ideation with Some Intent to Act, Without Specific Plan, or Active Suicidal Ideation with Specific Plan and Intent) and whose most recent episode meeting the criteria for C-SSRS Item 4 or Item 5 occurred within the last 6 months, OR Participants who answer "yes" on any of the 5 C-SSRS Suicidal Behavior Items (actual attempt, interrupted attempt, aborted attempt, preparatory acts, or behaviour) and whose most recent episode meeting the criteria for any of these 5 C-SSRS Suicidal Behavior items occurred within the last 2 years, OR Participants who, in the opinion of the investigator, present a serious risk of suicide
11. Any medical or psychological condition or social circumstances which may impair their ability to participate reliably in the study, or who may increase the risk to themselves or others by participating in the study
12. Significant ocular pathology
13. Concomitant medication that has a clinically relevant interaction with the CYP2C19 or CYP3A classes of liver enzymes will not be permitted from two weeks before inclusion until the end of the study. Examples of co-medication that will be not allowed will include CYP3A4 inhibitors (such as itraconazole, ketoconazole, posaconazole, fluconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, nefazodone, telaprevir, boceprevir, imatinib, ticagrelor, voriconazole), CYP3A4 inducers (such as carbamazepine, efavirenz, nevirapin, etravirin) and CYP2C19 inhibitors (such as moclobemine, fluvoxamine, chloramphenicol, fluoxetine)
14. Female patients who are pregnant or lactating
15. Female patients of childbearing potential who are not willing to use a highly effective method of contraception for the duration of the trial to prevent pregnancy, or abstain from heterosexual activity
*Females of childbearing potential are females who have experienced menarche and are not surgically sterilised (e.g. by hysterectomy, bilateral salpingectomy) or post-menopausal (defined as at least 1 year since last regular menstrual period).
** Highly effective methods of birth control are those with a failure rate of < 1% per year when

employed consistently and correctly, e.g. combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation: oral, intravaginal, transdermal; progestogen-only hormonal contraception associated with inhibition of ovulation: oral, injectable, implantable; intrauterine device (IUD), intrauterine hormone-releasing system (IUS); vasectomised partner
Sexual abstinence is considered to be highly effective method only if defined as refraining from heterosexual activity from the date of consent until end of treatment and for 2 weeks after. The reliability of this method should be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant
16. Known hypersensitivity to CBD, gelatine or micro-crystalline cellulose
17. Mechanistic sub-study only: Patients who have any contraindications to MRI, including: pacemakers, metallic foreign body in the eye, aneurysm clip in their brain, severe claustrophobia where patients would not be able to tolerate the scan etc

Date of first enrolment
19/10/2020

Date of final enrolment
02/03/2025

Locations

Countries of recruitment
United Kingdom

England

Scotland

Wales

Study participating centre
King's College Hospital NHS Foundation Trust (lead centre)
-
London
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Study participating centre
South London and Maudsley NHS Foundation Trust
-
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Study participating centre
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NE9 6SX

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Sponsor information

Organisation
King’s College London and South London & Maudsley NHS Foundation Trust

ROR
https://ror.org/015803449

Funder(s)

Funder type
Charity

Funder Name
Parkinson's UK; Grant Codes: G-1901

Alternative Name(s)
Parkinson's Disease Society

Funding Body Type
Private sector organisation

Funding Body Subtype
Associations and societies (private and public)

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No