Safety and Efficacy of Psilocybin for Body Dysmorphic Disorder

NCT04656301

January 10, 2023

Study Protocol and Statistical Analysis Plan

Protocol Title:
Safety and Efficacy of Psilocybin for Body Dysmorphic Disorder

Version Date:
01/10/2023

Protocol Number:
7950

First Approval:
02/27/2020

Research Area:
Anxiety, Mood, Eating & Related Disorders
Division:
Anxiety/PTSD/OCD

Expiration Date:
02/09/2024

Contact Principal Investigator:
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Co-Investigator(s):
David Hellerstein, MD

Research Chief:
Helen Simpson, MD

Cover Sheet

Choose ONE option from the following that is applicable to your study
If you are creating a new protocol, select "I am submitting a new protocol." As 5 Year Renewals are no longer required, this option remains for historical purposes.
I am submitting an annual continuation without modifications

Department & Unaffiliated Personnel

Department

What Department does the PI belong to?
anxiety-mood-eating and related disorders
Within the department, what Center or group are you affiliated with, if any?
anxiety disorders clinic

Unaffiliated Personnel

List investigators, if any, who will be participating in this protocol but are not affiliated with New York State Psychiatric Institute or Columbia University. Provide: Full Name, Degrees and Affiliation.
Consultant Jamie Feusner, MD; University of Toronto

Application for Continuation of Research

Status

Current Status of Study:
All research interventions were completed. Only data analysis is ongoing.

Summary of Experiences to Date

Please provide a summary of scientific progress of the study and the experience of research participants, to date. This requirement is designed to allow for the investigator and the IRB to reassess the study's risks and benefits in terms of developments in the field, changing practice patterns, and new IRB policies and procedures.
The study has concluded and is in the data analysis stage. Recruitment is closed and subject follow-ups have been completed. A total of 12 participants were enrolled in the study with 5 participants enrolling in the past year. None of the participants were withdrawn from the study or discontinued. There are no Serious Adverse Events to report.

Funding

Have there been any changes in funding status since the prior approval?
No
Have the principal investigator and other investigators made all required disclosures of financial interest in the study sponsor/product?
Yes

Summary

Have there been any study findings, recent literature, or untoward events occuring here or at other sites in the past year which might affect the analysis of the safety, risks or benefits of study participation?
No
Have there been any serious adverse events (serious and/or unanticipated problems involving risks to subjects or others at this site which occured in the past year)?
No
Have all study staff with a significant role in the design or implementation of the human subject components of this study received required training in human research subject protections?
Yes
Is the study covered by a certificate of confidentiality?
Yes
Certificate expiration date (mm/dd/yyyy)
12/13/2023

Overall Progress

Approved sample size
12
Total number of participants enrolled to date
12
Number of participants who have completed the study to date
12
Have there been any significant deviations from the anticipated study recruitment, retention or completion estimates?
No
Comments / additional information

Sample Demographics

Select the # of samples applicable
Fair
Specify population
White Participants
Total number of participants enrolled from this population to date
8
Specify population #2
Asian Participants
Total number of participants enrolled from this population to date
3
Specify population #3
Other
Total number of participants enrolled from this population to date
1
Specify population #4
Female
Total number of participants enrolled from this population to date
8
Specify population #5
Male
Total number of participants enrolled from this population to date
4
Gender, Racial and Ethnic Breakdown
Gender Breakdown 8 female participants 4 male participants Racial Breakdown 8 White participants 3 Asian Participants 1 participant who identified as other Ethnic Breakdown 1 participant who identified as Hispanic/Latino 11 participants who did not identify as Hispanic/Latino

Summary of Current Year's Enrollment and Drop-out

Number of participants who signed consent in the past year
5

Number of participants currently enrolled
0
Did the investigator withdraw participants from the study?
No
Did participants decide to discontinue study involvement?
No

Procedures

To create the protocol summary form, first indicate if this research will include any of the following procedures
✓ Collection of Biological Specimens
✓ Internet-based Data Collection or Transmission
✓ Medication Trial
✓ MRI
✓ Psychiatric Assessment
✓ Use of Investigational Drug or Device

Population

Indicate which of the following populations will be included in this research
✓ Adults
✓ Adults over 50

Protocol Summary Form

Research Support / Funding

This section is to describe the funding sources for your protocol.

If an internal account is to be used, please describe.

The internal account is ☐ RFMH ☐ CU

If the project is using, or planning to use, external funding, provide the details for each external funding source.

Compass Pathways

Principal Investigator on grant/contract	Franklin Schneier
Status of Grant (select one)	is currently funded
Source of Funding (select one)	Industry
Institute / Agency	N/A
Grant Name	Safety and Efficacy of Psilocybin for Body Dysmorphic Disorder
Grant Number	N/A
Sponsor	Compass Pathways
Is this research initiated by the investigator?	Yes
Site description (select one)	Single Site
Business Office (select one)	RFMH
If the grant/contract includes a subcontract, please describe. (To / From, Name of institution(s). Be sure to specify To or From)	N/A

Study Location

Indicate if the research is/will be conducted at any of the following:

☒ NYSPI ☐ Washington Heights Community Service ☐ Other Columbia University Medical Center Facilities

This Protocol describes research conducted by the PI at other facilities/locations:

☐ Office Of Mental Health Facilities

☐ Binghamton Psychiatric Center	☐ Bronx Children's Psychiatric Center
☐ Bronx Psychiatric Center	☐ Brooklyn children's Psychiatric Center
☐ Buffalo Psychiatric Center	☐ Capital District Psychiatric Center
☐ Central New York Psychiatric Center	☐ Creedmoor Psychiatric Center
☐ Elmira Psychiatric Center	☐ Greater Binghamton Health Center
☐ Hudson River Psychiatric Center	☐ Hutchings Psychiatric Center
☐ Kingsboro Psychiatric Center	☐ Kirby Forensic Psychiatric Center
☐ Manhattan Psychiatric Center	☐ Middletown Psychiatric Center
☐ Mid-Hudson Psychiatric Center	☐ Mohawk Valley Psychiatric Center
☐ Nathan S. Kline Institute	☐ Pilgrim Psychiatric Center
☐ Queens Children's Psychiatric Center	☐ Rochester Psychiatric Center
☐ Rockland Children's Psyciatric Center	☐ Rockland Psychiatric Center
☐ Sagamore Children's Pyschiatric Center	☐ St. Lawrence Psychiatric Center
☐ South Beach Psychiatric Center	☐ Western NY Children's Psychiatric Center

Or type in location(s)..

Click or tap here to enter text.

☐ Hospitals, clinics and other healthcare facilities

☐ Bridge Plaza Medical Center

☐ Harlem Hospital

☐ St. Luke's-Roosevelt Hospital Center

☐ Mount Sinai Medical Center

☐ Weill Cornell Medical Center

Or type in location(s)..

Click or tap here to enter text.

☐ Schools/Educational Institutions

Type in location(s)..

Click or tap here to enter text.

☐ Prison System(includes Parole)

Type in location(s)..

Click or tap here to enter text.

☐ International Sites

Type in location(s)..

Click or tap here to enter text.

☐ Other Facilities

Type in location(s)..

Click or tap here to enter text.

☐ Community Sources

Type in location(s)..

Click or tap here to enter text.

Lay Summary of Proposed Research

This section is intended to provide a basic overview of the study including a description of its purpose, study procedures, and subject population. The summary should provide a concise overview of the study for non-scientific and scientific members of the IRB. Please avoid medical or technical terminology. In general, the abstract of a grant does not provide a suitable lay summary.

Body dysmorphic disorder is a common condition characterized by symptoms of "imagined ugliness" with debilitating distress, checking and avoidance behaviors, and seeking unnecessary cosmetic medical procedures. Serotonin reuptake inhibitor medications and cognitive behavioral therapy helps some patients, but many do not benefit from existing treatments, and no medications are FDA-approved for this indication. Psilocybin is under development as a treatment of several psychiatric disorders, with placebo-controlled trial evidence of safety and prolonged efficacy for major depression when administered as a single dose with intensive support by a therapist on the day of administration. A single case report in body dysmorphic disorder suggests psilocybin might also have efficacy for this disorder.

In this proposed pilot study, up to 12 adults with body dysmorphic disorder that has not responded to at least one adequate trial of a serotonin reuptake inhibitor will be treated openly with a single oral dose of psilocybin. Procedures will follow those previously established in depression studies of psilocybin. Patients will receive intensive preparation and support from two therapists, including 8-9 hours accompanying the patient on the day of medication administration in the Biological Studies Unit. Follow-up visits to monitor safety and clinical outcome will be conducted at day 1, week1, and months 1, 2, and 3 post-administration. Resting state MRI will be conducted prior to and one day after psilocybin administration to assess the effect of medication on brain circuits.

Background, Significance, and Rationale

In this section, provide a brief summary of the status quo of the relevant work field and how the proposed study will advance knowledge. Specifically, identify the gaps in knowledge that your project is intended to fill. If no gaps exist that are obviously and directly related to your project, explain how your proposed research will contribute to the overall understanding of your field. Describe potential impacts of your project within your field of study and in a broader context. Provide a critical evaluation of existing knowledge. The literature review does not have to be exhaustive.

Significance and Rationale

Body dysmorphic disorder (BDD) is a debilitating psychiatric disorder in which individuals are preoccupied with perceived defects of their appearance that are not noticeable or appear slight to others, causing significant distress and functional impairment (Phillips 2005). Compulsive checking may occur, and sufferers may seek out unnecessary or risky cosmetic procedures. Most common concerns in BDD involve skin, hair, and nose. BDD has a high prevalence in the general population of 1.7%-2.9% (Buhlman et al., 2010), but it is under-studied. To date, there have only been controlled clinical trials to evaluate a single medication class – serotonin reuptake inhibitors (Phillips et al 2002, 2006; Hollander et al 1999) – and a single psychotherapy modality – cognitive-behavioral therapy (Wilhelm et al 2014). Although these treatments can be effective in many, they typically result in only partial symptom improvement and some individuals do not respond to either. There is a need for new intervention approaches.

The rationale for considering psilocybin as a potential treatment for BDD includes a case report (Hanes 2003), in which unsupervised use of psilocybin resulted in symptomatic improvement, as well as evidence for psilocybin efficacy in conditions that frequently co-occur or overlap with BDD, such as obsessive-compulsive disorder (Moreno et al, 2006) and major depressive disorder. The first step in further evaluation of the efficacy and safety of psilocybin for BDD is this proposed open trial, utilizing methods established in prior controlled trials of psilocybin for other disorders.

Psilocybin Background (see Studerus, et al., 2011, for a useful review)
"Magic mushrooms" have been used ceremonially and recreationally for thousands of years. psilocybin produces an altered state of consciousness (ASC) similar to LSD, characterized by marked alterations in perception, mood, and thought, including changes in the experience of time, space, perceptual hypersensitivity, illusions, and pseudohallucinations (i.e. hallucinations with intact reality testing and insight) intensification of affective responses, enhanced ability for introspection, regression to primitive and childlike thinking, and activation of vivid memory traces with pronounced emotional undertones (Fischer, 1971; Geyer and Vollenweider, 2008; Isbell, 1959; Leuner, 1962; Nichols and Chemel, 2006; Rümmele and Gnirss, 1961; Wolbach et al., 1962). These effects are similar to those of LSD, except of shorter duration (4-6 hours instead of 8-12 hours) and psilocybin tended to produce less anxiety, fewer panic reactions and affective disturbances, and milder vegetative side effects than LSD.

Direct pharmacologic effects of psilocybin appear to occur through stimulation (agonism) of various serotonin receptors, including 5-HT2A, 5-HT2B, 5-HT2C and 5-HT1A. The 5-HT2A receptor seems particularly important as many, but not all of psilocybin's effects are blocked by 5-HT2A receptor antagonists. Serotonergic hallucinogens such as psilocybin are considered relatively safe physiologically and do not produce dependence (Johnson et al., 2008; Leuner, 1981; Nichols, 2004).

Studerus et al., 2011, summarized patient experience, physiologic effects and follow-up from 8 studies in which 110 non-psychiatrically ill volunteers were given oral psilocybin 2-28 mg (depending on the study) or placebo and followed for up to 16 months. They report the following dose-dependent symptoms (i.e., the higher the dose, the greater the effect):

- Positive experienced derealization

- Positive experienced depersonalization
- Changed sense of time
- Positive mood
- Mania−like experience
- Anxious ego dissolution
- Negative experienced derealization
- Thought disorder
- Paranoia
- Loss of thought control
- Loss of body control
- Visionary restructuralization
- Elementary hall. & illusions
- Scenery hallucinations
- Synesthesiae (that is, stimulation of one sensory organ elicits a response from another sensory organ)
- Changed meaning of percepts
- Facilitated recollection
- Facilitated imagination

Psychological Adverse Events included:
- inactivation
- poor concentration
- tiredness
- dazed state
- introversion
- self-confidence (initially increased, later slightly decreased)
- heightened mood
- emotional excitation
- sensitivity
- slight increase in anger
- apprehension-anxiety
- depression
- dreaminess

Most of these adverse events returned to or toward baseline by 24 hours. The main exceptions were what they call "inactivation" and "tiredness" which remained nearly as high at 24 hours as at 3 hours. In addition, though closer to baseline, concentration remained decreased and dazed state and dreaminess were still increased at 24 hours. Griffith, et al. (2016) reports next day headache even with low dose psilocybin (1 mg or 3 mg).

Physical Adverse Events included (in parentheses are % experiencing at highest dose [.315 mg/kg = 22 mg in a 70 kg person (154 pounds)]):
- fatigue (60%)
- exhaustion (22.5%)
- headache, head pressure or facial pain (37.5%)
- lack of energy (22.5%)
- excessive sleep requirement (15%)
- fast exhaustibility (17.5%)
- lack of appetite (17.5%)
- heavy or tired legs (12.5%)
- sleeplessness (5%)
- abdominal pain (7.5%)
- throat pain/irritation (7.5%)
- diarrhea (7.5%)

Long-term Negative Effects

We found a single case report of persistent psychological effects ("flashbacks") following psilocybin use (Espiard et al., 2005). Griffiths et al. (2016), followed 51 depressed and/or anxious terminal cancer patients for six months after they received 30 mg or 22 mg of psilocybin, reporting “all . . . adverse events resolved fully by the end of the session” except headache which persisted into the next day in two subjects, and "There were no cases of hallucinogen [sic] persisting perception disorder or prolonged psychosis.".

While not definitive, given there are hundreds of reported dosings of psilocybin plus unknown numbers of recreational usages, a single case report suggests continuing symptoms long past the drug's active effects are likely rare. Several authors point out that early reports of continuing flashbacks following uncontrolled use of hallucinogens mainly refer to LSD, not psilocybin, and did not address whether other drugs were also used or whether pre-existing psychiatric conditions that will be excluded in the present study were also present. Also, such uses were rarely closely monitored by a facilitator as will occur in the present study.

We are not aware of a study comparing facilitator to no facilitator. Intuitively, it makes sense that having someone present who might assist the individual in making sense of their experience might mitigate against it being as negative an experience as it might otherwise be, and we are not aware of reports of "flash-backs" or other late negative effects in individuals who used psilocybin in the presence of a trained facilitator.

Addiction Potential

As psilocybin is a Schedule I drug (meant to mean "no currently accepted medical use and a high potential for abuse") it is reasonable to have concern that study participants will become addicted to psilocybin. Our understanding is there is no documented case of an individual becoming addicted to "magic mushrooms" or psilocybin. In fact, individuals who have used either magic mushrooms or psilocybin repeatedly space their use out as if their repeat use is less than several months after a prior use, they achieve only a fraction of the earlier effect. This also argues against there being addiction potential for this compound.

Rationale for the Psilocybin Doses use in this Study

Carhart-Harris, et al. (2016), suggested efficacy for depression with 10 and 25 mg and Griffiths, et al. (2016) found 20 and 30 mg doses to be effective for depression. Carhart-Harris reported 25 mg was well-tolerated with most adverse events being transient (1-3 hours) and mild, while Griffiths decreased their "high dose" from 30 mg to 22 mg because of poor tolerance of the 30 mg dose (vomiting); they reported 22 mg to be well tolerated with none of the adverse events requiring intervention beyond the supportive therapist. Both Carhart-Harris and Griffiths reported the only delayed (next day) adverse events were headaches lasting < 24 hours. Personal communication with Carhart-Harris (2019), supported use of the 25 mg dose as optimal to maximize efficacy while minimizing risk of adverse events, based on his published studies and subsequent unpublished experience with psilocybin.

Specific Aims and Hypotheses

Concisely state the objectives of the study and the hypothesis or primary research question(s) being examined. There should be one hypothesis for every major study procedure or intervention. For pilot studies, it is important not to overstate the study's objectives. If there are no study hypotheses, describe broad study goals/aims.

1. Psilocybin will be acceptable to, and safe and well tolerated by, patients with BDD
2. Symptoms of BDD will improve after psilocybin administration, with persistent improvement over 3 months of follow up
3. Resting state functional connectivity of the default mode network will increase from pre- to post-treatment

Description of Subject Population

In this section, you are to describe each subject population of the study. The demographics of the population should reflect the gender and ethnic distribution of each population being studied. Enter each subject population's sample size, Gender, Racial, and Ethnic breakdown, and finally, describe each subject population.

Example:

Sample subject population:

Subject Population	Number of completers required to accomplish	Projected number of subjects who will be enrolled to obtain required	Age range of subject population

	study aims	number of completers	
Adults with BDD	12	12	18-55

Gender, Racial, and Ethnic Breakdown:

Gender Breakdown

4 male participants

8 female participants

Racial Breakdown

8 White participants

3 Asian participants

1 particopant who identified as "Other"

Ethnic Breakdown

11 Non-Hispanic/Latinx Participants

1 Hispanic/Latinx participant

Description of subject population:

Study sample will consist of adult participants between the ages of 18-55 with a diagnosis of Body Dysmorphic Disorder.

Suicide Risk Management Plan

This section will include all information regarding the Suicide Risk Management Plan.

The study is in data analysis and is not currently enrolling or recruiting participant so this would not be applicable to us.

Recruitment Procedures

This section will include all information regarding your study's recruitment process/procedures.

Describe settings where recruitment will occur. Virtual through websites RecruitMe.com, Craigslist and ClinicalTrials.gov. Recruitment has ended for this study.

How and by whom will subjects be approached and/or recruited? Recruitment has closed for this study as of April 2022. When recruitment was open, sujects were recruited through the above websites and were approached by study coordinator, Gloria Gomez.

How will the study be advertised/publicized? Study will be advertised on the above websites, but recruitment has closed as of April 2022.

Attach any ads/recruitment materials requiring review at this time in the Uploads section.

Clinical Trials:

Please provide the NCT Registration Number for your Clinical Trial. NCT04656301

YOU MUST REGISTER AT ClinicalTrials.gov IMMEDIATELY UPON RECEIPT OF IRB APPROVAL AND PRIOR TO ENROLLMENT OF THE FIRST SUBJECT. YOU WILL BE PROVIDED WITH A NCT REGISTRATION NUMBER ON REGISTRATION. PLEASE REVISE THIS SECTION OF THE PROTOCOL SUMMARY FORM TO INCLUDE THE NCT NUMBER AND RE-SUBMIT AS AN AMENDMENT TO THE IRB.

Concurrent Research Studies

In this section, please identify if subjects in this study participate in or will be recruited from other studies.

Describe where subjects are recruited from. N/A

Describe the recruitment source for (Must provide IRB Number, PI and Title). N/A

Inclusion/Exclusion Criteria

This section details your study sample(s) and addresses the requirement for risk minimization.
You may choose to divide your sample by population (healthy controls vs. patient population) or by procedure (subjects who will have an MRI vs. those who will not) and then define different sets of criteria for each.

For each sample, create or insert a table to describe detailed criteria for study inclusion and exclusion and the method you will use to ascertain each criterion. The method of ascertainment may describe tests, scales and instruments. When relevant, indicate the level of training of the person who will make the assessment (e.g. clinical interview by a psychiatrist).

Inclusion/Exclusion Criteria need to be numbered and listed in outline form (see Table template below).

Adults (18-55) with a Diagnosis of Body Dysmorphic Disorder

CRITERION	METHOD OF ASCERTAINMENT

Inclusion:	
1.Age 18-55	Date of birth
2. DSM-5- body dysmorphic disorder, non-delusional subtype, for >6 months by history. Non-delusional subtype will be operationalized by Brown Assessment of Beliefs Scale (BABS) 6-item total <18 (Phillips et al., 2006)	SCID -5 BDD module, BABS
3. At least moderate severity of BDD, operationalized by total score >24 on the Yale-Brown Obsessive-Compulsive Scale Modified for Body Dysmorphic Disorder (BDD-YBOCS),	BDD-YBOCS
4. At least moderate overall severity, operationalized by score of at least moderate (4 or greater) on the CGI severity scale	CGI severity scale
5. History of intolerance of, or nonresponse to, a prior adequate trial of an SSRI (≥ 2 months of fluoxetine **20** mg/day or equivalent), SNRI, or clomipramine	Psychiatric History
6. Currently in psychotherapy (other than CBT for BDD)	Psychiatric History
7. Able to provide informed consent	Psychiatric Assessment
Exclusion:	
1. Current major depressive disorder of greater than moderate severity (17-item Hamilton Rating Scale for Depression total >20)	Hamilton Rating Scale for Depression

2. Current or past DSM-5 bipolar disorder, psychotic disorder, or borderline personality disorder. First degree relative with psychotic disorder or bipolar I disorder.	MINI, **family history**
3. DSM-5 alcohol or drug use disorder in the past 3 months, or positive result on urine drug screen for illicit substance of abuse (except that prior cannabis use subthreshold for abuse diagnosis will be permitted if discontinued >24 hours prior to dosing)	MINI, urine drug screen
4. Current clinically significant suicidality or a suicide attempt within the past year	Psychiatric Assessment, MINI, CSSR (items 3 or 4 rated "yes" for active suicidal ideation)
5. Need for inpatient or partial hospital treatment	Psychiatric Assessment
6. Mental retardation, dementia, brain damage, or other cognitive impairment that would interfere with participation	Psychiatric Assessment and History
7. Body image concerns accounted for primarily by an eating disorder	Psychiatric Assessment
8. Body dysmorphic disorder criteria not met if weight concerns are excluded	Psychiatric Assessment

9. Use of: investigational medication within **past** 3 months; depot antipsychotic within **past** 6 months; serotonergic medication within **past** 2 weeks (6 weeks for fluoxetine). The ADC will not take subjects off medication for the purpose of entering this study.	Psychiatric and Medical History
10. Current cognitive-behavioral therapy (CBT) specific for BDD	Psychiatric History
11. History of seizure disorder, other than febrile seizure in childhood	Medical History
12. Presence of significant or unstable medical illness	Medical History, vital signs, EKG, blood and urine tests, physical examination
13. Females who are pregnant, breastfeeding, or sexually active and not willing to use adequate contraception	Medical History, urine pregnancy test
14. Presence of any other conditions that would preclude safe administration of psilocybin based on clinical judgement of the PI and/or therapist. This includes but is not limited to any behaviors suggesting the participant will be unable to establish therapeutic alliance with the therapist	Psychiatric Assessment
15. Enrollment in any investigational drug or device study in past 30 days	Psychiatric History
16. Dissociative Disorder	Psychiatric Assessment

17. Prior adverse effects from psilocybin	Psychiatric History

Consent Procedures

Explain, in this section, the procedures for obtaining consent from study participants.

If the eligibility screening for this study is conducted under a different IRB protocol, enter the NYSPI IRB# 7094R

Currrently, the study has concluded and is not enrolling or recruiting new participants. When the study was enrolling participants, consent was obtained by designated clinicians, Franklin Schneier, MD, Rapahel Campeas, MD, and Jose Arturo Sanchez Lacay, MD. 7950 participant consent forms were stored on our REDCap database. Consent procedures were also documented in EMR Progress Notes by clinicians.

Waiver of Consent / Authorization

The following sections are to be completed for the appropriate waiver/alteration of consent.

Waiver of Consent for use of Protected Health Information (PHI)

What records do you wish to review? N/A

What information are you seeking access to? N/A

Describe your plan to protect identifiers from improper use and disclosure. N/A

Describe your plan to destroy the identifiers as soon as possible, consistent with the conduct of the research, or provide a health or research justification for retaining the identifiers or explain how retention is required by law. N/A

Explain why the research could not be practicably carried out without the information (for which you are requesting access). N/A

Explain why the research cannot be practicably carried out without the waiver. N/A

Explain how/if subjects will be provided with additional pertinent information after participation. N/A

Justification for Waiver or Alteration of Consent

Waiver of consent is requested for the following. N/A

Explain why your research cannot be practicably carried out without the waiver or alteration. N/A

Describe whether and how subjects will be provided with additional pertinent information after participation.
N/A

Waiver of Documentation of Consent

Would the consent form signature be the only link between the subject's identity and the research data? N/A

Is breach of confidentiality the main study risk? N/A

Is consent for this research procedure ordinarily not required outside of the research context? Explain.
N/A

Describe the study component(s) for which waiver of documentation is requested. N/A

Waiver of Parental Consent

Explain why parental/guardian consent is not a reasonable requirement to protect the minor participants in this study. N/A

If parental consent is waived, describe a mechanism that will be substituted to provide appropriate protections for the subjects. N/A

Assent Procedures

In this section, please describe the procedures by which subject assent will be assessed and / or recorded.

N/A

Persons Designated to Discuss and Document Consent

Please list all the names of persons designated to obtain consent / assent. All persons must complete CITI training for NYSPI. The PI affirms that each name listed has completed the appropriate training.

Franklin Schneier, MD

Raphael Campeas, MD

Jose Arturo Sanchez Lacay, MD

Independent Assessment of Capacity

This section is designated for those studies that have been identified where subjects May Lack capacity to consent.

Describe the Methods/procedures for capacity assessment. N/A

If your study involves subjects who DO LACK capacity to consent, please justify. N/A

Procedures for surrogate consent. N/A

Study Procedures

Provide a clear, concise narrative of study procedures with special attention to the subjects' involvement. Detail the overall study timeline and location of study procedures, list all interventions, assessments and interviews, estimate the duration of each procedure, provide dosing schedules, identify study personnel involved in each procedure, and provide credentials for relevant personnel. If treatment is provided, specify the minimum credentials for providing that treatment. For complicated study designs, we strongly encourage attaching tables, flow-charts, and study algorithms.

I attest to follow the COVID-19 Safety Guideline for Columbia Psychiatry and NYSPI Re-Entry outlined in the NYSPI Director's June 1, 2020 memo, which include but are not limited to:

- Infection Control/PPE – Guidelines
- Research participants will only come on-site if absolutely necessary for study procedures.
- Clinical research teams will screen heir participants for COVID symptoms (night before and day of onsite visit, documenting this in the chart), and escort them in and out of the building.
- COVID/COVID-like symptoms in participants will be reported to the IRB via PRISM as an SAE.

COVID testing: Depending on COVID conditions in the community, the participant and the two therapists scheduled to be with the participant during the psilocybin day may be tested at NY State Psychiatric Institute on the day before psilocybin dosing, to determine if any may currently be infected with the virus that causes COVID-19. The test involves collecting a sample by putting a cotton swab several inches into the nose. If the test shows that the participant or either therapist has COVID-19, your research treatment visit will be postponed.

Internet-based data collection or transmission will be conducted following HIPAA and NYSPI guidelines.

1. Visit 1 (Screening). A complete psychiatric and physical examination will be performed, including Psychiatric, Medical and Social Histories, MINI Structured Psychiatric Interview, SCID-5 BDD module, Hamilton Rating Scale for Depression, Columbia Suicide Severity Rating Scale, and standard laboratory testing including EKG, urine for routine analysis, drugs of abuse and (if appropriate) pregnancy and blood for hematologies and

chemistries including thyroid function. A physical examination will be performed at the screening or between screening and Visit 2 (Day -1), with results obtained before psilocybin administration day.

Additional screening will specifically assess eligibility for the MRI portion of the study with the self-rated PhenX Toolkit Hand Dominance Measure and MRI Metal Screening Questionnaire. Contraindications to MRI scanning are:

- Paramagnetic metallic implants or devices
- Contraindicating magnetic resonance imaging or any other non-removable paramagnetic metal in the body (e.g., pacemaker, paramagnetic metallic prosthesis, surgical clips, shrapnel, necessity for constant medicinal patch, some tattoos)
- Being unable to tolerate the scanning procedures (i.e., severe obesity, claustrophobia)

Patients with contraindicated metal or left-handedness will not be offered MRI participation but will complete all other parts of the protocol.

Additional visits (V1a, V1b) will be scheduled as needed to follow up on any lab abnormalities and for patient to establish relationship with study therapist.

Participants will be invited to bring to the screening a companion (friend/family member) whom they would like to support them through the study. Such a companion will be informed of their potential role and will be asked to sign a “caregiver” consent form at the Screening Visit. Caregivers will receive information about the signs of worsening of depression and suicide risk and ways to contact the study team if necessary. The caregiver will complete a questionnaire at screening, Week 3 and Week 12.

2. Visit 2 (Baseline, Day -1). Eligibility and willingness to participate will be reassessed. At this visit, the patient meets with the therapist who describes what the experience might be like and how the therapist will handle any difficulties the patient may have with the experience. MRI-eligible subjects will complete acquisition of resting state fMRI. Subjects will also complete an inverted face computer task in which they will view an image of a face and then will be shown an image of two faces (one matching and one non-matching morphed face) and asked to select the matching face as rapidly and accurately as possible. The matching and non-matching faces will be presented either upright or inverted, in various combinations. This task assesses global vs. local visual processing, and it has previously been shown to be abnormal in BDD (Feusner, 2010).

3. Visit 3 (Psilocybin Day, Day 0). The next day, a study psychiatrist again assesses eligibility; those eligible and agreeable receive their dose of psilocybin (25 mg) and spend the next eight hours (longer if needed) with the two therapists; when deemed appropriate, the patient is accompanied home either by a person of their choosing or a staff member. The patient will be reminded that they should not drive or drink alcohol at least until after the end of Visit 4 (next day). Vital signs are taken prior to their dose of psilocybin and prior to leaving the clinic and a study psychiatrist evaluates prior to their departure for whether their condition requires them not to leave. In the latter case, they will either remain in the Biological Studies Unit (BSU) until

cleared by a study psychiatrist or admitted to 5-South inpatient service if they require additional observation overnight.

Psychological Approaches to Anxiety

- During Visit 2 and prior to ingestion of psilocybin during Visit 3, explain anxiety, even fear, may occur
- During Visit 2, train patient in relaxation and breathing techniques that may alleviate anxiety
- On Visit 3, shortly after psilocybin ingestion, remind subject of possible anxiety reaction and that therapist will walk them through it should it occur
- During Visit 3, if patient reports excessive anxiety or fear, walk them through relaxation and breathing techniques taught during Visit 2
- Encourage exploration of psilocybin experience
- Call M.D. if fear is not alleviated by the above

Rescue Medications

- Anxiety: Lorazepam or alprazolam
- Psychosis: Risperidone
- Headache: Acetaminophen
- Symptomatic elevation in BP: Beta-blocker (e.g., propranolol)
- Nausea/vomiting: Ice chips

Hospitalization if needed

- Given prior experience with psilocybin treatment, the need for inpatient hospitalization appears unlikely
- In the event that patients require hospitalization they may be admitted to NYSPI 5-South unit.
- Prior to psilocybin dosing Dr. Mary Bongiovi will be contacted (email or text 917-301-1584) to ascertain
- whether backup 5S inpatient bed at NYSPI will be available. In event of lack of availability for such a bed on 5S after it has been offered (e.g., unanticipated issue on inpatient unit) the NYPH. Emergency Room will serve as backup.

4. Visit 4 (Post-Psilocybin Day 1). The patient returns to the anxiety clinic and reports any experiences since leaving the clinic as well as having blood, urine, and EKG tests. MRI eligible patients will have another resting state fMRI session, The inverted face task will be repeated.

5. Visits 5-8 (Post-Psilocybin Weeks 1-3 and 12). The patient returns 1, 2, 3 and 12 one week later for standard evaluation of psychiatric symptoms, functioning and AE's. These visits may be conducted by phone or secure video.

6. Telephone visits (Weeks 6 & 9). The patient is contacted by telephone 6- and 9-weeks post-psilocybin for standard evaluation of psychiatric symptoms and AE's.

7. Early Withdrawal Visit. Should the patient or study doctor decide to end the study visits prior to Week 12, if the patient agrees, all Visit 10 (Week 12) ratings including Independent Evaluation will be made.

Extra Visits

1. Extra visits (or in-person visits when phone visits are called for) will "kick in" if:
2. Patient reports on-going or intermittent negative effects, including but not limited to:
    a. "Flash-backs"
    b. Psychotic or quasi-psychotic (e.g., illusions, non-paranoid worries re. how others are viewing or treating them) experiences
3. Significant (e.g., > 25% increase in BDD-YBOCS) worsening from original severity.
4. Significant suicidality (e.g., patient reports suicidal thinking with any intent to act)
5. Physician's clinical judgment

Detailed Procedure for Staff Escort Home

In the event that it is deemed appropriate for a patient to return home following their psilocybin experience and said patient has not provided a responsible party to accompany him or her home, a staff member will accompany the individual from the BSU treatment room to the exterior door of their home. Transportation will be via a car service for which we will pay. The staff member will be instructed to contact the Anxiety Disorders Clinic doctor on call should he or she note grogginess or unsteady gait or other reasons to think the subject might have trouble being alone and the doctor will determine whether to have the staff member bring the subject back to NYSPI for further observation, erring on the side of further observation. Else, the staff member will allow the individual to enter their home and close the door, the staff member remaining outside and relieved of escort duties.

Table - Schedule of Study Procedures

Visit	**1**	**1a, 1b, 1c, etc.**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Day	**Screen Visit**	**Screening Period**	**-1**	**Psilo-cybin**	**+1**	**+7**	**+14**	**+21**	**+42**	**+63**	**+84**
Informed Consent	X										
Medical History	X		X								
MINI Interview	X										
Documentation of Birth Control Method	X										
Prior/Concomitant Meds	X	X	X	X	X	X	X	X	X	X	X
Hamilton Rating Scale for Depression	X		X		x				x		X
Columbia Suicide Severity Rating Scale	X				X						X
BDD-Yale-Brown OCD Scale	X		X	X	X	X	X	X	X	X	X

BDD-REBUS-Q	X		X	X	X	X	X	X	X	X	X
Brown Assessment of Beliefs Scale	X		X	X	X	X	X	X	X	X	X
Physical Examination	X										
ECG	X				X						
Urinalysis	X		X		X						
Urine for drug/alcohol screening	X		X								
Urine for pregnancy testing*	X		X		X						
Blood for routine laboratory assays	X				X			X			
Vital signs	X		X	X	X						
Height and Weight	X										
PhenX Toolkit Hand Dominance Measure	x										
MRI Metal Screening Questionnaire	x		x		x						
Inclusion & Exclusion Criteria	X		X								
Adverse Events/SAE		X		X	X	X	X	X	X	X	X
Resting State fMRI			x		x						
Inverted Face Task			x		x						
Clinical Global Impression - Change					X	X	X	X	X	X	X
5Dimension-Altered States of Consciousness				X							
Emotional Breakthrough Inventory					X						
Positive and Negative Affect Schedule			X		X			x	x		
Liebowitz Social Anxiety Scale			x		X				x		X
Psychological Insight Scale					X			X	X		x
Somatomap – 2D Tool			x		x						x
Sheehan Disability Scale			X						x		X
Qualitative Interview				x	x						
Sleep Questionnaire			x		x						
Dysmorphic Concerns Questionnaire			x		x			x	x		x

At any visits in which patient reports clinical worsening, HamD, CSSR, and CGI will be repeated.

Criteria for Early Discontinuation

Define criteria that will be used to exit or drop subjects from the study and operationalize. Indicate the time points when such criteria will be applied, and describe the rating instruments, parameters, and thresholds that will lead to a decision

to terminate a subject's participation and the role of the person who will make these determinations. Studies which include a medication taper and discontinuation may be asked to include an independent medical monitor (an MD not on the study team) who will aid the study team in determining whether study discontinuation is needed. In addition, explain procedures for managing subjects who are withdrawn from the protocol.

For treatment studies: To minimize risks to subjects, operationalized drop-out criteria should be defined so that subjects who worsen, or in some cases, fail to improve, are removed from the study and offered standard care. The threshold for drop-out should consider the level of risk associated with non-improvement for the specific disorder, the availability of alternatives, and the typical required duration of treatment. For example, emergence of suicidal intent, or psychosis, should prompt immediate clinical evaluation and withdrawal from the study.

1. Patient withdraws consent
2. Study personnel determines it is not in the patient's best interest to continue in the study.
3. Clinical worsening
4. At each assessment participants will be evaluated for clinical worsening, and any participant who reports symptomatic worsening (CGI Change Score >4) will be further evaluated for need for urgent clinical treatment. Further evaluation will include the Hamilton Depression Scale, the Columbia Suicide Severity Rating Scale (C-SSRS), and the Clinical Global Impression Change Scale, but the ultimate decision to provide or refer to non-study treatment will be based on clinical judgement, with reasoning documented in the chart.
5. Any participant who evidences need for non-study clinical treatment before psilocybin administration will be removed from the study and offered appropriate referrals, including transitional treatment in the Anxiety Disorders Clinic, or being walked to the emergency room if indicated. After psilocybin administration, clinical deterioration will be treated the same way, except that patients will be permitted to continue participation in remaining study assessments.
6. Potential pregnancy: Participants who prior to dosing have a positive pregnancy test or report suspecting pregnancy will be removed from the study. Participants who after dosing have a positive pregnancy test will be excluded from the repeat MRI but will be allowed to continue in study assessments of symptoms. They will be offered assistance with obstetrical follow-up

Blood and other Biological Samples

Describe how the sample will be used and indicate, when relevant, the amount of the sample. The IRB wants to know that the sample is sufficient for the purposes of the study, but that sampling is limited to what is minimally necessary.

If you've indicated that you intend to store a sample for future use, indicate where the sample will be stored, how long the sample will be stored, and to what purposes the sample will eventually be put. Check the IRB website at

https://irb.nyspi.org/investigators/guidance/genetic-research for specific guidance and additional information about future use of DNA samples.

Blood will be drawn for routine testing of hematology (i.e., number, size and hemoglobin content of red blood cells and number and type of white blood cells) and chemistries (e.g., liver enzymes, electrolytes and renal function) on each of three occasions: initial evaluation, 1day post psilocybin and three weeks post psilocybin. Approximately 20 cc (= 4 teaspoons) of blood will be obtained on each occasion, or 60 cc = 3 tablespoons total over 4-6 weeks. By contrast, 500 cc is taken on a single occasion when one donates blood.

Assessment Instruments

List all assessment instruments, indicate who will administer them and their credentials/qualifications. Provide an estimate the duration of each measure. The IRB wants to know that assessments instruments are appropriate measures for the purposes of the study and are no more burdensome than necessary. The IRB will consider the burden of assessment instruments (in terms of time, sensitivity of material, etc.) in the risk/benefit analysis. Please attach copies or otherwise provide all non-standard instruments.

- 5D-ASC – The Five Dimension Altered States of Consciousness Questionnaire measures the acute drug effects in terms of various ways of determining state of consciousness. 10 min.
- BDD-YBOCS – The Yale-Brown Obsessive-Compulsive Scale Modified for BDD is a standard clinician-rated measure of BDD symptom severity. 10 min.
- BDD-REBUS-Q – 2-item questionnaire rating certainty of negative beliefs about self and appearance. 1 min.
- BABS – The Brown Assessment of Beliefs Scale is a clinician-rated scale assessing the intensity of body image belief in BDD. 10 min.
- CGI Clinical Global Impression Scales, Severity and Change – global clinician-rated measures of symptom severity and Change 5 min.
- CSSR – Columbia Suicide Severity Scale 10 min.
- EBI – The Emotional Breakthrough Inventory is an 8-item brief measure intended to index the degree to which an individual experiences his/her emotion during a psilocybin session. It is a visual analogue style scale, typically with units from 0 to 100. 5 min
- QLESQ – The Quality-of-Life Enjoyment and Satisfaction Questionnaire is a self-rated measure. 5 min.
- HAM-D-17 – The 17-item Hamilton Rating Scale for Depression measures the degree of symptom severity in depressed patients.
- Liebowitz Social Anxiety Scale – 24 item scale assessing fear and avoidance of social anxiety 5 min
- MRI Metal Screening Questionnaire - self-rated 5 min.
- MINI - the Mini International Neuropsychiatric Interview, Version 7.0.2, is a standardized, semi-structured interview that produces DSM-5 diagnoses. It is similar to the SCID. 30 min
- PANAS - Positive and Negative Affect Schedule measures the acute emotional drug effects.5 min

- PhenX Toolkit Hand Dominance Measure – self rated form 5 min.
- Psychological Insight Scale – 7 question assess changes in insight on a visual analogue scale. 5 min
- Qualitative Interview
- SDS – The Sheehan Disability Scale is a patient-reported outcome measure used to assess functional
- impairment and associated disability. 5 min.
- Somatomap 2D (Ralph-Nearman et al. 2019) – A HIPAA-compliant web-based self-assessment tool for measuring body image perception. It displays an androgynous manikin; the user is asked to imagine it as their own body and draw directly upon it to outline an area of bodily concern. They then provide emotion ratings for each area of concern. Somatomap was built on Chorus, a HIPAA (Health Insurance Portability and Accountability Act)-compliant visual development platform. Chorus is a hosted service provided through the University of California Los Angeles (Areivan et al., 2018). 15 min
- Sleep Questionnaire – 2 items assessing sleep quantity and quality.
- Dysmorphic Concerns Questionnaire (Oosthuizen et al., 1998) – A 7-item self-rated scale assessing dysmorphic beliefs.

Sections to be completed for studies using IND/IDE Drugs and Devices.

Prior to the submission of any study involving a faculty held IND or IDE being approved by the IRB, the IND/IDE holder is required to submit a form signed by the IND/IDE holder and PI.

Which are applicable to your study: ☐ Drug ☐ Device ☐ Radiolabeled drug/compound

Off Label and Investigational Use of Drugs

Enter the information for all drugs to be used in this study:

Name of the drug	
Manufacturer and other Information	
Approval Status (select one)	IND application is pending IND is approved No IND is required
IND #	
Who holds the IND (i.e., IND Sponsor). If other than PI/CU Investigator, type name of holder.	

Which applies:	FDA has determined the IND is not required (provide correspondence) FDA conditions are met (see "Rules") – Explain

Off Label and Investigational Use of Devices

Enter the information for all devices to be used in this study:

Name of the device	
Manufacturer and other Information	
Approval Status (select one)	IDE application is pending IDE is approved No IDE is required
IDE #	
Who holds the IDE (i.e., IDE Sponsor). If other than PI/CU Investigator, type name of holder.	
Is the device marketed?	
Which applies:	FDA has determined that IDE is not required FDA conditions are met (see "Rules") – Explain Device is "Non-significant risk" – Explain

Off Label and Investigational Use of Radiolabeled Drugs / Compounds

Enter the information for all radiolabeled drug/compounds to be used in this study:

Name of the radiolabeled drug/compound	N/A
Manufacturer and other Information	N/A

Approval Status (select one)	IND application is pending IND is approved RDRC approval is pending RDRC is approved No FDA/RDRC approval is required - Explain
IND #	N/A
Who holds the IND (i.e., IND Sponsor). If other than PI/CU Investigator, type name of holder.	N/A

Research Related Delay to Treatment

Research involving participants who are in need of treatment invariably involves delay to care, and this delay is associated with risk. Scheduling of procedures must be carefully organized to minimize delay. Other delay must involve only that minimally necessary to accomplish the aims of the research while respecting subject well- being and safety. Describe the delay, by virtue of research participation in this study, before a participant can receive treatment of known efficacy or standard care routinely offered in the community.

Participants in the study will need to be free of SSRI medication for at least 2 weeks prior to psilocybin administration and for 3 weeks thereafter, so total delay to an established treatment will be 5 weeks. Patients who for clinical reasons need treatment intervention sooner will be offered established treatment. If patients need to restart SSRI's prior to the psilocybin session, they will be excluded. If they restart after the session, the reason will be documented, and the patient will be followed until the end of study visit provided that informed consent is maintained.

Clinical Treatment Alternatives

Describe what other treatment or assessment options are available to subjects who do not participate in research.

There are no FDA-approved medications for BDD, but SSRIs and specialized BDD-specific CBT have been shown to be efficacious in controlled trials.

Risks/Discomforts/Inconveniences

"Risk" is a broad term used to convey the potential for harm, burden, and inconvenience related to research participation. Use this section to provide a comprehensive description of foreseeable physical, psychological, social, interpersonal, and economic risks introduced by the research. Include the source of the information. Consider both the probability and magnitude of harm and its impact. Describe the foreseeable harms associated with the research (untoward effects of a medication) and those related to delay to individualized treatment. Include data from the literature, and local data, if available, on risk rates and subject experiences with research procedures. Describe procedures in place to minimize risk. In general, please create a numbered list of risks/categories of risk, and in general put the list in the order of significance or level of risk, the most significant risks should be listed first.

1. BDD might not remit or may worsen
2. Psilocybin has not been extensively studied, so both short and especially long-term consequences of its use may not be known at present
3. Known psychological effects of psilocybin include:
    a. Euphoric mood
    b. Dissociative experience (i.e., feeling outside one's body or unreal, a distorted sense of time
    c. Hallucinations **(which may persist for weeks after dosing)**
    d. Psychotic experience such as paranoia
    e. Difficulty with cognition (e.g., trouble adding or solving puzzles)
    f. Disturbance in attention
    g. Mood alteration
    h. Inappropriate affect (e.g., crying when one is not sad or laughing when nothing odd occurred)
4. Known medical effects of psilocybin include:
    a. clumsiness
    b. feeling weak
    c. headache
    d. hyperreflexia (e.g., the lower leg reacts too strongly when the knee tendon is tapped)
    e. hyporeflexia (e.g., the lower leg under-reacts when the knee tendon is tapped)
    f. increased blood pressure
    g. increased pupil size
    h. rapid heart beat
    i. tremor
    j. vomiting
5. Discomfort of needle sticks and ECG
6. Time commitment to completing forms, and attending evaluation, treatment and follow-up sessions
7. Harm to an unborn or newborn child
8. MRI

Describe procedures for minimizing risks:

1. BDD might not remit - standard medication treatment, such as with an SSRI will be instituted and patient will be referred for CBT or other therapy as clinically indicated.
2. Psilocybin has not been systematically studied, so both short and especially long-term consequences of its use may not be known at present - while unknown risks cannot be minimized, we will minimize the likelihood of such risks occurring unnoticed during the study period by asking re AE's at every post-psilocybin visit and encouraging patients to call between visits should any untoward events occur, whether they think they may be related or not.
3. Known psychologic effects of psilocybin include:
    a. Euphoric mood - the risk of feeling too good is it can result in rash behavior, as in mania. We anticipate that if euphoria occurs, it will happen on the psilocybin day when the therapist and others are present to monitor and talk the patient down from an overly euphoric mood. As overly euphoric mood is a characteristic of bipolar illness, so to minimize risk the study excludes patients with known bipolar disorder.
    b. Dissociative experience (i.e., feeling outside one's body or unreal, a distorted sense of time) – We anticipate that if the patient has a dissociative experience, it will occur on the psilocybin day when the therapist will be present to "talk them down" and other clinicians will also be readily available.
    c. Hallucinations - as with b)
    d. Psychotic experience such as paranoia - as with b); our anticipation is psychotic experiences will spontaneously remit within hours of the subject receiving psilocybin. If not, the on-call psychiatrist can determine whether to give an antipsychotic medication.
    e. Difficulty with cognition (e.g., trouble adding or solving puzzles) - again, this will occur on the psilocybin day and will be minimized by therapist support, and it is anticipated to dissipate by the time the patient goes home, or at least by the next day.
    f. Disturbance in attention - this is also anticipated to mainly occur on the day the patient receives psilocybin, but its impact on functioning will be monitored out to Week 12 using the SDS.
    g. Mood alteration – mood will be monitored using the HAM-D-17 and the PANAS
    h. Impaired Psychomotor skills - this will be monitored by clinical observation and is expected to resolve during the treatment day.
    i. Inappropriate affect (e.g., crying when one is not sad or laughing when nothing odd occurred) – this will be monitored by clinical observation and the PANAS and dealt with as part of the therapist's interaction with the patient.
4. Known medical effects of psilocybin:
    a. Clumsiness - a staff member will remain with patient at all times ready to prevent falls as needed (e.g., traveling to and from the bathroom)
    b. Feeling weak - ditto
    c. Headache - standard headache remedies (i.e., NSAID's)

d. Hyperreflexia - reassurance and waiting
e. Hyporeflexia – reassurance and waiting
f. Elevated blood pressure - watchful waiting as to date, the blood pressure has not been documented to get to dangerous levels (i.e., systolic pressure may get to 160 mm Hg); as blood pressure rises typically last 1-3 hours, a short-acting blood pressure lowering medication such as nifedipine could be considered
g. Increased pupil size - keep in darkened room (this is the standard lighting in psilocybin rooms
h. Rapid heartbeat - watchful waiting as to date, fast heart rate has lasted 1-3 hours; propranolol could be used but to my knowledge no "rescue" med has been required to date.
i. Tremor - this typically lasts 1-3 hours so should not require anything besides reassurance; if severe enough, do not allow hot liquids
j. Vomiting - this is unusual and time limited; probably too short-lived for anti-emetic medication to help; could try ginger ale or ginger tea

5. Discomfort of repeated needle sticks and other procedures: experienced, trained phlebotomists will obtain blood
6. Time commitment to completing forms, and attending evaluation, treatment, and follow-up sessions - we will do everything we can to limit time spent; e.g., if patients must wait for their doctor, they will be instructed to complete their self-report forms
7. Psilocybin is not considered safe during pregnancy or breast-feeding, because such safety testing has not been done. Therefore, potential participants will be excluded if pregnant, breast feeding or planning to become pregnant during the next 3 months. A pregnancy test will be done at screening. Pregnancy tests will be repeated at least twice during the study (on the day prior to taking psilocybin, and on the day taking psilocybin). Participants will be cautioned that even if a pregnancy test is negative, they could still be pregnant, because these tests cannot detect very early pregnancies (that is, within the first few days). Participants will be excluded if they do not agree use an effective form of birth control before and throughout study participation. Methods of birth control considered to be effective include double barrier methods (condom plus spermicide, or diaphragm plus spermicide), birth control pills, birth control shots and intrauterine devices. Men who are sexually active will also be excluded if they do not agree to using adequate contraception. Female partners of men participating in this study should use one of the acceptable methods of contraception (contraception pills, intrauterine device, bilateral tubal occlusion).
8. To minimize the risk of MRI we will observe United States Food and Drug Administration (FDA) guidelines for magnet strength and exposure to radio waves. We will exclude people with magnetic metal in their body through careful review and checklist. Participants will be specifically warned about risks of a pacemaker or metal objects inside the body, as well as the need to remove all metal from their clothing and all metal objects from their pockets. Also, although there are no known risks to pregnancy, we will not scan someone who is pregnant, and women in childbearing years will take a pregnancy test just before each MRI scan.

In addition, and not specific to any one of the above, a physician will always be available should the therapist become uncomfortable, whether with physical reactions (such as elevated blood pressure) or behavior (e.g., belligerence) or reported symptoms (reports of psychotic symptoms or suicidality). The therapist's training will be to err on the side of calling the physician unnecessarily rather than allowing the patient's condition to worsen further. While our read of others' experiences with similar doses of psilocybin is situations requiring medical interventions are highly unlikely, we recognize it is important to be prepared for such an eventuality. I have not seen articles documenting the need for rescue medication so can only make the generic suggestion that for difficult psychiatric symptoms, one might first consider a short acting benzodiazepine, such as lorazepam, and then an antipsychotic medication, such as quetiapine. Medical symptoms would be counteracted using appropriate medications, e.g., nifedipine for hypertension. As the half-life of psilocybin and its first metabolite are a few hours it is not surprising that the adverse effects of psilocybin typically last 1-3 hours, so it is likely that should rescue medication be needed it would only require short acting drugs; adverse events that continue into the next day are reported as having been mild (e.g., Hasler et al., 1997) while the only reported late appearing (i.e., not present acutely following psilocybin dose) adverse event is mild-moderate headache lasting < 24 hours.

Methods to Protect Confidentiality

Describe the data management plan and the methods you will employ to protect subject privacy and the confidentiality of research data. The section should detail how information will be collected, recorded, coded, stored, transmitted, and as applicable, shared with other investigators so as to minimize risks related to breach of confidentiality. Confirm that identifiers are removed, to the extent possible, from research data, and explain if there are links between subject identity and research data, or if the data are anonymous. Also, indicate where the data are stored, who is responsible for data safekeeping, and who has access to subject identity and codes, if any, which cross-link research data and subject identity. Confirm that identifiable data are not collected, stored, or transmitted by mail, fax, on removable drives, laptops, or via the internet without proper protections, e.g. encryption.

Confidentiality will be maintained by keeping physical data in locked file cabinets. Any electronic data, including laboratory results will be communicated within strict HIPAA rules. Methods by which confidentiality is protected include HIPAA-compliant videoconferencing and web-based platforms. Any data sent to the company will include initials, gender, marital status, SES and education and date of birth only without additional potential identifying information. Should it become necessary for the treating psychiatrist to contact the subject's primary physician to obtain copies of their medical records or release our records to other providers, explicit written agreement for such record transfers will be obtained from the patient. Any electronic data stored at the Anxiety Disorders Clinic will be kept behind the NYSPI firewall with access only to authorized personnel by individual password. We will be applying for a certificate of confidentiality.

We will provide Compass with safety data from the Study, for storage by Compass on a central database. Such information shall be provided to Compass on a regular and on-going basis throughout the Study. Notwithstanding the foregoing, patients must be consented to have their data stored in this secure centralised database, maintained by Worldwide Clinical Trials (WCT). Only patients who consent to this process will have their personal data transferred.

All types of adverse event will be promptly reported to Compass for use in the Compass/WCT safety database, they do however have different recording and reporting requirements, as set out below.
For the purposes of reporting to the safety database, and subject to data protection requirements, we will promptly report to Compass all Serious Adverse Events ("SAEs") regardless of the causal relationship to the Study Drug.

Assessment of Seriousness

For the purposes of the reporting of the adverse events to Compass, each adverse event will be assessed for its seriousness. An SAE is any event that meets any of the following criteria:

- Death
- Life-threatening
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect in the offspring of a subject who received the study drug.

Other: Important medical events that may not result in death, be life-threatening, or require hospitalisation, may be considered an SAE when, based upon appropriate medical judgment, they may jeopardise the Subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events are:

- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias or convulsions that do not result in inpatient hospitalisation
- Development of drug dependency or drug abuse

Adverse Events of Special Interest

For the purposes of the safety database, an adverse event of special interest ("AESI") is an adverse event (serious or non-serious) of scientific and medical concern specific to the study drug, for which ongoing monitoring by the Clinical Investigator is required. Such adverse events may require further investigation to characterise and understand them.

The following events will be reported as AESI:

- Euphoric mood
- Dissociative disorder
- Hallucination
- Psychotic disorder
- Cognitive disorder
- Disturbance in attention
- Mood altered
- Psychomotor skills impaired
- Inappropriate affect
- Overdose
- Intentional product misuse

All AESIs will be followed until resolved or stable.

Reporting Adverse Events

Each adverse event will be assessed to determine whether it should be classified as a SAE. If the adverse event is considered serious, we will report this event in line with requirements of the study sponsor and the IRB. This may include completing a sponsor specific SAE reporting form, within 24 hours of learning about the event, regardless of causal relationship to the Study Drug.

For the purposes of reporting to the safety database, these events will also be recorded on a specific Compass adverse event database CRF, within 24 hours of our becoming aware of them. This will also be the case for AESI.

If we detect an SAE in a Subject after the last scheduled follow-up visit, and consider the SAE related or possibly related to the administration of the Study Drug, will report this to the sponsor. We will also report the event, on the Compass adverse event database CRF and send this in accordingly.

We will report all other adverse events promptly to the Compass safety database after first becoming aware of such adverse event. These events will be reported and transferred on our Institution's own study CRFs.

All information about adverse events will be collected and once the relevant form is completed, it will be scanned and sent by email message or facsimile to WCT. The initial report should include the following information:

- Event

- Study code
- Reporter name and contact information

Site staff will complete the paper Compass AE Database CRF form and email it to the following address: drugsafety@worldwide.com

In cases where the email system is unavailable, site staff will send the SAE by fax to: +18663875539 (US) and +44 208 043 4813 (ROW).

Category of Adverse Event	Time Frame to Report to Compass/WCT Database	How to Report to Compass/WCT Database
Adverse Event (AE)	Timely Manner/ Before the end of the study	Submit site specific AE CRF to WCT
Serious Adverse Event (SAE)	Within 24 hours of becoming aware of event	Submit a copy of the Compass provided AE CRF to WCT
Adverse Events of Special Interest (AESI)	Within 24 hours of becoming aware of the event	Submit a copy of the Compass provided AE CRF to WCT

Fig 1. Reporting requirements

Due to the limited safety data that have been collected formally for the Study Drug, all SAEs that are considered to be related will also be unexpected and therefore classified as Serious, Unexpected, Suspected Adverse Reactions (SUSARs). Classification of an SAE as a SUSAR will be determined on a case by case basis by WCT. Once an unexpected event has occurred, it will become expected in the future. The IBD will be updated annually to reflect changes in expected adverse events.

GDPR

As owners of the external safety database, Compass Pathways are the “data controller” for this aspect of the research. WCT and the research team will act as “data processors”.

Subjects will have the following rights regarding accessing their data stored in this database:

1. To request to review their data held in the safety database.

2. To request for any inaccuracies to be corrected.
3. To raise objections to its content and to the continued processing of their data in this database.
4. To request to have their data removed from this database.

If any subject requests any of the above points regarding their safety data held in the safety database, we will notify Compass as soon as the request is made. Requests will be reviewed on a case-by-case basis and where Compass sees fit to action the request; they will work with us to resolve them as needed.

Direct Benefits to Subjects

Describe only benefits to individual subjects that are likely to accrue during the study itself. Do not include subject compensation or treatment to be provided at the end of the study, as these do not figure into the IRB's risk/benefit considerations. Do not describe diagnostic and evaluation components unless subjects receive clinical feedback. Do not describe the anticipated scientific benefits of the research. Some studies offer no direct benefit to subjects.

There may be no direct benefit. The information we get from this study may help us treat people with BDD better in the future

Compensation and/or Reimbursement

If compensation or reimbursement for expenses will be offered to subjects, please describe and indicate total amount and schedule of payment(s). If transportation is reimbursed, state if receipts are necessary for reimbursement. Include justification for compensation amounts and indicate if there are bonus payments.

$300 after completion of the pre-dosing visit, dosing visit, and the post dosing visit ($100 each visit).

$250 after completion after completion of 5 follow up visits. ($50 each visit)

Total compensation will be $550

Protocol Specific Plans (PSPs)

All federally funded, more than minimal risk studies are required to include a Training Plan, an Internal Monitoring/Quality Assurancee Plan, and a Data Management Plan. Collectively, these plans are called the Protocol Specific Plans or PSPs. More information can be found on the IRB website (irb.nyspi.org) regarding these plans and should be reviewed prior to submission.

Training Plans

A training plan should describe, in detail, ALL training required for each member of the study team, frequency of the training, and location of the Training Log and training certificates. Elements of an effective training plan include: all sessions documented with an attendance list, all members of the study team listed on the Delegation of Authority log must be in compliance with the training plan and be trained for each study procedure they are authorized to perform, the training log is maintained by the Research Coordinator in the Regulatory Binder, and sample timepoints for the Training Log are before protocol initiation meeting, protocol initiation meeting, annual protocol meeting, and new staff training. The study is in data analysis and is not currently enrolling or recruiting participant so this would not be applicable to us.

Internal Monitoring/Quality Assurance Plan

Please utilize the Quality Assurance Monitoring plan template on the NYSPI IRB website (irb.nyspi.org) and cut & paste to this section. A lead QA monitor will need to be designated and named in the study's monitoring plan. Section A will describe the monitoring schedule and reporting. Section B will describe the data that will be reviewed on an ongoing basis. The study is in data analysis and is not currently enrolling or recruiting participant so this would not be applicable to us.

Data Management Plan

The required elements of the Data Management Plan include: identification of the database platform (e.g., REDCap) and inclusion of an attestation that it is Part 11 compliant, identification of a qualified staff member who designs and maintains the database, design and implementation of data system training for all Principal Investigators & research coordinators & all protocol staff, and significant changes to the data management plan will be submitted as protocol amendments in PRISM. The study is in data analysis and is not currently enrolling or recruiting participant so this would not be applicable to us.

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Please limit references, preferably no more than twenty.

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Statistical Analysis Plan

The primary efficacy measure was BDD symptom severity, as measured by the BDD-YBOCS, a clinician-rated scale (total score range: 0-48, with higher scores indicating greater severity). Response to treatment has been defined and validated as $\geq$ 30% decrease in total score, and partial-to-full remission as total score $\leq$16 (Fernandez de la Cruz et al. 2019).

Statistical Analyses: For YBOCS and other repeated outcome measures, repeated measures ANOVAs with Greenhouse-Geiser corrections will be conducted across time points from baseline to week 12 using SPSS Version 23.0 (IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp), with post hoc pairwise Bonferroni-corrected comparisons. For the HRSD a paired samples *t*-test will be performed to compare baseline to week 12 scores.