A study to investigate the effects of repeated low doses of psilocybin and ketamine on cognitive and emotional dysfunctions in Parkinson*s disease and to understand its mechanism of action

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The primary objective is to investigate the effects of repeated small doses of psilocybin and ketamine on affect (self-rated). Secondary objectives are to is to investigate the effects of repeated small doses of psilocybin and ketamine on [1] well-...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Neurological disorders NEC
Study type	Interventional

Summary

ID

NL-OMON52045

Source
ToetsingOnline

Brief title
Microdosing and Parkinson*s disease

Condition

- Neurological disorders NEC

Synonym
Parkinson's disease

Research involving
Human

Sponsors and support

Primary sponsor: Universiteit Maastricht
Source(s) of monetary or material Support: Silo Pharma Inc.;US

Intervention

Keyword: Emotional functioning, Ketamine, Parkinson's Disease, Psilocybin

Outcome measures

Primary outcome

Main study parameter will be a (statistically significant) change in a subjective parameters (mood) after treatment with low doses of psilocybin and ketamine compared to placebo treatment.

Secondary outcome

Secondary parameters are to is to investigate the effects of repeated low doses of psilocybin and ketamine on [1] well-being, [2] (emotional) attention, [3] neuroplasticity, [4] cognitive performance measures of memory and executive functioning, known to be impaired in Parkinson*s disease (computer tasks), [5] emotion regulation, [6] Parkinson*s symptoms, and [7] biological markers of wellbeing (microbiome, immune system, cortisol).
A tertiary parameter is to investigate the effects of repeated low doses of psilocybin on and ketamine the endocannabinoid system, by measuring endocannabinoid concentrations (AEA and 2-AG) in blood plasma.

Study description

Background summary

Parkinson's disease is a neurodegenerative disorder with an estimated

prevalence of 2-3% in the population older than 65 years. Treatment is symptomatic and focused on motor symptoms, while patients also suffer from non-motor symptoms, including cognitive and emotional problems. Emotional state has been shown to negatively affect quality of life and levels of stress affect motor symptoms. The need for alternative drugs with fewer side effects that can also improve emotional and cognitive processes is clear.
Ketamine and psychedelics, previously shown to improve mental well-being and mood, have also been shown to positively affect the immune system and enhance neuroplasticity, the brain's ability to form new neural connections and neurons. In animal models of Parkinson's disease (PD), enhanced neuroplasticity (BDNF) has been shown to aid the survival of dopaminergic neurons, resulting in improved dopaminergic neurotransmission and motor performance.
Recently, we have shown that a low dose of LSD increases BDNF levels up to 6 hours after administration. In addition to increased neuroplasticity, low dose LSD also increased positive mood, improved connectivity in brain regions involved in emotional processing, and improved attention performance. Ketamine has been shown to have a rapid antidepressant effect in patients with depression. An increase in BDNF is hereby suggested to underlie the positive effects of psilocybin and ketamine.
Low doses of psilocybin and ketamine are therefore proposed to alleviate cognitive and emotional disturbances in patients with Parkinson's disease.

Study objective

The primary objective is to investigate the effects of repeated small doses of psilocybin and ketamine on affect (self-rated).
Secondary objectives are to is to investigate the effects of repeated small doses of psilocybin and ketamine on [1] well-being (self-rated), [2] emotional and cognitive attention (computer tasks), [3] biological markers of neuroplasticity (BDNF in blood samples), [4] cognitive performance measures of memory and executive functioning, known to be impaired in Parkinson*s disease (Robbins & Cools, 2014) (computer tasks), [5] emotion regulation (self-rated), [6] Parkinson*s symptoms, and [7] biological markers of wellbeing (microbiome, immune system, cortisol). A tertiary objective includes investigating the effect of repeated low doses of psilocybin and ketamine on the endocannabinoid concentrations in blood samples.

Study design

The study design will be double-blind, placebo-controlled, randomized cross-over, with three treatment conditions. Treatments will be psilocybin (5 mg), ketamine (35 mg) and placebo, administered three times, with one day in between each dose. There will be six possible treatment orders, and participants will be assigned randomly to one of these orders. Participants will be assessed on cognitive and emotional skills after the first and third dose of each drug condition. They will be assessed before and after dosing to

have a baseline measurement and an *acute* treatment effect measurement. On the dose-less days they will be asked to fill out their diary. There will be one week wash-out in between the treatment conditions.

Intervention

Psilocybin is a serotonin 2A receptor agonists. Ketamine is a glutamate receptor (NMDA) antagonist. Effects are expected to last up to 4 hours. Participants will receive three doses of psilocybin (5 mg), ketamine (35 mg) and 3 times placebo.

Study burden and risks

The patients will be enrolled for minimally seven weeks. In this period they will undergo medical screening (blood and urine sample will be taken), a training (familiarization with procedures, tasks, and questionnaires), and three treatment periods (psilocybin, ketamine, placebo). During a treatment period they will receive three doses, with one day in between treatments. On the first test day of each condition, five blood samples will be taken. Blood samples will serve to determine markers of immune function, neuroplasticity, cortisol and endocannabinoid levels. Questionnaires and tests assessing mood and cognitive functions will be offered during the day. Potential discomfort will be linked to the blood draw, and the administration of placebo, in case low doses of psilocybin and ketamine boost their emotional and cognitive performance, which will not be experienced in the period when they receive a placebo. Also, standard medication for Parkinson's disease will be postponed for 7 weeks while being enrolled in the study, this can be considered a disadvantage for patients who want to take this medication and would experience benefit from it.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- At least 18 years of age
- Being diagnosed with Parkinson*s Disease
- Underwent a DAT scan as part of the diagnostic process
- Being able to provide details about the duration of the disease or provide medical records
- Free from conventional Parkinson medication (i.e., Levodopa, dopamine agonist, amantadine, adenosine a2a antagonist, COMT inhibitors, anticholinergic drugs, MAO inhibitors)
- The participant is, in the opinion of the investigator, generally healthy based on assessment of medical history, physical examination, vital signs, electrocardiogram (ECG), and the results of the haematology, clinical chemistry, urinalysis, serology, and other laboratory tests
- A resting pulse and heart rate (as read on the ECG) *51 bpm and *100 bpm. For participants in good physical condition, the lower limit is *45 bpm.
- A resting systolic blood pressure *91 mmHg and *140 mmHg and a resting diastolic blood pressure *51 mmHg and *90 mmHg.
- Clinical laboratory test values within clinical reference ranges at screening. Borderline values may be accepted if they are, in the opinion of the investigator, clinically insignificant.
- Normal binocular visual acuity, corrected or uncorrected
- Absence of any major medical, endocrine and neurological condition (apart from Parkinson*s disease), as determined by the medical history, medical examination, electrocardiogram and laboratory analyses (haematology, clinical chemistry, urinalysis, serology).
- Normal weight, body mass index (weight/height2) between 19,5 and 28 kg/m2
- Being able to communicate in Dutch or English
- Written informed consent

Exclusion criteria

- Previous experience of serious side effects to psychedelic drugs (anxiety or panic attacks)
- Use of conventional Parkinson*s disease medication or other psychiatric medication (i.e., Levodopa, dopamine agonist, amantadine, adenosine a2a antagonist, COMT inhibitors, anticholinergic drugs, MAO inhibitors)
- History of drug addiction (determined by the medical questionnaire, drug questionnaire and medical examination)
- Depression or dementia
- Excessive alcohol consumption (>20 units a week)
- Excessive smoking (>20 cigarettes a week)
- Current or history of psychiatric disorder (determined by the medical questionnaire and medical examination)
- Hypertension (diastolic >90; systolic >140)
- Liver dysfunction
- History of cardiac dysfunctions (arrhythmia, ischemic heart disease, etc)
- Pregnancy or lactation
- For women of childbearing potential: absence of reliable contraceptive measures
- Experience with a full dose of a psychedelic within the last three months

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	34

Type:	Anticipated

Ethics review

Approved WMO Date:	10-11-2021
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	22-02-2022
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2021-000041-40-NL
CCMO	NL76320.068.21