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Psilocybin vs escitalopram for depression

Submission date	Recruitment status	[X] Prospectively registered
03/08/2018	No longer recruiting	[_] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
10/09/2018	Completed	[X] Results
Last Edited	**Condition category**	[_] Individual participant data
28/06/2022	Mental and Behavioural Disorders	

Plain English summary of protocol

Background and study aims
Depression is the leading cause of disability in the world, according to the World Health Organisation. Despite this, treatment of depression has not significantly advanced since the discovery and marketing of selective serotonin reuptake inhibitor drugs (SSRIs) in the 80s and 90s. While SSRIs work well for some people, many do not want to have to rely on taking them every day and can suffer a variety of side effects. Additionally, about 20% of people with major depression are “treatment-resistant”, meaning that no currently licensed anti-depressant treatment seems to work for them at all.
Psychedelic substances such as psilocybin (the active ingredient in so-called ‘magic mushrooms’) act via the same system of the brain as SSRIs. Between the 1940s and 1960s, before psychedelics were made illegal, nearly 2000 scientific papers were published on them, several of which suggested potential for treating disorders such as depression, addiction, PTSD, etc.
In 2016, we (the Psychedelic Research Group at Imperial College London) carried out a study where we provided 20 patients with severe treatment-resistant depression with psilocybin. This study was mostly focused on safety, but the results were encouraging, with 50% showed improvement after 3 weeks, with some patients in remission over a year later. This study aims to build on this research, comparing psilocybin with a standard SSRI, escitalopram. We want to look at the different effects that psilocybin and escitalopram on the brain's response to emotional faces, changes in depressive symptoms, anxiety, side-effects and personality.

Who can participate?
UK residents between the ages of 18-80 who have been diagnosed with moderate to severe unipolar major depressive disorder by a UK general practitioner

What does the study involve?
All participants will receive two doses of psilocybin, three weeks apart. Psilocybin dosages will vary across the study. Some participants will also take escitalopram for 6 weeks (10mg for 3 weeks then 20mg for a further 3 weeks) and the rest will take daily placebo capsules instead. The study is double-blind, so neither the participants nor the researchers will know what treatments each participant is receiving. All participants will be scanned before the first psilocybin dose and then 6 weeks later. There will be 7 study visits over the course of 3-4 months and participants will be expected to complete weekly questionnaires. There will also be a Skype interview 6 months after treatment and further monthly measures during that time period.

What are the possible benefits and risks of participating?
The possible benefit of taking part in this study is that the treatment may help to improve depressive symptoms; however, there is no guarantee of this. Additionally, enrolling in this research will help us understand more about the potential of psilocybin as a treatment for depression, contributing to knowledge that may help make this new form of therapy legal in the United Kingdom. It will also help us understand the differences in mechanisms between this new potential treatment and ones currently used in the NHS.
However, any participant who wishes to be involved must come off any anti-depressant medication they are currently on, which can take weeks and can be difficult. We will liaise with each participant's GP to make sure that this is done safely. If participants are randomised into a group that will be taking escitalopram, they might experience side-effects associated with this drug. Common side effects include agitation, restlessness, diarrhoea, sleeping difficulties, dry mouth, headache, nausea, sexual difficulties, dizziness and sweating. Less common side effects include frequent urination, indigestion, increased or decreased appetite, taste alterations, shaking, tingling, weight changes, influenza-like symptoms and pain in neck or shoulders, serotonin syndrome, suicidal thinking and behaviour, abnormal bleeding, seizures, manic episodes, low sodium and angle closure glaucoma. Psilocybin has been shown to be quite safe within a research setting, and side-effects only include pre-dose anxiety and headaches the next day. This study requires a lot of time commitment and so we would like to make sure that participants are fully aware of this before they enrol.

Where is the study run from?
Imperial College Hammersmith Campus, London

When is the study starting and how long is it expected to run for?
January 2017 to October 2020

Who is funding the study?
Alexander Mosely Charitable Trust (UK)

Who is the main contact?
Ms Bruna Giribaldi
b.cunha@imperial.ac.uk

Contact information

Type(s)
Scientific

Contact name
Ms Bruna Giribaldi

Contact details
Imperial College London Hammersmith campus
Du Cane Rd
London
United Kingdom
W12 0NN

Additional identifiers

ClinicalTrials.gov (NCT)
NCT03429075

Clinical Trials Information System (CTIS)
2017-000219-18

Integrated Research Application System (IRAS)
221666

Protocol serial number
IRAS ID: 221666, sponsor: 17HH3790

Study information

Scientific Title
Psilocybin versus escitalopram for major depressive disorder: comparative mechanisms

Acronym
Psilodep

Study objectives
Primarily this study aims to compare the mechanisms by which the psychedelic substance psilocybin and the selective serotonin reuptake inhibitor (SSRI) escitalopram may exert antidepressant action in 50 patients with moderate-severe major depressive disorder. Specifically, the amygdala's BOLD (blood-oxygen-level-dependent signal) response to emotional faces in a functional magnetic resonance imaging (fMRI) task.

Ethics approval required
Old ethics approval format

Ethics approval(s)
NRes Brent Research Ethics Committee, 31/07/2018, 17/LO/0389

Primary study design
Interventional

Study design
Interventional double-blind randomised controlled phase II clinical trial

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Moderate to severe major depressive disorder (17+ HAMD)

Interventions
After enrolment, patients are randomly assigned randomisation numbers by our unblinded team that will correspond to treatment arms. These numbers are provided to us by the company that labels the psilocybin bottles. Participants will be randomised into 2 groups. Participants in both groups will receive 2 doses of psilocybin, 3 weeks apart from each other. One group will then

also receive a placebo for 6 weeks. The other group will receive 6 weeks of escitalopram (10 mg daily for 3 weeks, followed by 20 mg daily for the remaining 3 weeks).
Participants will be asked to attend the study centre 7 times. Visit 1 is a screening, where participants will enrol on the study and sign informed consent. 2-4 weeks later, visit 2 will involve preparation for the first psilocybin dosing session and their first fMRI scan. Visit 3 will be 1 day later, where participants receive psilocybin for the first time, and either escitalopram or placebo capsules (depending on group allocation) to take daily for the next 6 weeks. Visit 4 will occur 1 day later, which involves a follow-up with study guides and therapists who were present at the psilocybin dosing session to discuss what they experience. 3 weeks after the first dose, visit 5 will involve the second psilocybin dosing session. Visit 6 is 1 day later, which again involves a follow-up with study guides and therapists who were present at the psilocybin dosing session. 3 weeks after the second dose, visit 7 will be a final follow-up and a second fMRI scan.
Participants will be asked to complete weekly questionnaires for 6 months following the final session and to take part in a Skype interview 6 months after the final session.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Psilocybin Escitalopram

Primary outcome(s)
Amygdala's BOLD-response to fearful faces in fMRI emotional faces task, assessed at the baseline (1 day before first psilocybin dose) and at final follow-up (6 weeks after first psilocybin dose)

Key secondary outcome(s)
1. Self-rated depression, assessed using:
1.1. Quick Inventory of Depressive Symptomatology (QIDS-16), assessed weekly from the point of enrolment until visit 7, then monthly up to 6 months after visit 7, along with at visit 2, visit 4, 1 day before visit 5 and at visit 6
1.2. Beck's Depression Inventory (BDI-II), assessed at visit 1, visit 2, 2 weeks after visit 3, 4 weeks after visit 5 and visit 7
2. Clinician-rated depression, assessed at visit 1, visit 2, just before visit 5 and at visit 7 using:
2.1. Hamilton Depression Scale (HAM-D)
2.2. Montgomery and Asberg Depression Rating Scale (MADRS)
3. Trait anxiety, assessed using Spielberger's Trait Anxiety Inventory at visit 2, 1 week post first psilocybin dose and visit 7, and just before both psilocybin doses (visit 3 and visit 5)
4. Wellbeing, assessed using the Warwick-Edinburgh Mental Wellbeing Scale (WEMWBS) at visit 1, visit 2, 2 weeks after visit 3, 4 weeks after visit 5 and visit 7
5. Self-perceived success, assessed using the Flourishing Scale (FS-8) at visit 2 and visit 7, and 3 and 6 months after visit 7
6. Anhedonia, assessed using the Snaith Hamilton Anhedonia Pleasure Scale (SHAPS) at visit 2 and visit 7
7. Optimism and pessimism, assessed using the Life Orientation Test (LOT-R) at visit 2 and visit 7
8. Meaning in life, assessed using the Meaning in Life Questionnaire (MLQ) at visit 2 and visit 7, and 3 and 6 months after visit 7
9. Resilience, assessed using the Brief Resilience Scale (BRS) at visit 2 and visit 7

10. Dysfunctional attitudes, assessed using the Dysfunctional Attitudes Scale (DAS) at visit 2 and visit 7
11. Personality traits, asssessed using the 44-item Big Five Inventory (BFI) at visit 2 and visit 7, and 3 and 6 months after visit 7
12. Delusion, assessed using Peters 21-item Delusions Inventory (PDI-21) at visit 2 and visit 7
13. Rumination, assessed using the Ruminative Responses Scale (RRS) at visit 2 and visit 7
14. Thought suppression, assessed using the White Bear Suppression Inventory (WBSI) at visit 2 and visit 7
15. Impulsivity, assessed using the Barrett Impulsivity Scale (BIS) at visit 2 and visit 7
16. Experiential avoidance, assessed using the Brief Experiential Avoidance Questionnaire (BEAQ) at visit 2 and visit 7
17. Absorption, assessed using the Modified Tellegen Absorption Questionnaire (MODTAS) at visit 2 and visit 7
18. Relationship between patient and guide from both perspectives, assessed using the Scale To Assess The Therapeutic Relationship (STAR) at visit 2 and before visit 5
19. Expectation, assessed using the Credibility/Expectancy Questionnaire (CEQ) at visit 2 and before visit 5
20. Connectedness to nature, assessed using the Connectedness to Nature Scale (CNS) at visit 2 and visit 7, and 3 and 6 months after visit 7
21. Political views, assessed using the Political Perspective Questionnaire (PPQ) at visit 2 and visit 7, and 3 and 6 months after visit 7
22. Connectedness to others, assessed using the Social Connectedness Scale (SCS) at visit 2 and visit 7, and 3 and 6 months after visit 7
23. Compassion, assessed using 5 items of the Revised Santa Clara Brief Compassion Scale (SCBCS) at visit 2 and visit 7
24. Gratitude, assessed using the Gratitude Questionnaire (GQ-6) at visit 2 and visit 7
25. Suggestibility, assessed using the Short Suggestibility Scale (SSS) at visit 2 and visit 7
26. Self-esteem, assessed using 4 items of the Rosenberg Self-Esteem Scale (RSE) at visit 2 and visit 7
27. Experience of 'spiritual transcendence', assessed using the Universality subscale of the Spiritual Transcendence Scale (STS) at visit 2 and visit 7
28. Emotional intensity, assessed using Lauks Emotional Intensity Scale (LEIS) at visit 7
29. Suicidal ideation, assessed using the Suicidal Ideation Attributes Scale (SIDAS) at visit 2 and visit 7
30. Sexual dysfunction, assessed using the Psychotropic-Related Sexual Dysfunction Questionnaire (PRSEXDQ-SALSEX) at visit 7
31. Sexual function, assessed using the Brief Index of Sexual Functioning for Women (BISF-W) (used for both genders) at visit 2 and visit 7
32. Sexual perceptions, assessed using the self-constructed 2-item Sexual Perceptions Questionnaire (SPQ) at visit 2 and visit 7
33. Work productivity and activity impairment, assessed using the Work Productivity and Activity Impairment Questionnaire (WPAI) at visit 2 and visit 7, and 3 and 6 months after visit 7
34. Impairment in functioning, assessed using the Work and Social Adjustment Scale (WSAS) at visit 2 and visit 7, and 3 and 6 months after visit 7
35. Connectedness to self, others and the world, assessed using the self-constructed Connectedness Questionnaire at visit 2, visit 4, visit 6 and visit 7, and 3 and 6 months after visit 7
36. Personality disorders, assessed using the Standard Assessment of Personality - Abbreviated Scale (SAPAS) at visit 2 and visit 7
37. Insight, assessed at visit 2 and visit 7 using:
37.1. Mastery Insight Scale (MIS, taken from the Therapeutic Realisations Scale)
37.2. Self-reflection and insight, assessed using the Self-Reflection and Insight Scale (SRIS)
37.3. Self-constructed Psychological Insight Scale (PIS)

38. Metaphysical beliefs, assessed using the self-constructed Metaphysical Beliefs Questionnaire (MBQ) at visit 2 and visit 7
39. Spiritual bypassing, assessed using the self-constructed Spiritual Bypassing Scale (SBS) at visit 2 and visit 7
40. Adverse childhood experiences, assessed using the Adverse Childhood Experience Questionnaire (ACE) at visit 2 and visit 7
41. Experience of a particular song in session, assessed using the self-constructed Therapeutic Music Experience Questionnaire (TMEQ) at visit 4 and visit 6
42. Experience of setting, assessed using the self-constructed Setting Questionnaire (SQ) at visit 4 and visit 6
43. Ability to become 'absorbed' when listening to music, assessed using selected items from the Absorption in Music Scale (AIMS - revised) at visit 2 and visit 7
44. Patient's mindset prior to psychedelic experience, assessed using the self-constructed psychedelic predictor scale, completed just before both psilocybin dosing days (visit 3 and visit 5)
45. Surrender, assessed using the self-constructed surrender scale just before both psilocybin dosing days (visit 3 and visit 5)
46. Emotional processing, assessed using the Emotional Processing Battery at visit 2 and visit 7
47. Autobiographical memory content, assessed using the Cued Autobiographical Memory Task (AMT) at visit 2 and visit 7
48. Prediction of future life events, assessed using the Prediction of Future Life Events (POFLE) task at visit 2 and visit 7
49. Emotional response to music, assessed using the Geneva Emotional Music Scales (GEMS) at visit 2 and visit 7
50. Verbal learning and memory, assessed using the California Verbal Learning Test (CVLT) at visit 2 and visit 7
51. Digit Symbol Substitution Test (DDST) at visit 2 and visit 7
52. Subjective states during psilocybin dosing sessions, assessed at the end of the dosing sessions (visit 3 and visit 5):
52.1. Ego dissolution, assessed using the Ego Dissolution Inventory (EDI)
52.2. Mystical experiences, assessed using the Mystical Experience Questionnaire (MEQ)
52.3. Altered states of consciousness, assessed using the 11 Dimension Altered States of Consciousness Scale (11D ASC)
52.4. Visual Analogue Scales (VAS)
52.5. Challenging aspects of experiences, assessed using the Challenging Experience Questionnaire
52.6. Imperial Emotional Breakthrough Inventory (EBI)
52.7. Near-death experiences, assessed using the Near-Death Experience scale (NDE)

Completion date
17/10/2020

Eligibility

Key inclusion criteria
1. Major depressive disorder (DSM-IV)
2. Depression of moderate to severe degree (17+ on the 21-item HAM-D).
2. No MRI contraindications
3. No SSRI contraindications
4. Has a GP or other mental healthcare professional who can confirm diagnosis
5. Aged 18-80
6. Sufficiently competent with English language

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Upper age limit
80 Years

Sex
All

Total final enrolment
59

Key exclusion criteria
1. Current or previously diagnosed psychotic disorder
2. Immediate family member with a diagnosed psychotic disorder
3. Medically significant condition rendering unsuitability for the study (e.g. diabetes, epilepsy, severe cardiovascular disease, hepatic or renal failure e.g. CLRC < 30 ml/min etc)
4. History of serious suicide attempts requiring hospitalisation.
5. Significant history of mania (determined by study psychiatrist and medical records)
6. Psychiatric condition judged to be incompatible with establishment of rapport with therapy team and/or safe exposure to psilocybin (e.g. borderline personality disorder)
7. Blood or needle phobia
8. Positive pregnancy test at screening or during the study, women who are planning a pregnancy and/or women who are nursing/breastfeeding.
9. Participants who do not agree to use an acceptable contraceptive method throughout their participation in study.
10. Current drug or alcohol dependence
11. No email access
12. Use of contraindicated medication
13. Patients presenting with abnormal QT interval prolongation at screening or with a history of this (QTc at screening above 440ms for men and above 470ms for women)

Date of first enrolment
10/09/2018

Date of final enrolment
04/03/2020

Locations

Countries of recruitment

United Kingdom

England

Study participating centre
Imperial College London Clinical Research Facility (ICRF)
Imperial College London Hammersmith campus
Commonwealth building
Du Cane Road
London
W12 0NN
London
United Kingdom
W12 0NN

Study participating centre
Invicro LLC
Imperial College London Hammersmith campus
Burlington Danes building
Du Cane Road
London
W12 0NN
London
United Kingdom
W12 0NN

Sponsor information

Organisation
Imperial College Joint Research Compliance Office (JRCO)

ROR
https://ror.org/041kmwe10

Funder(s)

Funder type
Not defined

Funder Name
Alexander Mosely Charitable Trust

Results and Publications

Individual participant data (IPD) sharing plan
Not provided at time of registration

IPD sharing plan summary
Not expected to be made available

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		15/04/2021	28/06/2022	Yes	No
Results article	Increased global integration in the brain after psilocybin therapy for depression	01/04/2022	28/06/2022	Yes	No
Results article	Therapeutic Alliance and Rapport Modulate Responses to Psilocybin Assisted Therapy for Depression	31/03/2022	28/06/2022	Yes	No
HRA research summary			28/06/2023	No	No
Interim results article		01/02/2018	28/06/2022	Yes	No