Sub(acute) Neuropsychopharmacological Profiling of 2C-B vs Psilocybin

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Primary Objective: Idenitfying 2C-B*s effects in relation to the commonly used psychedelic psilocybin and placebo on neurocognition by using the Digit Symbol Substitution Task.
Secondary Objective(s): Probing different aspects of the acute changes...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON50024

Source
ToetsingOnline

Brief title
Sub(acute) Profiling of 2C-B vs Psilocybin

Condition

- Other condition

Synonym
Not applicable

Health condition

drug effects, drug metabolites

Research involving
Human

Sponsors and support

Primary sponsor: Universiteit Maastricht
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Metabolomics, Neuropsychopharmacology, Novel psychoactive substance, Psychedelics

Outcome measures

Primary outcome

-Acute Digit Symbol Substitution Task performance (DSST)

Secondary outcome

- Acute fMRI cognitive reappraisal task performance and fMRI activation

-Acute embodiment reality task and questionnaire performance

- Subjective effect questionnaires scores

- Neurocognitive task performance

- fMRI resting state functional connectivity

- Magnetic resonance spectroscopy neurotransmitter concentrations and metabolic activity

- Plasma metabolomics (steroid hormones, neurotransmitters, endocannabinoids, drug metabolitex) concentrations

- Plasma and ear-wax drug kinetics

- Subacute and prepost persisting effect questionnaires scores

- Subacute and prepost behavioural task performance

Study description

Background summary

Novel psychoactive substances (NPS) are emerging at a fast pace (EMCDDA 2018, UNODC 2019) These are psychotropic drugs that are not controlled by the 1961 United Nations Single Convention on Narcotic Drugs or the 1971 United Nations Convention on Psychotropic Substances, but which are liable to abuse and dependence, producing similar effects on the central nervous system compared to scheduled compounds (Schifano, Orsolini et al. 2015). The risk they pose is indicated by their prevalence across 94 countries/territories and recreational drug users, with some 5% of 19-24 years old Europeans having already experimented with some forms of an NPS (UNODC 2014).

Information on their clinical pharmacology and toxicity is in most cases very limited. Given the large number of new compounds released on the market each year a timely evaluation of NPS by current standards in ex-vivo and in-vivo animal models or expert evaluations is unfeasible. Here we we intend for a targeted imaging-metabolomics approach in humans that provides fast classifications of NPS and their effects on brain function. In order to do so, we will conduct placebo-controlled clinical trials to assess acute effects of on resting state brain networks, neurocognition and metabolomics. A predictive model based on machine learning algorithms will use the quantification of neurotransmitters, endocannabinoids, steroid hormones and their metabolites in blood, functional connectivity in resting state brain networks and neurocognitive function to predict the similarity of a new drug to classical drugs of abuse. This initiative is based on previous preclinical work in rodent models (Olesti, De Toma et al. 2019). In order to collect the necessary parameters for the algorithm, a series of clinical trials employing NPS (2C-B, 4-fluoroamphetamine, JWH-018 and mephedrone) in healthy volunteers are to be carried out.

The present study marks the first of this series and will investigate the effects of 2C-B which shows substantial effect overlaps with classical stimulants and psychedelic drug classes. 2C-B belongs to the 2C class of phenylethylamine derivatives and is a hallucinogenic substituted phenethylamine NPS and since its development in the 1970s, has spawned a number of NPS phenylethlamines with a significantly higher risk profile.
These developments are the result of its similarities with popular recreational psychedelics, which generate similar changes to consciousness and have a long-lasting impact on behaviour and mood.

As a result, 2C-B is an optimal template compound for distinction of NPS harms from classical psychedelics such as psilocybin which show low to modest risk. Further due to its equivalent popularity and the absence of data on its neuropsychopharmacology, it may represent a potentially high level of societal risk, which requires investigation.

Methods and results produced by the outcome of this research project can be implemented in NPS risk assessment procedures at European and national levels and can be adopted by emergency departments in any hospital. Metabolomics screenings at emergency departments would allow a fast classification of unknown NPS relative to a reference NPS and/or classical drugs of abuse and inform clinicians on which treatment protocol to select. The current research will therefore improve identification and classification of NPS, improve knowledge on health risks associated with NPS, and advance evidence-based policy making..In addition, public knowledge about the hazards of NPS will also contribute to a better weighted opinion about these substances by drug users and can result in use reduction or harm reduction in the future and may therefore prevent serious health consequences.

Study objective

Primary Objective: Idenitfying 2C-B*s effects in relation to the commonly used psychedelic psilocybin and placebo on neurocognition by using the Digit Symbol Substitution Task.

Secondary Objective(s): Probing different aspects of the acute changes to neurocognition, phenomenology and the underlying neural correlates of 2C-B by using neurocognitive tests, subjective effect questionnaires and fMRI. Further, to map out 2C-B*s pharmacokinetics and metabolomics using blood samples and MRS investigations. Specific to psychedelic experiences, drug-induced changes in emotional regulation and self-embodiment will be investigated by employing an fMRI emotional regulation task and a VR scenario. Lastly, to investigate subacute effects of psychedelic drugs on neurocognition, social cognition, aggression and impulsivity.

The overarching goal is to use this data to provide a complete neuropsychopharmacological mapping of 2C-B's effects as to incorporate the data in a predictive algorithm which can aid in judicial drug classification and harm-reduction.

Study design

The present study will employ double-blind, randomized, placebo controlled, within-subject crossover design. Participants will receive on three separate occasions either placebo, 20 mg 2C-B or 15 mg psilocybin. One day and five days following each acute dosing session, participants will be evaluated for subacute behavioural effects. Each drug condition will be subject to a fourteen-day washout period, commencing upon completion of each five-day follow-up. A 14-day washout has been decided on the basis of minimising carryover effects that may arise from persisting psychedelic drug effects, which are found to be absent in previous studies when employing a similar timeframe (Kraehenmann 2015).

Intervention

20mg 2C-B, 15 mg Psilocybin, placebo (bitter lemon soft drink)
Each to be administered orally, dissolved as a solution in bitter lemon soft drink.

Study burden and risks

During acute dosing days participants will need to stay for 6 hours at the unit and have blood, earwax and urine samples taken. They will need to partake in an fMRI scanning session in which they will need to stay still for over 55 minutes, complete a series of computer/tablet neurocognitive tasks, subjective effect questionnaires and a virtual reality paradigm.
The morning after they will need to return for 3 hours to complete further computer-based behavioural tasks and persisting effect questionnaires. They will also need to email a patient diary 5 days after each dosing visit 1h to provide a patient diary in which they noted all side effects they may have experienced, along with the completion of persisting effect questionnaires online via Qualtrics.
Including the medical screening and training day, the total participation time is 33 hours over the course of 9 weeks (including washouts and training).
Participants must also refrain from drug-use, alcohol and pregnancy throughout the trial and cannot smoke during dosing days.
They must also provide demographic data.

The acute effects of the stated dose of 20mg 2C-B indicated in the literature include; pro-sociability, euphoria, stimulation, changes in perception, hallucinations, internal narratives, introspection, emotionality
The acute common risks of the stated 20mg 2C-B indicated in the literature include; nausea, tremors, difficulty focusing gaze, hypertension, tachycardia, sweating. Survey data has indicated insomnia, headaches, involuntary reoccurrences of the psychoactive effects and hallucinations ("flashbacks") as common potential subacute effects (+48h). An indirect case of persistent psychosis has been reported in the literature.

For 15mg psilocybin, the main effects include; hallucinations, introspection, changes in perception, disembodiment, emotionality and the main side effects are anxiety, paranoia and tachycardia.

For both of these drugs, the principal concern is long lasting adverse psychological reactions which may manifest as panic attacks, anxiety and paranoia.

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

• Previous experience with at least one psychedelic substance (e.g., psilocybin, LSD, DMT, ayahuasca, psilocybe fungi >=1 times) but not within the past three months
• Aged between 18 and 40 years
• Free from medication (any drug prescribed for a medical indication)
• 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, 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
• Written informed consent

Exclusion criteria

• Previous experience of serious side effects to psychedelic drugs (anxiety or panic attacks)
• Use of medication (other than paracetamol)
• History of drug addiction (determined by the medical questionnaire, drug questionnaire and medical examination)
• 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 (hepatitis, cirrhosis, cancer, biliary cholangitis, hemochromatosis
alcoholic liver disease, etc as determined by the medical examination)
• Renal insufficiency (as indicated by the medical examination)
• History of cardiac dysfunctions (arrhythmia, ischemic heart disease, etc)
• Pregnancy or lactation
• For women: absence of reliable contraceptive measures
• fMRI contraindications (pacemakers, metal implants, claustrophobia, permanent eye makeup)

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)

Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	23-06-2021
Enrollment:	24
Type:	Actual

Ethics review

Approved WMO

Date:	06-05-2021
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
CCMO	NL73539.068.20
Other	NL8813