Title: Neural correlates of the effects of psilocybin in obsessive-compulsive disorder: a double-blind, placebo-controlled study.

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Introduction

1. **Statement of Purpose:** State the scientific aim(s) of the study, or the hypotheses to be tested.

   We aim to investigate the effects of oral psilocybin on OCD symptomatology and provide the first evidence of the neural mechanism that may mediate psilocybin's purported therapeutic effects on OCD, using a randomized active-placebo-controlled, double-blind study design, coupled with state-of-the-art functional neuroimaging.

   Aim 1: To investigate the effects of psilocybin on OCD symptomatology. OCD symptom severity will be assessed before treatment and 24 and 48 hours after treatment; one week after treatment, two weeks; one, two, and three months after treatment.
   Hypothesis: We hypothesize that 0.25mg/kg of psilocybin will lead to greater symptom improvement than niacin (as the active-placebo-control agent) at all assessment points.
   Primary outcome measure will be Acute Yale-Brown Obsessive-Compulsive Scale (YBOCS) scale at 48 hours.

   Aim 2: To explore the relationship between the psilocybin-induced brain connectivity changes and neuronal activation following symptom provocation in OCD. Resting-state brain connectivity will be assessed before and 48 hours after treatment. Neuronal activation induced by OCD-relevant provocative stimuli will be assessed 48 hours after the treatment.
   Hypothesis: We hypothesize that (i) psilocybin will normalize abnormal fronto-striatal functional connectivity in patients with OCD; (ii) psilocybin will decrease activation of anterior cingulate cortices, amygdala, and putamen in response to symptom-provoking stimuli [23; 34; 38; 39; 46], and (iii) normalization of one or more of these abnormalities will correlate with improvement in symptomatology after psilocybin treatment.
   Secondary outcome measures will include depression, anxiety, and several personality questionnaires, as well as assessments of perception of symptoms and mystical experiences.

Background and Rationale

Obsessive-compulsive disorder (OCD) is a common neuropsychiatric disease; it has a lifetime morbid risk of 2.7% [1]. It is characterized by obsessions (intrusive, irrational thoughts accompanied by a great deal of anxiety and discomfort) and compulsions (repetitive actions undertaken in an effort to reduce that anxiety and discomfort, with short-term or limited effect) [2]. The disease course is typically chronic; over 60% of OCD sufferers describe their symptoms as having a major effect on the social and/or occupational functioning [1; 3]. Available treatments are limited. Serotonin reuptake inhibitors (SRIs) represent first-line pharmacological treatment. However, in spite of established efficacy of SRIs in the treatment of OCD, these treatments are sub-optimal; the therapeutic response is slow, most patients do not show significant effects until at least 4 weeks (and often up to 8 weeks) of continuous treatment, and even when optimally delivered, 30-40% of patients do not respond [4; 5]. Psychotherapy is beneficial to a comparable percentage; but access to appropriately trained therapists is limited, and effective therapy requires a degree of insight

and effort, and an ability to tolerate symptom discomfort that is difficult for many patients to muster [3; 6].

Furthermore, many who are classified as treatment responders remain symptomatic and lead restricted lives. The problem of severe, treatment-refractory disease is such that OCD is one of the few psychiatric disorders in which invasive brain surgery is an option, for the worst cases. Fundamentally novel, more effective and faster acting interventions are urgently needed.

Numerous case reports and a small open-label treatment study have shown acute, and sometimes enduring, beneficial clinical effects after administration of a single dose of psilocybin, 4-phosphryloxy-N,N-dimethyltryptamine, a high-affinity agonist of 5-HT2A and 5-HT2C receptors [7], in patients with OCD [8-11] and related disorders such as body dysmorphic disorder [12], anxiety and depression in patient diagnosed with terminal illness [13], addiction [14], and depression [15]. In a small proof-of-concept pilot study of nine treatment-refractory subjects with OCD, psilocybin was shown to reduce symptoms in all subjects (23%-100% reduction in Yale-Brown Obsessive Compulsive Scale [YBOCS] score), and most subjects experienced relief beyond the expected pharmacological life of psilocybin, and well beyond the 24-hour assessment [8]. One subject maintained full remission at 6-month follow-up. Moreover, in a recent open-label study testing the feasibility of administering two different doses of psilocybin to 12 patients with treatment-resistant depression, a marked reduction of depressive symptoms was sustained at 3-month follow-up after treatment with 25mg [15]. In another study, 80% of long-term heavy tobacco smokers demonstrated abstinence at 6-month follow-up after two treatments with 20mg and 30mg of psilocybin [16]. Patient with treatment-refractory alcohol-dependence demonstrated significantly reduced drinking behavior over 8 months after one or two psilocybin 30mg sessions [17]. Significantly decreased anxiety and depression scores were observed at 3 and 6 months after single moderate-dose (20mg-25mg) psilocybin in patients with anxiety related to end-stage cancer [13], and improvements in wellbeing lasting for more than 1 year were observed in healthy individuals given a single dose of psilocybin [18]. In a recent double-blind, placebo-controlled study in the treatment of anxiety and depression in patients diagnosed with life-threatening cancer, single moderate-dose psilocybin was shown to produce rapid, substantial, and sustained decreases at 6-month follow-up in clinician and patient-rated measures of depressed mood and anxiety, along with increases in quality of life, life meaning and optimism [19; 20]. More than 2000 subjects have received psilocybin under controlled experimental conditions during psychological and psychiatric research (including testing of high doses of oral and intravenous psilocybin) without causing any serious or unexpected psychological or medical adverse events [21-24]. These reported clinical effects justify investigating the efficacy and duration of psilocybin in a randomized, double-blind, placebo-controlled study. **Thus, this research proposal aims to investigate the effect of psilocybin on OCD symptomatology in a randomized fashion.**

Neural Correlates of psilocybin effects and of OCD Symptomatology

We have known for many years that a specific circuitry is pathologically affected in many individuals with OCD. Neuroimaging studies have identified hyperactivity in basal ganglia, amygdala, and key frontal cortical structures, including orbitofrontal cortex (OFC), medial

prefrontal cortex (mPFC), and anterior cingulate cortex (ACC), in individuals with OCD, compared to healthy controls [25]. Furthermore, a number of studies have shown that this hyperactivity correlates with the degree of symptomatology and improves with successful psychotherapeutic or pharmacological treatment, supporting a causal role in pathophysiology [26]. This strong association between regional brain hyperactivity and symptomatology has led to ongoing interest in invasive treatments targeting this circuitry as last-resort interventions in the most severe cases [27].

Moreover, this hyperactive circuitry can be conceptually linked to the phenomenology of OCD. The cortico-basal ganglia circuitry, especially that linking sensorimotor cortices and the dorsal putamen, has been associated with the formation of inflexible sensory-response behavioral patterns – habits [28]. A bias towards habit learning has been described in OCD [29], and dysregulation of automated cognitive and behavioral processes may be key to the disorder. In addition, neuroimaging studies have shown a greater activation of a network of the brain regions associated with internally-focused thought and valuation (ventromedial PFC (vmPFC), parahippocampus, middle temporal cortex and amygdala in individuals with OCD compared to health controls, which may contribute to the greater subjective experience of doubt that characterizes the disorder [30; 31]. This hyperactive circuitry is also observed in neuroimaging studies employing symptom provocation tasks, which entails the visual presentation of OCD relevant stimuli (i.e., pictures of hand washing) to elicit OCD symptoms, and normalization of circuitry with successful treatment [32-35]. There is thus a striking conceptual convergence between the functional anatomy that is abnormal in patients, and whose activity is correlated with symptomatology, and current thinking as to the normal function of these circuits.

A recent fMRI study with psilocybin in healthy controls showed a decrease of both BOLD (blood-oxygen-level-dependent) signal and cerebral blood flow (CBF) in fronto-temporo-parietal regions and in the important connectivity hubs of thalamus, putamen and midline cortex (anterior and posterior cingulum) [36]. The intensity of the subjective effects of psilocybin was predicted by decreased activity in the ACC and mPFC. Subsequent mPFC seed connectivity analysis revealed that psilocybin induced reduced connectivity between the PCC and mPFC, [37]. In another neuroimaging double-blind, placebo-controlled study in healthy controls, psilocybin relative to placebo was shown decrease amygdala activity during presentation of socially threatening stimuli [38; 39]. Another double-blind, placebo-controlled study in healthy controls using behavioral and event-related potential measurements demonstrated that psilocybin increases goal-directed behavior toward positive compared with negative cues, and facilitates positive but inhibits negative sequential emotional effects [40]. Furthermore, a recent preclinical study showed that psilocybin facilitates extinction of the classically conditioned fear response and increased hippocampal neurogenesis [41]; this may have clinical implications for drug-facilitated extinction-based therapy for OCD, as extinction, especially extinction recall, and the associated neural activation in the vmPFC are blunted in patients with OCD [42]. Although psilocybin has been shown to modulate brain activity in OCD-relevant regions in healthy controls [43], consistent with our hypothesis that psilocybin-induced modulation of these brain regions may underlies the therapeutic effects of the drug, this has not been tested in patients with OCD. **Thus, we aim to provide the first evidence of the neuronal mechanism that may mediate psilocybin's therapeutic effects on OCD symptomatology.**

The neurobiological mechanisms underlying these robust clinical effects remain poorly understood. If it can be established that 5-HT2A/C agonists can indeed lead to a rapid and substantial reduction in OCD symptoms, it would represent a dramatic and impactful advance in our ability to treat the illness, especially in its severe and refractory forms. It would also open the way for future studies of neurobiological mechanism that may shed light on the mechanism of action of existing pharmacotherapies in the treatment of OCD and related disorders.

Potential Risks and Benefits

Benefits: This study will evaluate the use of 5-HT2A agonist for OCD. A greater understanding of the neurobiology involved in OCD and the mechanism of anti-obsessive action could provide an impetus for development of more effective and rapid treatments for this debilitating disorder. The impact of this on the treatment of OCD could be enormous and would balance off the negative risks associated with participating in this study.

Potential Benefits:

Patients may benefit from the thorough medical and psychiatric evaluations that they will receive while participating in the study. During the study, subjects will also receive a higher level of evaluation and care than routine treatment.

Patients may also benefit by learning about their OCD and gaining insight about their anxieties through their participation. Some of the exposures are similar to the methods used in standard behavioral treatment and may provide patient with knowledge that they may not have possessed prior to participating.

What we learn in this study may contribute to the understanding of OCD and may possibly benefit future patients with OCD.

Risks to Participants

Risk of the Experimental Drug (psilocybin)

According to the most recent and comprehensive review, serotonergic hallucinogens “are generally considered to be physiologically safe molecules” that chiefly alter consciousness [44]. Recent reviews and searches of the literature indicate that psilocybin is not associated with harm or damage to any organ or system in the body [43]. Psilocybin can produce changes in blood pressure and heart rate, but these changes are not as strong or consistent as those seen after psychostimulants (amphetamines), and sometimes these changes only occur at one time point [45]. More consistently, psilocybin can produce rapid and intense changes in mood including periods of anxiety or panic. Both

these physiological and psychological effects are transient and do not last beyond the duration of drug effects.

Researchers studying the effects of 30 mg psilocybin took precautions similar to the ones we will use in this study [8; 20] and no reactions requiring pharmacological intervention occurred.

Safety Pharmacology

Studies in humans and nonhuman animals indicate that psilocybin has very low toxicity (Nichols 2016) (Passie et al. 2002). The LD_{50} ranged from 285mg/kg in rats and mice (Usdin and Efron 1972), cited in Merck Manual, 19th edition). The maximum tolerated dose of psilocybin in humans has not been defined or established. The best estimate of a lethal dose for pure psilocybin in humans is about 19 grams. The full dose of psilocybin that will be administered in this study is over 100 times smaller than LD_{50} in nonhuman animals and in humans. A Phase I trial of psilocybin at oral doses of up to 0.6 mg/kg demonstrated no serious adverse events. Psilocybin is not associated with disease or damage to any organ or system (Nichols 2016). More commonly, damage or disease to organs (as renal failure) is associated with mistakenly consuming poisonous mushrooms under the belief that they are psilocybin-containing mushrooms (Franz et al. 1996).

Three cases of death possibly related to the direct toxic effects of Psilocybe mushrooms (the natural source of psilocybin) have been reported in the world literature (Lim et al. 2012). One fatality occurred in a post-cardiac transplant patient who ingested Psilocybe mushrooms. It is not known however whether psilocybin was the proximal cause of death or whether death occurred secondary to the cardiac stimulant phenethylamine, which is also present in the mushrooms. In the French literature, another fatality linked to Psilocybe mushroom use was associated with far higher blood concentrations of the active metabolite of psilocybin than would be expected with the doses proposed in this study. A final fatality from Psilocybe mushroom ingestion was poorly characterized, and no psilocin concentrations were reported.

In a review of other adverse effects of Psilocybe mushrooms, an additional 10 individuals were reported to have experienced accidental deaths associated with Psilocybe mushroom ingestion (van Amesterdam et al. 2012). In most cases, these accidental deaths resulted from falls from buildings. Given the long and uncontrolled use of *Psilocybe* mushrooms in various societies and cultures, that there are only 3 known fatalities at best indirectly linked to the physiologic effects of mushroom ingestion is an argument for the general safety of this natural product. We believe that the use of pure psilocybin will decrease the risk of cardiac toxicity by avoiding any additive or synergistic effect of phenylethylamine. Further, a recent review of the potential harm of the ingestion of *Psilocybe* mushrooms by the Dutch medicinal advisory board found that the risk of acute or chronic toxicity was low (van Amsterdam, Opperhuizen, and van den Brink 2011).

To date, over 2000 participants have received psilocybin under controlled conditions in scientific studies with no reports of the occurrence of a significance of adverse events deemed to be associated with drug administration. The most commonly reported adverse events from the scientific literature are psychological in nature and include the induction of

negative emotional states and paranoid/delusional thinking during psilocybin sessions, as well as far less frequent reports of Hallucinogen Persisting Perception Disorder (HPPD) (Johnson, Richards, and Griffiths 2008, Tyls, Palenicek, and Horacek 2014). A review of studies conducted worldwide between 1999 and 2008 identified only one subject (out of 110) who experienced any persistent perceptual symptoms associated with HPPD and these symptoms were mild, brief, and resolved within three days of psilocybin exposure (Studerus et al. 2011). Rates of prolonged psychiatric symptoms of any kind following psilocybin exposure in healthy study participants are estimated to be 0.08-0.09%. As in the phase 2 studies, common physical adverse events associated with psilocybin administration include increased BP and heart rate, nausea, and headaches. In the phase 2 studies of cancer related anxiety and depression no cases of HPPD were identified and no participants developed any symptoms of paranoia or anxiety that required pharmacological intervention or anything more than reassurance from session facilitators (Ross et al. 2016, Griffiths et al. 2016). In a survey of 1993 individuals in the context of illicit use of psilocybin-containing mushrooms, 11% put self or others at risk of physical harm. Of the respondents, 2.6% behaved in a physically aggressive or violent manner and 2.7% received medical help. Of those whose experience occurred >1 year before, 7.6% sought treatment for enduring psychological symptoms. 3 cases appeared associated with onset of enduring psychotic symptoms and 3 cases with attempted suicide (Carbonaro et al. 2016).

To date, there have no reports of physical harm in patients who have received psilocybin under controlled conditions, and no fatalities have been associated with its use in a controlled clinical trials. The difference in the side-effect profile between the unknown doses of psilocybin-containing mushrooms consumed in an uncontrolled setting and dose-controlled medically prepared oral psilocybin consumed in a controlled setting is thought to be in part doe the focus on the set and *setting* of the experience. The *set* refers to the emotional/cognitive/behavioral state/mindset and expectations of study participants just prior to psilocybin exposure and *setting* refers to the physical environment in which the exposure occurs (Johnson, Richards, and Griffiths 2008).

There are no confirmed reports of an overdose of pure psilocybin. In the United States, use of chemically synthesized psilocybin does not occur (DEA 2000). Although psilocybin in the form of mushrooms is sometimes used non-medically, medical emergencies due to psilocybin mushrooms are very rare (psilocybin is mentioned in only 0.1% of drug-related emergency department visits) (SAMHSA 2004 a,b). It can be anticipated that an overdose of psilocybin might present in a manner similar to “serotonin syndrome”. Removal of any residual gastric drug, supportive care, and cautious administration of a serotonin antagonist such as risperidone are reasonable interventions; however, to date no cases have described similar responses with respect to psilocybin, and the doses of psilocybin that might provoke these physiological effects would be many times greater than even the highest doses used in early human studies.

Common side effects

Common acute side effects of psilocybin are almost all psychological, and include anxiety, changes in thought (experiencing thinking speeding up or slowing down), changes in motion perception, changes in time perception (time slowing down or speeding up), depersonalization (feeling as if one is “outside oneself”), derealization (feeling as if the world is unreal or as if one is “in a dream”), dizziness, fatigue, impaired concentration, inattention, mood lability (rapid and sometimes profound changes in mood), nausea,

nervousness, parasthesias (strange bodily sensations or feelings), perceptual alterations (general), altered time perception, alteration in visual perception (distortions, illusions and imagery seen with eyes open or closed), and unusual thought or feelings about the self or the world (Carter et al. 2004; Carter et al. 2005b; Fischer 1966; Gouzoulis-Mayfrank et al. 1999b; Griffiths et al. 2006; Hasler et al. 2004; Hollister 1961; Hollister and Sjoberg 1964; Umbricht et al. 2002; Vollenweider et al. 1997). Most of these effects are acute and last no longer than six hours (Hasler et al. 2004; Hollister 1961; Passie et al. 2002; Vollenweider et al. 1998). For the most part, people receiving psilocybin maintained insight concerning the nature and source of their experience. However, some participants occasionally exhibited paranoid ideation or temporarily lost insight into the experimental situation (Gouzoulis-Mayfrank et al. 1999b; Griffiths et al. 2006; Vollenweider et al. 1998).

Psilocybin produces slight sympathetic system activation. Physiological effects include pupillary dilation and detectable but moderate increases in blood pressure or heart rate (Griffiths et al. 2006; Hasler et al. 2004). Researchers sometimes detected changes in blood pressure and heart rate only at one point in time, as sixty minutes after drug administration (Hasler et al. 2004). These effects are transient and are generally gone approximately six hours after drug administration. People in previous human studies have tolerated doses of psilocybin equal to or greater than the doses employed in this study. Researchers studying the effects of 30 mg psilocybin took precautions similar to the ones we will use in this study [8; 20] and no reactions requiring pharmacological intervention occurred.

Acute side effects

The most likely potential adverse effect of psilocybin is anxiety, or possibly panic, delusion, and cognitive impairments, particularly at higher doses (> 25 mg po) during the period of acute drug action. In recent studies of psilocybin in healthy humans conducted over the past 15 years (Hasler et al. 2004, Nichols 2016) no adverse reactions other than the expected occasional episodes of fear or anxiety during the time of drug effect have been reported. Such transient episodes of fear or anxiety respond well to reassurance and have not required pharmacological intervention. Some individuals have been reported to develop paranoid and psychotic states while under the influence of psilocybin.

Insomnia

Although rare, insomnia following psilocybin administration has been reported in the literature; it has been described as self-limiting and responded well to reassurance from the study team. In the event that a participant experiences insomnia, a study physician may initially prescribe a sleep aid (i.e. diphenhydramine or hydroxyzine) and if the initial reassurance, education about sleep hygiene and pharmacological intervention was unsuccessful, a one-time dose of short-acting benzodiazepine (specifically lorazepam) and/or zolpidem will be considered.

Prolonged side effects

In addition to fear, panic, and paranoia during the drug session, there is the possibility of prolonged adverse psychological reactions, such as psychosis and depression. It is generally believed that individuals with previous psychiatric conditions, particularly psychosis or mania, are at an increased risk for hallucinogen-induced psychosis (Nichols 2016, Abraham, Aldridge, and Gogia 1996). Furthermore, the risk that, in vulnerable individuals, psilocybin

could precipitate enduring psychiatric illness such as schizophrenia is very low, but cannot be excluded completely (Abraham, Aldridge, and Gogia 1996). For this reason, all potential participants with personal or family histories of Schizophrenia, Psychotic Disorder, or Bipolar I or II disorder are to be excluded from participation. Nevertheless, although the risk is believed to be minimal, it is possible that some participants may develop a brief psychotic reaction while under the influence of psilocybin.

The low rate of enduring psychological symptoms is consistent with a summary of such effects from 110 psilocybin research participants reported in a meta-analysis conducted by Studerus et al in their laboratory (Studerus et al. 2011). In that report, 7 participants endorsed negative changes in psychological well-being, but only 1 participant (0.9%) reported a level of distress sufficient for him to contact the researchers. Those symptoms resolved after a few sessions with an experienced psychotherapist.

Johns Hopkins recently completed an internet survey of hallucinogen users who reported having a challenging experience after taking psilocybin mushrooms. The rates and severity of both acute and enduring problems shown in the survey are notably higher than those observed in laboratory research studies involving administration of high doses of psilocybin to carefully screened, well-prepared, and closely monitored volunteers. This observation appears to support the efficacy of the standard screening, preparation, monitoring, and follow-up procedures designed to minimize the possibility of any enduring problems.

Benefits: This study will evaluate the use of 5-HT2A agonist for OCD. A greater understanding of the neurobiology involved in OCD and the mechanism of anti-obsessive action could provide an impetus for development of more effective and rapid treatments for this debilitating disorder. The impact of this on the treatment of OCD could be enormous and would balance off the negative risks associated with participating in this study.

Potential risks of Niacin (active-placebo-control agent)

A participant's OCD might change or perhaps worsen during the course of the study (as symptoms might change during a normal course). There is no reason to believe that niacin as an active-placebo-control would exacerbate OCD symptoms. Niacin has some expected physiological side effects which is why it is used as an “active placebo”. These include flushing, tingling, itching, and redness of the face, arms, and chest, as well as headaches. Other minor but expected side effects include upset stomach, intestinal gas, and dizziness. Participants will be informed about these potential side effects and they will be monitored throughout the drug administration visits.

Risk in Changes or delay in treatment

Participants will be asked to refrain from starting new medications during the study procedures. Should circumstances warrant a change in treatment, then participants will be asked to immediately notify the study team. If medically warranted, the participant begins to experience a decline, or their provider believes a treatment change is necessary, then the participant will be withdrawn from the study and encouraged to seek treatment.

Risk of involuntary hospitalization for patient safety

As part of enrollment in this study, participant must agree to staying overnight at the CNRU for up to 4 nights for evaluations and for monitoring after receiving psilocybin. If participant is not compliant with the requirement or it is deemed a safety concern, then there is possibility that the participant may be involuntarily hospitalized against his/her will. Also, if there is concern about participants being a risk to themselves or others during the study, there is potential for participants to be hospitalized against their will. Participants will be monitored and discharged only after study physician believes that it is safe to do so.

Risks of Emotional Responses, Discomforts During Administration & follow-up meetings: During non-drug and experimental sessions, participants will be asked to think about and to discuss their thoughts and emotions about carrying a diagnosis of OCD, including anxiety and the impact the OCD has had on their lives. They may experience emotional responses to speaking about these thoughts, feelings and concerns. The drug session will take place at CMHC and will be staffed by two investigators. The PI and/or investigators who will be present during the drug session will meet the patient several times prior to drug administration. This will be done as part of psychoeducation, discussing several procedures in coping with anxiety and distress should it be necessary during the drug session.

The other risks involved in this research are generally considered minimal and include those normally associated with clinical care or research such as psychiatric evaluations, medical examinations, ECG, lab work - urine drug screening, blood draws, clinical / research assessments, stimuli exposure, fMRI, and clinical tests:

Psychiatric Evaluation, and Clinical Assessments: Participants must answer personal questions, which may feel unpleasant or tiring, or may find discussing their symptoms and their illness during the psychiatric evaluation unpleasant or upsetting. Screening is necessary to assess participant eligibility. The major disadvantages of these assessments are the time that it takes to complete them. These clinical and research methods represent minimum risk(s).

Medical examination with ECG: is considered a routine procedure for a research study involving admission of a patient onto the CNRU at CMHC and for administration of a study drug. Screening is necessary to assess participant eligibility and uncover potential risks. The ECG will help us to discover any cardiac abnormalities that might be of concern.

Lab work - Pregnancy testing, Urine drug screen and Blood draws: are necessary for the routine clinic screening, laboratory testing and usually required by CMHC to register patients in our clinic.

The urinary drug screen is necessary to verify abstinence from illicit substances or nonprescription stimulants upon study enrollment and prior to the psilocybin session.

As part of the registration labs, participants will undergo a blood draw for standard labs, a comprehensive metabolic panel, pregnancy test, thyroid tests, and standard liver panel. These tests prior to the psilocybin session allow the investigators to ensure that there are no contraindications to subjects' participation in the study. e.g. Liver function panel results will allow the investigators to detect poor metabolism, which could produce higher than expected levels of psilocybin. Higher levels of psilocybin may produce prolonged

duration or greater intensity of subjective effects. Weighing the risks and benefits of a blood draw versus potentially unpredictable levels of psilocybin, the liver panel conveys more benefits than risks. Serum pregnancy and / or urinary pregnancy tests are conducted to avoid the risk of unintended psilocybin exposure in utero. Less than 50mL will be drawn per collection. There will be a total of 1 blood draw (baseline labs) over the course of study. The blood draw may produce temporary discomfort as a result of sampling blood, and discomfort or bruising at the blood drawing site.

Neuropsychological and cognitive assessments, and online measures: Participants will complete a battery of assessments, self-report and clinician-administered measures of OCD symptoms, anxiety, depression, quality of life, spirituality and cognitive assessments. There is minimal risk associated with assessments and ratings. Some subjects may experience some mild anxiety, frustration or find answering questions boring. Utilization of online questionnaires and tasks allow subjects to pace themselves, answer some questions in their free time, or to take breaks as needed. In person assessments by our trained clinical research staff provide opportunities for breaks and allow for the exercise of sensitivity during questioning. There is minimal risk associated with answering questionnaires.

MRI / fMRI Studies: Functional magnetic resonance imaging (fMRI) scans have a low risk with proper screening. Some people may feel uncomfortable or anxious. On rare occasions, some people might feel dizzy, get an upset stomach, have a metallic taste or feel tingling sensations or muscle twitches but these usually go away quickly.

There are risks for those who have a pacemaker or metal in their body, and can be grounds for exclusion. The most significant hazard concerns metal objects. If brought into the magnet room they may be drawn forcefully into the magnet, flying through the air toward the magnet, and hitting someone. Nothing metal can be brought into the magnet

room.

> Pre-MRI plain radiography (x-ray) rule-out for metallic objects is to ensure that it is safe to have an MRI. Willing participants may receive an x-ray, as needed on a case by case basis, to clarify scanning status. This procedure will be performed at the Radiology department of Yale New Haven Hospital. Plain film radiography is a routine clinical procedure involving ionizing radiant energy and so represents exposure to a low level of radiation for research purposes only. The total radiation exposure amount of one skull x-ray that a subject will receive is the same as the exposure a body normally gets from natural background radiation in a 12-day period. This use involves minimal risk and is necessary to obtain the research information desired (16).

Confidentiality: Clinical information of a personal nature will be collected as part of this study. A potential risk of the study is therefore a breach of the confidentiality of the data collected. The significance of this study lays primarily in the potential of producing results that may shed light on the neurobiological mechanisms of the clinical effect of psilocybin in the treatment of OCD, and more generally, contribute to the accumulating evidence for the value of drug- facilitated psychotherapy in OCD.

Minimizing Risks:

Study drug - Clinical and medical staff will be available to evaluate any change in condition. All patients will be closely monitored during the study period. All participants will be asked to contact us at any time if any unpleasant effects occur.

Psilocybin: Reviews of the drug and the literature indicate that the physiological and psychological effects are transient. The patient will be monitored at all times by trained research and/or medical staff. The study medical doctors and nursing staff who are trained in dealing with drug challenge studies (such as ketamine, psilocybin, yohimbine, and various cannabis compounds) will remain in attendance during the entire session. Participants will be asked to remain on the CNRU until effects wear off. Procedures will be immediately stopped if participants request or if they are exhibiting significant distress.

To minimize risk associated with psilocybin, participants will undergo a thorough screening for contraindicated psychological conditions or interacting medications. Dosing with psilocybin must be performed in a setting that minimizes distraction and interruption, and the participant must be attended following the dose by research staff trained in providing reassurance and a safe environment until the effects of the single dose have dissipated.

The PI may prescribe a designated rescue medication in the event of symptoms that require it during or after the experimental session. Rescue medications may be a benzodiazepine, zolpidem, or other anxiolytic or sedative according to the physician's clinical judgment.

If any participant presents with an adverse reaction to the psychopharmacological agent as reported by them or assessed by a member of the research team, we will discontinue the study and call for medical assistance. Finally, the participant may be withdrawn from the

study if his/her withdrawal is in the best interests of either the participant or of the research (e.g., due to a medical condition making the procedures unsafe or any condition making interpretation of the results difficult).

Niacin: (active-placebo-control agent): There is no reason to believe that niacin would exacerbate OCD symptoms. Participants will be informed about Niacin's potential side effects and they will be monitored throughout the drug administration visits.

The rationale for using an active-placebo-control agent rather than active low dose of psilocybin (ranging 2mg -4mg), which have been used in the recent palliative care studies and OCD study, is because a partial response has been reported even with these low doses. Psilocybin acutely attenuated OCD symptoms even after low doses (Moreno et al., 2006, (8))(Moreno et al. 2006), raising questions as to interpreting results with respect to whether the lowest dose served as placebo and whether it was in fact devoid of therapeutic effects.

Changes or delay in treatment: Participants will be asked to refrain from starting new medications to allow the participant and this study to safely proceed. If medically warranted, the participant begins to experience a decline, or their provider believes a treatment change is necessary, then the participant will be withdrawn from the study and encouraged to seek treatment.

Involuntary holding, overnight for safety: The medical staff will closely monitor the participant's medical status during study administration. The staff take whatever medical steps are safely possible to reduce the need for an additional holding period including ongoing evaluations during the testing period. However, if there was concern about participants being a risk to themselves or others during the study, or if investigator feels it is medically necessary, and/or if the participant is not compliant, then the participant may need to be involuntarily held for his/her own safety. Participants will be discharged after the study physician believes that it is safe to do so.

Emotional Responses and Discomforts During Administration, Psilocybin Session, and follow-up appointments: Trained staff will be on hand to help participants deal with their responses to the study.

Administration and follow-up appointments: Only the trained clinical staff will conduct such sessions. Staff will assist patients who require help with their anxiety. The anxiety experienced is no more than normally reported in any standard therapeutic session.

Psychiatric evaluation and clinical assessments: All participants must first give permission for the investigators to review medical records and later undergo a psychiatric evaluation and a urinary drug screen to ensure that participants are eligible to be in the study. We will try to schedule and to complete tasks quickly. Each participant is told that he/she does not have to answer any question that he/she does not want to answer. Only the trained clinical staff conducts such evaluations and all exercise utmost sensitivity.

Medical examination with ECG: Screening is necessary to assess participant eligibility and to uncover sometimes unknown contraindications. We minimize risk by having only skilled medical staff conduct the brief physical examination and the ECG to rule out any cardiac

abnormalities. This ECG is reviewed by medical staff and by a trained cardiologist.

Urine toxicology and blood drawing-labs: We minimize medical risk by having skilled nurses and phlebotomists do our blood drawing. If a blood draw produces temporary discomfort, then nursing staff can offer ice or cool compresses. There is also a remote possibility of inflammation or infection at the blood drawing site. Liver panel results will allow the investigators to detect poor metabolism, which could produce higher than expected levels of psilocybin. Higher levels of psilocybin may produce prolonged duration or greater intensity of subjective effects.
Weighing the risks and benefits of a blood draw versus potentially unpredictable levels of psilocybin, the liver panel conveys more benefits than risks.

The urinary drug screen is necessary for verifying the participant's report of current substance use and to eliminate potential risks of drug - medication interactions. The research staff utilizes their extensive experience and practices the utmost discretion with subjects.

Subjects are informed of this testing in advance of the screening appointment, and may choose to not participate in the study.

Neuropsychological and cognitive assessments and online measures: The research staff will inform all participants that they may take breaks or stop if experiencing too much frustration, or anxiety. Participants may take breaks from completing measures and online tasks. Ratings will be administered with sensitivity by trained staff, either in paper-format or utilizing secure servers and data capture systems. All online responses will be captured on secure servers. This use of online measures speeds up the assessment process and seems to reduce some subject stress. All information will be kept strictly confidential.

Pre-MRI plain radiography (x-ray) rule-out for embedded metallic objects should this be suspected: an x-ray will only be ordered in cases where the participant reports some exposure from working with metal and is willing. Participants will be informed that the procedure involves some exposure to radiation. Participants may refuse this option and will then be ruled out for MR scan due to safety concerns.

MRI/ fMRI Studies: will be performed at the Yale Magnetic Resonance Center (MRRC) by trained
research technicians, observing FDA guidelines. All research staff will be trained in MRRC safety.

- Participants will be required to read and to answer very carefully the questions on the MR Safety Questionnaire related to personal safety, and trained staff will review these answers.
- Each subject will be screened in the MRRC for metal objects prior to being allowed into the magnet room. All metal from clothing or metal objects from participant's pockets will be removed prior to entering the scanner room. Persons with a pacemaker or some metal objects may be excluded from participation
- Once the subject is in the room, only the study personnel, MRRC staff and the scientist running the MR system is allowed into the room.
- The scan room door will be closed, so that no one from outside accidentally goes

near the magnet.

- ï Should an accident occur, 911/EMS will be activated. All personnel are trained in an established procedure for removing the subject from the magnet. Due to the close proximity to the hospital, the time required for the ambulance to arrive will be under 5 minutes. All study personnel involved are trained in this procedure.
- ï If a subject becomes anxious or uncomfortable and expresses a desire to leave the magnet then he/she may ask to stop the scan or to be taken out, and the scan is immediately terminated.
- ï The subject will be monitored by at least one staff member via visual and verbal contact throughout the scanning process. Confidentiality – Active patient medical charts and written research records will be stored in locked offices on a locked research unit, and accessible only to the principal investigator and other study personnel. Medical charts are kept indefinitely by the State of Connecticut according to state/CMHC policies after study participation has ended. Electronic records of clinical and research data will be stored in research folders on encrypted Yale servers, accessible only by identified study personnel using netids and passwords. Research databases will be coded (all identifiers except id number will be removed) during data analyses and are also kept on Yale servers or encrypted computers.

Confidentiality – Active patient medical charts and written research records will be stored in locked offices on a locked research unit, and accessible only to the principal investigator and other study personnel. Medical charts are kept indefinitely by the State of Connecticut according to state/CMHC policies after study participation has ended. Electronic records of clinical and research data will be stored in research folders on encrypted Yale servers, accessible only by identified study personnel using netids and passwords. Research databases will be coded (all identifiers except id number will be removed) during data analyses and are also kept on Yale servers or encrypted computers.

Benefits

This study will evaluate the use of 5-HT2A agonist for OCD. A greater understanding of the neurobiology involved in OCD and the mechanism of antiobsessive action could provide an impetus for development of more effective and rapid treatments for this debilitating disorder. The impact of this on the treatment of OCD could be enormous and would balance off the negative risks associated with participating in this study.

Study Design and Endpoints

Description of the Study Design

This is a randomized, double-blind, placebo-controlled study with option to receive open-label psilocybin.

Research Methods and Design:

This study will pilot a single-center, randomized, active-placebo-controlled, double-blind design (Randomized phase Tables 1, 2 and 3; and Open label phase 4 and 5) to examine the clinical and neural effects on OCD, of either 0.25mg/kg of psilocybin or active placebo-control agent (niacin 250mg), given along with non-drug preparatory and follow-up support appointments to 30 study participants.

The duration of the randomized study phase is from consent until one week after drug administration. Participants will be followed for 12 weeks (approximately 3 months) post-study drug administration.

Study Duration:

The study intends to run for 7 years from its inception to accommodate for the impact the COVID-19 pandemic has had on study recruitment and enrollment goals. To account for data analyses and other processes post the study closing to enrollment, the study duration is extended 2 more years, intending to close in 2026.

Study Endpoints

Primary Endpoint

Primary endpoint will assess OCD symptoms measured using YBOCS at 48 hours post drug administration. YBOCS will be administered at evaluation, 1 day prior to drug administration, 1-day post-drug, 2 days post-drug, 1 week post-drug, 2 weeks post-drug, 4 weeks post-drug, 8 weeks, and 12 weeks post-drug.

Secondary Endpoints

Secondary outcome measures will look at the effect of psilocybin on symptoms depression, quality of life, beliefs about spirituality and self-boundaries, community observer-rated changes in participant behavior and attitudes, mystical experiences, personality dimensions, symptoms of perception.

In addition, a secondary objective of this study is to determine the feasibility of administering psilocybin to this patient population, with regards to the following issues: safety, patient recruitment, and retention. The duration of the proposed study will be long enough to administer the drug one time to each of the thirty participants and to conduct follow-up assessments.

Exploratory Endpoints

With respect to associations between resting state, functional and structural MRI in OCD and symptom clusters or treatment outcome variables, we will initially focus on connectivity abnormalities that have previously been described by us and others: altered global brain connectivity in the basal ganglia [47], increased seed-based functional connectivity between ventral striatum and medial prefrontal cortex [48; 49], and increased coherence between default and attentional networks [46].

We will also perform a fully data-driven analysis (as in our previous work with neurofeedback in Scheinost et al, 2013, Figure 4) [50] to identify regions beyond these initial hypotheses where changes in global brain connectivity correlate with clinical change after psilocybin treatment.

APPROVED BY THE YALE UNIVERSITY IRB 4/28/2025

Research Materials and Measures:

Participants will complete self-report and clinician-administered measures of OCD symptoms, anxiety, depression, quality of life, and spirituality at baseline, prior to psilocybin session, and during all designated study visits (see charts). All subjects will be asked to complete an extended set of research assessments: to examine symptom dimensions, life attitudes, motivation, ideation, core beliefs, and co-occurring conditions.

Patient Screening Visit:

1. Demographics (15 minutes)
2. MRI Safety Questionnaire (5 minutes)
3. Mini International Neuropsychological Interview 7.0 (MINI-7) (30-50 minutes)
4. Yale-Brown Obsessive-Compulsive Scale (YBOCS)
5. Y-BOCS Symptom Checklist (15- 20 minutes)
6. SCID – 2 Personality Questionnaire (SCID-II/PQ) (10-20 minutes)

Clinician Administered Ratings:

1. Montgomery-Asberg Depression Scale (MADRS) (6-8 minutes)
2. Columbia Suicide Severity Rating Scale (C-SSRS) (5 minutes)
3. Acute YBOCS (A-YBOCS) - examining specific participant OCD symptoms over prior 24 hours (5 minutes)
4. Y-BOCS- examining overall obsessive compulsive symptoms over prior week (5-10 minutes)
5. Clinical Global Impression – Clinician (CGI-C) (2 minutes)
6. Community Observer Ratings of Changes in Subjects' Behavior and Attitudes (COM-R) (5-10 minutes)
7. Yale Global Tic Severity Scale (YGTSS-Clinician) (3-10 minutes)

Self-Report:

1. Becks Depression Inventory (BDI) (5 minutes)
2. Obsessive Beliefs Questionnaire – 44 (OBQ-44) (5-10 minutes)
3. Obsessive-Compulsive Inventory – Revised (OCI-R) (5 minutes)
4. Obsessive-Compulsive Trait Core Dimensions Questionnaire (OC-TCDQ) (3-5 minutes)
5. Thought Action Fusion Scale (TAF) (3-5minutes)
6. Responsibility Attitude Scale (RAS) (5 minutes)
7. State-Trait Anxiety Inventory (STAI) (5 minutes)
8. Quality of Life Enjoyment & Satisfaction Questionnaire (Q-LESQ-SF) (3 minutes)
9. Mystical Experience Questionnaire (MEQ) (5 minutes)
10. Community Observer Ratings of Changes in Subjects' Behavior and Attitudes (COM-R) (5-10 minutes)
11. Post-Session Subjective Experience Questionnaire (PSEQ) (3 minutes)
12. Reactions to Research Participation Questionnaire (RRPQ) (3-5 minutes)
13. Big Five Aspect Scales (BFAS) (10 minutes)
14. Schedule for Meaning in Life Evaluation (SMiLE) (10 minutes)
15. Challenging Experience Questionnaire (CEQ) (5 minutes)
16. 5-Dimension – Altered States of Consciousness (5D-ASC) (10-15 minutes)
17. Positive and Negative Affect Schedule Expanded Form (PANAS-X) (10-15

minutes)
18. Persisting Effects Questionnaire (PEQ) (10 minutes)
19. Nature Relatedness Scale (NRS) (3 minutes)
20. Pro-Environmental Behavior Scale (PEBS) (3 minutes)
21. Individual Differences in Anthropomorphism Questionnaire (IDAQ) (3 minutes)
22. Mind-Body Dualism Scale (MBDS) (3 minutes)
23. Inclusion of Others in Self Scale (IOS) (1 minute)
24. Ethical Positions Questionnaire (EPQ) (3 minutes)
25. Alcohol Use Disorders Identification Test (AUDIT) (3 minutes)
26. Utilization of Facility and Emergent Care (UFEC) (3 minutes)
27. Drug Use Disorders Identification Test (DUDIT) (3 minutes)
28. Self-reported Nicotine Use (SRNU) (3 minutes)
29. Pittsburgh Sleep Quality Index (PSQI) (3 minutes)
30. Visual Analogue Scale (VAS) (2 minutes)
31. Behavior Identification Form (BIF) (3 minutes)
32. Magical Ideation Scale (MIS) (3 minutes)
33. University of Rhode Island Change Assessment (URICA) (3 minutes)
34. CGI-Self Report (2 minutes)
35. Physical Symptoms (Saftee) Checklist (PSC) (3 minutes)
36. Sheehan Disability Scale (SDS) (2 minutes)
37. Life Orientation Test Revised (LOT-R) (2 minutes)
38. Padua Inventory of OCD Symptoms (5 minutes)

Safety Measures (inpatient- visits 4 to 6):

Columbia Suicide Severity Rating Scale (C-SSRS), Subjective Units of Distress (SUD),

and vital signs including blood pressure, heart rate, and body temperature, Serious Adverse Events (SAEs), Adverse Events (AEs), spontaneously reported reactions, General Well-being, medications and changes to psychiatric medications will be collected.

Videotape/audiotape (optional):

Participants will be asked to allow us to audio-video record the preparatory psychoeducation and drug sessions in their entirety. These recordings will be used as review aid for participants and for the therapists, and for investigators for further analysis of patient behavior, defense mechanisms, therapist interventions, manual adherence, etc. Patients will be asked to allow us to keep these tapings indefinitely for not just for this study but also for education, future research and training purposes. Patients will be asked to initial separately audio-video taping choices in the informed consent. Patients can participate in the study in spite of refusing video recordings. The recordings will be given an identification code number, date and session number, stored in a locked file cabinet and treated confidentially.

Research Procedures

Initial Research procedures:

First the study, the conditions, and the procedures involved, will be explained and discussed with each subject. Each subject will have a chance to ask questions and to receive answers before deciding whether to participate, to be registered at CMHC, and to provide an informed consent. For safety, after completing the consent, the participants may designate 2 to 3 adults who will be expected to have continuing contact with the subject, who may provide patient transportation, and who may observe changes in the participants' behavior and attitude over time and report back. These observers may provide feedback to the research staff about the subject's behavior, mood, and attitude, in addition to the participants' self-report.

Study Research Evaluations and Procedures - Outpatient or Inpatient (see Tables 1 to 5):

Medication and life style changes may be required, including not ending nor starting new medications such as SSRIs (off recent selective serotonin inhibitors for five half-lives of the drug plus 2 weeks), abstaining from tobacco products, alcohol, or any street drugs such as marijuana. Study personnel may obtain a release to contact the participant's prescribing provider to discuss current prescriptions and medication history. This is decided on a case by case basis upon the discretion of the PI.

Medication contraindications will include anti-seizure medications, insulin and oral hypoglycemics, certain hypertension medications (clonidine, and aldomet specifically), cardiovascular medications and the following psychotropic medications: anti-psychotics (first and second generation agents), anti-depressants and mood stabilizers. Psychotropic medications cannot be taken in the previous two weeks, with Prozac (fluoxetine) not being taken within the last 5 weeks prior to receiving any study agents. Participants may only take prn (as needed) benzodiazepines (i.e. lorazepam) up to three days before the session. Participants will refrain from taking any medications the day of either the experimental or active-placebo-control

treatment session, except prescribed opiate pain medication or over-the-counter non-narcotic pain medication at any time. It will also be necessary to refrain from alcohol the day before, the day of, and the day after each experimental session.

Physical exam, ECG, blood and urine tests for registration and screening/ CMHC/CNRU patient registration: As part of the study and the subject screening, subjects will have a physical examination, ECG, and screening blood and urine tests (including comprehensive metabolic panel, chemistries, hematological tests, thyroid function tests, urinalysis, urine toxicology, and if applicable pregnancy tests). These results will also become part of the research case record.

Randomization and one-time Administration of the Study agent Psilocybin or active-placebo-control agent Niacin (v5) and requiring minimum of 3 overnights on CNRU (visits 3 to 6) with inpatient registration:

Psilocybin and niacin (active-placebo-control agent) will be administered in identically appearing opaque, size 0 gelatin capsule with approximately 180ml of water. The dose of psilocybin will be 0.25mg/kg and the niacin will be 250mg. Each participant will have the option of receiving the study drug and participating in the experimental treatment sessions. In the study, half of the participants will be randomized to receive psilocybin (n=15) or the active-placebo-control, niacin (n=15). Following the first treatment session of either the active agent or active-placebo-control, participants who were randomized to receive active-placebo-control will be offered the option to receive open-label psilocybin. (The blind will be broken at 48-hours to make this determination; this is after our primary endpoint. Clinical raters will remain blind to the treatment assignment). Data will be collected from all subjects after open-label treatment for descriptive purposes, but these data will not be analyzed as part of our primary analysis plan.

Psychiatric Evaluation, Clinical Assessments, **and Study Evaluations** - **paper or online measures, assessments, ratings, surveys, & tasks:** Online surveys and measures will be offered using secure data capture systems, e.g., Qualtrics or REDCap, or paper documents. These evaluations will include standard OCD Research clinic questionnaires, clinician administered diagnostic interviews and reports, medical and clinical assessments, patient self-report measures. This testing may last up to 1 to 2.5 hours.

Research study measures, follow-ups and assessments are outlined (in Tables 1 to 4) and represent study specific clinician administered and self-administered measures. Safety measures and checks will be completed at some inpatient study visits: C-SSRS, SUD, vital signs, SAEs /AEs, spontaneously reported reactions, general well-being, medications, and changes to psychiatric medications.

All participant responses to measures and assessments will be recorded either on traditional paper formats and scanned to a Yale share drive /server, or in online data capturing systems (Qualtrics, REDCap) which instantly upload responses or surveys to a secure server. All portable digital participant data will be uploaded immediately and stored in Yale OCD Research computer databases, on password-protected computers in locked offices, and/or on secure Yale servers.

MRI / fMRI Procedures:

Structural (sMRI) and Functional (fMRI) Magnetic Resonance Imaging will be performed at the Yale Magnetic Resonance Research Center (MRRC), located in the Anlyan Center, and overseen by faculty and trained MR research technologists at the MRRC. After documented, signed, informed consent, a review of the MRI Safety Questionnaire, and additional screening and safety determination if necessary, participants will be accompanied to the scanner by study personnel and given detailed instructions. Participants will be asked to remove everything from their pockets, and to remove any potentially ferromagnetic articles of clothing, and must then pass through a metal detector according to standard safety procedures. At this time, the participants will be presented to the research technologist who will facilitate entry into the scanner. Total MR acquisition may last between 1.5 and 2 hours depending on acquisition of all or a subset of sequences, and whether some series must be re-acquired due to motion or other confounds/artifacts.

sMRI will be acquired in horizontal, coronal or parasagittal planes using an SPGR sequence. Images will be skull-stripped and segmented into cerebrospinal fluid, gray matter, and white matter. Volumetric assessments will be made of the major lobes of cerebral cortex and of subcortical structures, including basal ganglia.

MRI acquisition will be conducted using a Siemens MRI scanner (i.e., "PrismaB," a 3 Tesla MRI) located at the MRRC and will ***use standard MRRC sequences already in use by other investigators***. Using a 64-channel head coil (HEA;HEP), the scan protocol will begin with a 3-plane localizer, scout image, and aligned 3-plane localizer that will serve as a localization series for the other acquisitions. The remaining multi-modal magnetic resonance pulse sequences will include: high resolution T1-weighted imaging (i.e., MPRAGE or FLASH); high resolution T2-weighted imaging (i.e., SPACE); spin echo field maps will be acquired in opposing phase encoding directions prior to each fMRI session; multi-band BOLD gradient echo planar imaging at rest and under challenge (i.e., task paradigm); diffusion weighted imaging (DWI), arterial spin labeling (ASL), and proton density weighted imaging (PD). The T1 MPRAGE and T2 SPACE acquisitions are set to use an "Adjust Volume" that matches the size and positioning of the spin echo field maps and resting state fMRI scans. Participants may be asked to return for a repeat session due to inadequate image acquisition or time constraints. In the case of failed MR studies, no more than three repeat sessions will be attempted. MR compatible equipment provided by the MRRC may be used to track eye movement during the MRI procedures. Illustrative sequence parameters are provided in the table below

MRI Sequence Parameter Summary

Sequence	TA	TR (ms	TE (ms)	TI (ms)	FOV (mm)	Flip °	VOX (mm)
Localizer	00:09	40	3	--	300	15	1.2 x 1.2 x 5.0
Scout	00:14	3.15	1.37	--	260	8	1.6 x 1.6 x 1.6
Localizer (aligned)	00:21	104	3	--	300	15	1.2 x 1.2 x 5.0
Spin Echo Field Maps	01:04	8000	66	--	208	90	2.0 x 2.0 x 2.0
fMRI & t-fMRI (each)	*varies*	800	37	--	208	52	2.0 x 2.0 x 2.0

T1 MPRAGE	06:38	2400	2.22	1000	256	8	0.8 x 0.8 x 0.8
T2 SPACE	05:57	3200	563	--	256	--	0.8 x 0.8 x 0.8
Diffusion MRI (each)	05:45	3230	89.2	--	210	78	1.5 x 1.5 x 1.5
T1 FLASH (40 sl)	01:26	300	2.43	--	220	60	0.9 x 0.9 x 3.0
Proton Density (40 sl)	00:50	1000	20	--	220	90	2.5 x 2.5 x 3.0
ASL (40 sl)	06:09	3000	20	--	220	90	2.5 x 2.5 x 3.0

Pre-MRI plain radiography (x-ray) rule-out for metallic objects: a pre-MRI X-ray may be ordered in accordance with the American College of Radiology MR safe practice guidelines (15) if participants indicate the possibility that any work in a metal shop or other areas which may have exposed them to imbedded metal.

The use of x-ray as a pre-screen for MR scans does involve exposure risk to radiation from a skull radiographic exam. The participants concerned will be informed that this exposure to radiation is for research purposes only. The total radiation exposure amount of one film skull x-ray is equivalent to a uniform whole-body exposure of 12 days of exposure to natural background radiation (16). This use involves minimal risk and is necessary to obtain the information required to participation in a MR scan.

For a skull radiographic (1 film) exam, the expected dose to a patient would be the following (16): Total Effective dose: 10 mrem or 0.1 MSv.

Dose to breasts: 1 mrad
Dose to red marrow: 20 mrad
Dose to thyroid: 40 mrad
Dose to uterus: 1 mrad
Dose to ovaries: 1 mrad

Follow-up Appointments: Ratings and evaluations will be conducted from 1 day post (v 6) to 12 weeks / 3 months (v12) post administration of the study medication to gather ratings and data about the participant's experience and to document any clinical changes. The ratings portion of the follow-up appointments will be aimed at obtaining the needed study data.

Post Unblinding and 48 hour Post ratings: The integrative session of the follow-up appointments will be aimed at providing opportunities for discussion of the participant's experience during the drug administration. With a designated investigator, the participant will be encouraged to discuss his/her thoughts and feelings that arise and to help integrate this information into his/her life.

Out of State Participants: Some participants live in another state and it may not feasible to have them come to the CMHC for an in-person follow-up visit. In this case we will conduct the follow-up visits via telephone or a secure video communication platform (i.e. Zoom, Skype, etc.).

Due to the COVID-19 pandemic we wish to expand this option to local participants as well. This will allow us to minimize in person contact which will reduce the risk of potential exposure to COVID-19.

Study Environment:

The Yale OCD Research Clinic has been a leader in neurobiological and treatment studies of OCD since the 1980s and is based on the Clinical Neuroscience Research Unit (CNRU) of the Connecticut Mental Health Center (CMHC). We see a large number of patients annually with obsessive compulsive disorder (OCD), other mood and anxiety disorders, and related conditions. Some patients come to us through community referrals or self-referrals, and have had little previous treatment; others are referred from local providers, and have had previous treatment. Some patients find our website or web ads, community flyers, or online ads and will contact us. We will offer this research opportunity to those patients who seem suitable after our standard clinic screening.

Study Enrollment and Withdrawal

Patient Population - Subjects with OCD: Participants meeting study inclusion / exclusion criteria after careful screening and examination will be invited to participate and will be provided with all the information needed to provide an informed consent. We will recruit 30 adult participants (21 to 65 years) of both sexes, with clinically significant obsession and/or compulsions, evidenced by a YBOCS score of >18.

Eligible participants will be admitted to the CNRU at CMHC as an inpatient for at least 3 nights / 4 days (visits 3, 4, 5, 6) surrounding the initial drug administration (or more, at the option of the subject and the investigator). Participants will be randomized into active medication and active-placebo-control groups, and will be blinded as to their study condition. This admission 2 nights prior to the drug administration will allow the participant to adjust to sleeping on the unit and allow them to settle in to the research unit routine. A return (visit 7) for an fmri scan (48 hours after the administration session, v 5) will be scheduled. The blind will be broken at 48 hours (visit 7), and the participants who received active-placebo-control will be offered the option to receive open-label psilocybin (as soon as two-weeks after the initial study administration).

In addition to the baseline and follow-up assessments of the participants' mood, anxiety, quality of life and spiritual beliefs and medical evaluation, the study will consist of at least two introductory psychoeducation sessions with the PI and/or study personnel, study debriefing and follow-up support appointments 24 and 48 hours (v6, v7), 1 week (v8) and 2 weeks (v9) after drug administration. Participants will also undergo two different fMRI sessions: 24 hours prior (v4) to drug administration and 48 hours' post-drug (v7).

Participants may designate 2 to 3 adults (spouse or other family members, friends, or co-workers) who can observe changes in the participants' behavior and attitude and report as part of the follow-up. The battery of follow-up assessments and measures will be repeated 1 week, 2 weeks, 4 weeks, 8 weeks, and 12 weeks post drug administration.

The Open label phase for participants who were assigned to the active-placebo control condition will follow similar procedure to the randomized phase (see Tables 4-5).

Participant Inclusion and Exclusion Criteria

The proposed study will involve 30 participants with primary diagnosis of OCD 21-55 years of age.

Inclusion Criteria:

1. DSM-5 diagnosis of OCD established by a trained clinician interview and confirmed by Mini International Neuropsychiatric Interview (edition 7).
2. YBOCS score of 18 or greater at evaluation
3. Patients must have failed at least one medication and/or therapy trial of standard care treatment for OCD.
4. English speaking – able to understand the process of consent and the risk and benefits associated with the study, and able to give written informed consent
5. Must be willing to sign a medical release for the investigators to communicate directly with their therapist and doctors to confirm a medication and/or medical history. This is decided on a case by case basis upon the discretion of the PI.
6. Must be medically cleared by the PI or another medical doctor before they can drive home the morning after the experimental sessions., after the 48-hour post session assessments. They can also be driven home by a driver arranged by the subject or by the site personnel or taxi.
7. Has been off selective serotonin inhibitors for five half-lives of the drug plus 2 weeks.
8. Must avoid starting a new psychiatric medication during the study. Should participant's doctor recommend starting a new psychiatric medication, participant will be required to notify the study team.
9. Must provide a contact (relative, spouse, close friend or other caregiver) who is willing and able to be reached by the Clinical Investigators in the event of a participant becoming suicidal.
10. Are willing to refrain from taking any psychiatric medications during the study period.
11. Must have a negative pregnancy test at study entry and prior to each experimental session if able to bear children, and must agree to use adequate birth control
12. Are willing to commit to medication dosing, experimental sessions, follow-up sessions, to complete evaluation instruments and commit to be contacted for all necessary telephone contacts.

Exclusion Criteria:

1. Personal or immediate family history of schizophrenia, bipolar affective disorder, delusion disorder, paranoid disorder, or schizoaffective disorder.
2. Active suicidal intent
3. Unremitted Tourette syndrome
4. Pervasive developmental disability
5. Current substance abuse disorder (except in the case of mild alcohol use disorder)
6. Anxiolytic, neuroleptic and SRI medications
7. Unstable neurological or medical condition; history of seizure, chronic/severe headaches.
8. Any contraindications to undergoing an MRI scan, including having metal implants or metal fragments in the body. With participants who may have been exposed to metal fragments and who wish to participate in the MRS scans, a plain film X-ray may be order to clarify their eligibility status. Women of childbearing potential who elected not to have the pregnancy test, will be excluded from MRI.
9. Any history of head injury with loss of consciousness for more than 30 minutes
10. Positive urine pregnancy test at the time of screening
11. Any unstable medical condition that my render study procedures unsafe.
12. Any use of psychedelic drugs within the prior 12 months.

Medication contraindications will include anti-seizure medications, insulin and oral hypoglycemics, certain hypertension medications (clonidine, and aldomet specifically), cardiovascular medications and the following psychotropic medications: anti-psychotics (first and second generation agents), anti-depressants and mood stabilizers. Psychotropic medications cannot be taken in the previous two weeks, with Prozac (fluoxetine) not being taken within the last 5 weeks prior to receiving any study agents. Participants may only take prn (as needed) benzodiazepines (i.e. lorazepam) up to three days before the session. Participants will refrain from taking any medications the day of either the experimental or placebo treatment session, except prescribed opiate pain medication or over-the-counter non-narcotic pain medication at any time. It will also be necessary to refrain from alcohol the day before, the day of, and the day after each experimental session.

Participants must agree to:

- ï Ingest only alcohol-free liquids after 24:00 (midnight) the evening before the Experimental Session
- ï Refrain from the use of any exclusionary medications. Except in the case that the PI prescribes benzodiazepine or zolpidem for insomnia.
- ï May use caffeine and nicotine within 24 hours of experimental session. However, they may not use caffeine or nicotine for two hours before and six hours after ingesting the drug, or until trained research staff deem it safe to do so.

Strategies for Recruitment and Retention

Participants will be recruited through the use of clinics, referrals, the community and various advertising/broadcast media, including radio/cable/internet/TV, flyers and print

advertising. Patients with OCD will be recruited from the general population and OCD research clinic. This clinic receives referrals from community physicians, patient advocacy group, and other resources (see advertisement fliers for detailed wording). Patients who express interest in participating in the study may be asked to complete an "Interest Form" question on a HIPPA-compliant database (i.e. Yale RedCap) to determine eligibility for enrollment into the study. Upon completing the form, research staff will determine next steps based on the information collected.

Participant Withdrawal or Termination

Participants may withdraw their consent for use of their data and/or terminate participation in the study at any moment during the study by calling the Principal Investigator or a member of the research team. To revoke authorization of the use and disclosure of Personal Health Information, the participant must follow-up the phone call by submitting a request in writing to the Principal Investigator. In this event, the Principal Investigator will indicate in the data base that consent from the participant is no longer active and that data can no longer be used.

Premature Termination or Suspension of Study

The principal investigator is responsible for monitoring the data, assuring protocol compliance, and conducting quarterly safety reviews. During the review process the principal investigator will evaluate whether the study should continue unchanged, require modification/amendment, or close to enrollment. Likewise, the principal investigator will periodically review the collection, storage, and distribution practices associated with clinical data bank, and determine whether changes to enhance confidentiality and privacy are required.

The principal investigator, the Medical Monitor and the Human Investigation Committee (HIC) have the authority to stop or suspend the study or require modifications.

1. Study Agent

Study Agent and Control Description and Accountability Procedures

Psilocybin, the study drug, is a 4-hydroxy-N,N-dimethyltryptamine and occurs in nature in many species of mushrooms, including the genera Psilocybe, Conocybe, Gymnopilus, Panaeolus, and Strophparia. Its chemical formula is $C_{12}H_{17}N_2O_4P$. Psilocybin is a potent agonist at 5-HT2A/C, and their binding potency to these receptors correlates with human potency as hallucinogens [7]. Psilocybin has been administered to normal volunteers to measure physiological and psychological parameters at doses ranging from 0.045mg/kg to 0.43mg/kg [45; 51]. It has also been safely administered to patients with OCD at doses ranging from 0.025mg/kg to 0.3mg/kg.

After the FDA has approved the content of the protocol, the psilocybin will be manufactured by Usona Institute, Inc., 2800 Woods Hollow Rd. Madison, WI 53711, who will provide this information as a supplement to this IND application. Using a 222 DEA form, the psilocybin will be shipped from Usona Institute, Inc. to be stored in DEA safe stored in Dr. Pittenger's lab at CMHC (3rd floor Clinical Neuroscience Research Unit) . To safeguard the psilocybin, a special storage safe will be provided by DEA to store only the psilocybin. Designated staff will be the only personnel with access to the psilocybin. Both the active and placebo will be prepared by designated study staff by a compounding process. A log of the psilocybin accountability, compounding, and dispensing will be kept by the designated staff at the IDS. This will provide strict safeguarding and accounting of the agent both for internal and external regulatory agencies.

Study Procedure and Schedule

Study Procedures/Evaluations

Psilocybin and niacin will be administered in identically appearing opaque, size 0 gelatin capsule with approximately 180ml of water. The dose of psilocybin will be 0.25mg/kg and the niacin will be 250mg. Each participant will have the option of participating in the experimental treatment sessions. In the study, half of the participants will be randomized to receive psilocybin (n=15) or the placebo, niacin (n=15). Following the first treatment session of either the active agent or placebo, participants who were randomized to receive placebo will be offered the option to receive open-label psilocybin. (The blind will be broken at 48 hours to make this determination; which is our primary endpoint. Clinical raters will remain blind to the treatment assignment). Data will be collected from all subjects after open-label treatment for descriptive purposes, but these data will not be analyzed as part of our primary analysis plan.

Study Schedule

This study will use a randomized, placebo-controlled, double-blind design to examine the clinical and neural effects of psilocybin-assisted psychotherapy with either 0.25mg/kg of psilocybin or placebo (niacin 250mg), given along with non-drug preparatory and integrative psychotherapy sessions. The duration of the randomized study phase is from consent until two weeks after drug administration, which is approximately 6 weeks. The blind will be broken at 48- hours, and the participants who received placebo will be offered the option to receive open-label psilocybin. Participants may also designate 3 adults who have continuing contact with the subject (i.e., spouse or other family members, friends, or co-workers) who can observe changes in the participants' behavior and attitude over time. Communication with community observers can be part of follow-up as a way to get an objective measure of participant outcome in addition to self-report.

In addition to the baseline assessments and medical evaluation, the study will consist of at least two introductory sessions with the study staff, integrative-psychotherapy follow-ups 24 and 48 hours, 1 week and 2 weeks after drug administration. Participants will also undergo two different fMRI sessions: 24 hours prior to drug administration and 48 hours post-drug.

Randomization Blinded Study Phase

Upon enrollment into the study, participants will be assigned to one of the two conditions, experimental intervention (25mg/kg) or placebo (niacin). The rationale for using placebo rather than active placebo (low dose of psilocybin, ranging 2mg -4mg), which have been used in the recent palliative care studies and OCD study, is because a partial response has been reported even with these low doses. Psilocybin acutely attenuated OCD symptoms even after low doses (Moreno et al., 2006)[8], raising questions as to interpreting results with respect to whether the lowest dose served as placebo and whether it was in fact devoid of therapeutic effects. The internal review committee coordinator at the study site will generate and maintain the randomization code and procedure. Condition assignment

will be maintained from study enrollment up through the course of the study, as there is no crossover design. If there is an adverse event or other emergency requiring knowledge of participant's condition assignment, as when pharmacological intervention is necessary, the blind may be broken for an individual participant. The key study personnel who will administer the questionnaires will remain blind as the participant's condition assignment.

Participants in the placebo condition will be eligible for an open-label study continuation. They will be re-screened after the blind is broken to make sure they still meet study criteria. If they are eligible and choose to enroll in the open-label continuation, they may do so, undergoing psilocybin-assisted sessions occurring within another seven to 14-day period. The open-label phase of the study will follow nearly identical procedures to those used in the randomized phase. Participants will be re-assessed on all study measures following the same schedule of the randomized phase. Participants need not complete any portion of the open-label phase or the several follow up phases for their participation in the study to be considered completed.

Pre-study methods / Clinic phone screening - all subjects:

Prior to participation in this research, subjects will receive an abbreviated Qualtrics (or REDCap) screening survey and then if still eligible, will be screened by phone to determine preliminary eligibility. All subjects will be informed about the Yale OCD Research Clinic, the phone screening, what the screening process involves, and the current research studies. All potential participants will be told that we collect demographic information, relevant medical history, and psychiatric history during the screening process. All patients are informed that participation will involve the creation of a medical chart that will identify him/her with CMHC, include registration blood draws and urine tests, and that he/she has the choice whether or not to participate or to have their information taken down. All willing adults will complete this phone screen which will be reviewed by the clinic to ascertain preliminary eligibility. This phone screen is entered directly into REDCap and is considered a source document.

All seemingly eligible adult subjects are asked to come in for baseline screenings on the CNRU in the Yale OCD Research Clinic. As part of this evaluation and CMHC registration process, each subject will be told that the visit includes standard laboratory admission tests for which the medical staff will collect blood and urine, and reminded of the CMHC medical chart creation. All participants must give permission for the investigators to review medical records, to undergo a psychiatric evaluation and to complete a urinary drug screen to ensure their eligibility. Subjects are free to decline participation in the clinic at CMHC and to withdraw from consideration.

Baseline study Procedures and evaluations - CMHC/CNRU (visits 1 to 3 Inpatient registration -Table 1 A), Study screening, and registration for Research:

Participants will present to CMHC / Yale OCD Clinic for the evaluation, the study procedures will be described and the subject's questions will be answered prior to

obtaining an informed consent. All study inclusion and exclusion criteria will be checked during by the principal investigator and the entire research team, and still eligible adult patients will be scheduled for the study baseline physical and other evaluations. The investigator or research staff member obtaining consent will ask the participant to provide a brief summary of the study to ensure they understand what is being asked of them and any potential risks and benefits. Once consent is obtained, subjects will participate in the following procedures: a biopsychosocial interview, psychological evaluation, a physical examination, and a standard liver panel taken prior to the study psilocybin session that will ensure that the patient possesses sufficient liver function to metabolize psilocybin.

If a female subject is pregnant, breast-feeding, intending to become pregnant, or does not agree to use an approved birth control method (i.e., oral, injectable, or implant birth control, condom, diaphragm with spermicide, intrauterine device, tubal ligation, abstinence, or partner with vasectomy) she will be excluded.

The participant will also fill out an MRI safety data sheet. If the participant is determined to be eligible they will be scheduled for their study visit. The duration of this visit will not exceed 4 hours.

The participant will have at least two introductory sessions with the PI, Co-I, and/or key study personnel in which the study, the scheduling and the procedures will be reviewed. All participants' questions will be answered prior to obtaining an informed consent. The 4 days /3 nights inpatient study dates (v3 to 6) will be thoroughly discussed with the participant. These discussions will include the initial neuropsychiatric testing and any additional study psychoeducation sessions needed will be scheduled with the PI or one of the Co-Is.

This clinical and medical information will be reviewed by the research staff for any other contraindications to research participation. Subjects who are found to be abusing controlled substances will be excluded from the study, and will not receive any economic compensation for their participation in the screening process. Subjects who, in the opinion of the covering study medical doctor, are eligible to continue with the protocol procedures (after the results of baseline measures and diagnostics are considered) will initially be admitted to the CMHC/CNRU as an outpatient, while preliminary study assessments are completed at the second visit. ECG, breathalyzer and blood samples for routine testing (see Table 1A). A urine sample will be collected for urine toxicology, pregnancy test, and urinalysis.

Eligible participants will be scheduled and then later admitted to the CNRU at CMHC as an inpatient for 3 nights / 4 days (visits 3, 4, 5, 6), surrounding the initial drug administration (or more, at the option of the subject and the investigator).

Clinic screening and patient registration (standard clinic operations):

All potential research participants who agree to be screened and registered as CMHC/ clinic patients and will be interviewed by the clinic staff and will have a CMHC medical chart created for them (paper copy and/or online). All agreeable patients will have blood drawn and urine specimens taken for CMHC clinical laboratory tests (including chemistries, hematological, thyroid function tests, pregnancy tests when applicable, urine drug screen and routine urinalysis). If the pregnancy tests are positive, then the subject will not be able to participate in the study. If the urine drug screen is positive (except in the case of prescribed benzodiazepines which are allowed up to three

days before the session), then the subject will not be able to participate in the study. Laboratory results will become part of that permanent CMHC medical chart and may later be included in a research case file for this study.

All seemingly eligible participants will have a clinical diagnostic interview with a trained clinician, including the Mini International Neuropsychiatric Interview (MINI), the Yale-Brown Obsessive-Compulsive Symptom Checklist, the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS); and the Yale Global Tic Severity Scale (YGTSS-Clinician) to assess current and past tics, and CGI-Clinician. At this baseline clinic screening, information/data will be collected utilizing standard screening instruments, both self-reports and clinician-administered reports (either in paper-format or utilizing secure web-based data capture applications, e.g., REDCap or Qualtrics) and will also include: demographics like gender, age, racial and ethnic background, BDI, MADRS, CGI-Self-Report, and the Sheehan Disability Scale. These clinic ratings will aid in establishing whether a client meets initial criteria for study participation.

All subjects will be asked to complete a MR Safety Questionnaire that is used by the Magnetic Resonance Research Center (MRRC) at Yale to determine the presence of any implanted metallic objects that may exclude a subject from being safely scanned or to indicate areas that may require further investigation, (e.g pre-MRI x-ray to rule out metal in orbits).

To expand the clinic knowledge base of what underlies OCD, participants will be given baseline research measures of obsessive compulsive dimensions (symptoms, life attitudes, motivation, ideation, core beliefs) and co-occurring conditions as self-reports - Life Orientation Test Revised (LOT-R), Magical Ideation Scale (MIS), Obsessive Beliefs Questionnaire (OBQ-44), OC Trait Core Dimensions Questionnaire-Incompleteness-Harm-Avoidance (OC-TCDQ-R2), Padua Inventory of Obsessive Compulsive Disorder Symptoms (Padua), Quality of Life and Satisfaction Questionnaire Short Form (QOLESQ-SF), Responsibility Attitude Scale (RAS), Thought-Action-Fusion Scale (TAF) and general demographics questions. Other measures to assess co-occurring conditions (stress and anxiety disorders, tics, trichotillomania, or hoarding) will be used as needed. These clinic measures will aid in establishing whether a client meets initial criteria for study participation. Some of these standard clinic measures will be repeated in the study ratings battery at the final follow-up assessment.

All preliminary clinic screening information will be discussed and reviewed by the principal investigator and the entire research team. Participants may give permission for the research investigators/staff to review the participants' medical records which is decided on a case-by-case basis upon the discretion of the PI. All adult patients who are still considered eligible based on the study inclusion and exclusion criteria and review of the baseline information from this Yale OCD Research Clinic pool, will be asked to consider the consent for this study.

As the clinic has in previous studies, we will assess all patients who provide an informed consent and who agree to participant in the study. All participants must give permission for the research investigators/staff to review medical records and sign a medical release for the researchers to communicate with the participant's current provider about their treatment and participation in the study. This study will be using primarily non-invasive measures of neuropsychological assessment, magnetic resonance brain structure and function scans (at baseline and after treatment with the study agent), and a series of follow-up assessments over about 3 months.

Screening for Out of State Participants:

Some potential participants live in another state and it may not feasible to have them

come to the CMHC for an in-person screening. In this case we will conduct the screening utilizing secure video communication platforms (i.e. Zoom, Skype, etc.). We will ask these participants to send us their last physical, EKG, and blood work, that was done by their PCP. This will be faxed to the Kelmendi Clinic and reviewed by the principal investigator and the research team. We will also do our own physical, EKG, and blood draw when they arrive for the inpatient stay.

Study Visits 3 to 8 (Tables 1A - 1B) /CNRU Inpatient admission & Discharge to Outpatient follow-up:

Study Visit 3 / CNRU inpatient admission - overnight / ongoing evaluations - During the third visit, the participant will be admitted as an inpatient on the CNRU and vitals will be taken. This will allow the participant to adjust to the CNRU and to get used to sleeping over. And it will allow the unit to conduct registration paperwork, and any labs required (if not already completed as an outpatient).

The participant will be encouraged to bring some personal possessions (photos, pictures, writings) with them to enhance their experience with the unit and the treatment session (v5). The participant will be administered the study-specific measures and assessments by a trained clinician. Participants will also complete neuropsychiatric evaluation / testing and any additional education (v3-4) about the experimental session prior to the drug administration (v5).

Table 1 - Time and Events Schedule for Randomized Phase												
Time and Events	Baseline and Screening			Dosing & Evaluation				Follow-up Evaluation				
Visit #	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12
Type of Visit	Screening & IC Review	Med Screening	Neuropsychiatric Evaluation, Education & Overnight	Imaging, Questionnaires, Education & Overnight	Drug Admin. & Overnight Stay	Evaluation, optional overnight stay	48 hr post-drug evaluation, imaging & unblinding	Follow-Up	Follow-Up	Follow-Up	Follow-Up	Follow-Up
Approximate Study Day	0	1 to 5	6	7	8	9	10	7 days post V5	2 weeks post V5	4 weeks post V5	12 weeks post V5	24 weeks post V5
Medical Examination (15-20 min)		X										
Informed Consent (20 - 30 min)	X											
Get Caregivers consents / contacts (3 min)	X	or X										
Comprehensive Metabolic Panel		X										
~~**Immunological Panel**~~		~~X~~					~~X~~		~~X~~			~~X~~
Blood draw (10-20 min.)		X										
Drug Screen (5 min)		X		X								
Pregnancy Screen		X		X								
Psychiatric Evaluation (40 - 60 min)	X											
Preparatory education (15 min)	X	X	X	X								
Post-Drug Follow-up support (10 -20 min)					**X**	**X**	**X**	**X**	**X**			
Vitals (BP, HR, Temp) (20 min)		X	X	X	X							
Post drug Telephone calls (10 min)							X	X				
Adverse Events (PI or Co-I)					X	X	X	X	X			
Registration												
Overnight Stay- 3 nights (& optional +)			**X**	**X**	**X**	(X) option						
MRI Safety Q * (5 min)	X			X			X					
Pre-Drug fMRI (40-60 min)				**X**								
Randomize (Psilocybin or Niacin)					**X**							
Post-Drug fMRI (40-60 min)							X					
Unblinding - End Randomized Phase							**X**					
Inpatient Discharge (options)						**X**	**(X) option**					
Clinician Administered Scales												
MINI 7 */ SCID II Psychosis (60 min)	X											
Y-BOCS Symptom Checklist *(15 -20 min)	X											
Y-BOCS * (5 - 10 min)	X			X			X	X	X	X	X	X
MADRS (6 - 8 min)		X					X	X	X	X	X	X
A-YBOCS (5 min)						X	X					
YGTSS - clinician (5-10 min)			X									
C-SSRS (5 min)	X	X	X	X	X	X	X	X	X	X	X	X
CGI - Clinician (2 min)			X									X

Table 1 - Time and Events Schedule for Randomized Phase												
Time and Events	Baseline and Screening			Dosing & Evaluation				Follow-up Evaluation				
Visit #	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12
Type of Visit	Screening & IC Review	Med Screening	Neuropsychiatric Evaluation, Education & Overnight	Imaging, Questionnaires, Education & Overnight	Drug Admin. & Overnight Stay	Evaluation, optional overnight stay	48 hr post-drug evaluation, imaging & unblinding	Follow-Up	Follow-Up	Follow-Up	Follow-Up	Follow-Up
Approximate Study Day	0	1 to 5	6	7	8	9	10	7 days post V5	2 weeks post V5	4 weeks post V5	12 weeks post V5	24 weeks post V5
Self-Report Scales												
Demographics (15 min)		X										
BDI-1 * (5 min)			X			X			X			X
BIF (3 min)			X	X				X				
OBQ-44 * (5 - 10 min)			X						X			
OCI-R (5 min)			X						X			
OC-TCDQ - R2 * (3 - 5 min)			X						X			
TAF * (3 - 5 min)			X									
Q-LESQ-SF * (3 min)			X						X			X
RAS * (5 min)			X									X
5D-ASC (10 - 15 min)					X							
STAI (5 min)			X				X	X	X	X	X	X
PANAS-X (10-15 min)				X			X	X	X	X	X	X
PSEQ (3 min)					X							
PEQ (10 min)							X			X		X
RRPQ (3 - 5 min)			X									
BFAS (10 min)			X									
SMiLE (10 min)			X					X				X
CEQ (5 min)					X		X					
VAS (5 min)			X		X	X	X					
MEQ (5 min)					X				X			X
PSC (3 min)			X	X	X	X	X		X			X
PSQI (3 min)			X	X			X					X
URICA (3 min)			X	X			X			X	X	X
COM-R (5-10 min)								X				X
PEQ (10 min)							X			X		X
MIS (3 min)			X	X				X				
EPQ (3 min)			X	X					X			
IDAQ (3 min)			X	X					X			
IOS (1 min)			X	X					X			
MBDS (3 min)			X	X					X			
NRS (3 min)			X	X					X			
PEBS (3 min)			X	X					X			
AUDIT (3 min)			X	X								X
DUDIT (3 min)			X	X								X
SNRU (3 min)			X	X								X
UFEC (3 min)			X	X								X
CGI - Patient (2 min)			X	X								X
SDS (2 min)			X	X								X
LOT-R (2 min)			X	X								X
Padua (5 min)			X	X								X
												X

Visit 4 / inpatient-overnight /fMRI/taping of discussion - after the initial neuropsychiatric evaluations are complete and the subject has been admitted as an inpatient to the

CMHC/CNRU. On the day before drug-administration the participant will have a pre-drug session fMRI and complete designated assessments. If not already completed, the participant will complete vitals and provide a urine sample for drug and pregnancy testing. Vitals will continue to be taken during inpatient study days (v4, v5): Blood pressure, heart rate, and temperature; suicidal ideation, subjective distress, and medications will be reviewed, with any changes noted.

The participants will present to the Anlyan MRRC for their first pre-drug MRI Scan. While in the scanner, participants will rest quietly for 10 minutes for the collection of resting-state data; the total time inside the scanner will be ~120 minutes. Once the MRI scan is completed, participants will be accompanied by research staff back to CMHC where they will again stay overnight.

Participant will meet with trained research staff to discuss life, goals, desires, beliefs, and past experiences, to be introduced to mindfulness techniques, spiritual cognitive-behavioral stress management and to address specific hopes, fears, and goals for the upcoming treatment sessions. Audio-video recordings (with coded id number) of this session will be made to allow the participant and the investigator-therapists to review the session discussion.

Visit 5 / Inpatient, Randomization to Study Medication or Active-Placebo Control/ Experimental treatment session

Randomization: On either the day before (v4) or the day of drug administration (v5), the participants will be randomly assigned to one of the two conditions, experimental intervention (psilocybin 0.25mg/kg) or active-placebo-control (niacin 250 mg). The rationale for using niacin as the active-placebo-control agent rather than active low dose of psilocybin (ranging 2mg -4mg), which have been used in the recent palliative care studies and OCD study, is because a partial response has been reported even with these low doses. Psilocybin acutely attenuated OCD symptoms even after low doses (Moreno et al., 2006)(Moreno et al. 2006).

The randomization will be handled by the designated staff (Dr. Christopher Pittenger and Elizabeth D'Amico), who will be the only personnel with access to the psilocybin. Both the active and placebo will be prepared by designated study staff by a compounding process. The condition assignment will be maintained from study enrollment up through the course of the study, as there is no crossover design. If there is an adverse event or other emergency requiring knowledge of participant's condition assignment, as when pharmacological intervention is necessary, the blind may be broken for an individual participant.

Study preparation the day of drug administration (v5): the CMHC/CNRU staff will wake the participant, begin study preparation and serve breakfast. The participant will be allowed to eat only a light breakfast of hot cereal or bread/toast on the day of the session. Caffeinated clear liquids or juices will be permitted, but no milk as drug absorption might be affected.

At approximately 09:00 am, the experimental session will begin. The participant will be settled into a study treatment room at CMHC on CNRU. The nursing staff will monitor the participant's vital signs at 15 minutes and thirty minutes post drug administration, then every thirty minutes thereafter for the first two hours. Vitals monitoring will continue at least hourly during the rest of the experimental session and then at regularly scheduled

CNRU shift checks for the balance of the inpatient stay. The prepared study medication will be delivered by Dr. Pittenger. The experimental medicine will be administered between 09:00 and 10:00 hours. Psilocybin or niacin will be administered in identically appearing opaque, size 0 gelatin capsule with approximately 180ml of water. The dose of psilocybin will be 0.25mg/kg and the niacin will be 250mg. (Each participant will have the option of participating in the experimental treatment session). In the study, half of the participants will be randomized to receive psilocybin and half the niacin.

The session duration will be expected to last up to 6 hours under supervision from the PI, Co-investigator/ or study Nurse, and/or key personnel. The key study personnel who will administer the questionnaires will remain blind as the participant's condition assignment. Participants will be expected to remain under observation until both the participant and investigator agree that their perception, cognition, functioning and judgment are no longer impaired by the drug.

Visit 5 Drug Administration – Schedule of procedures

Approximate Time	Procedure or Action
9:00	Urine drug screen and pregnancy test, participant acclimated to environment, Acute YBOCs, VAS, MADRS
9:30	Baseline BP, Pulse, Temp, SUD
10:00	**Drug Administration.** Begin video recording.
10:15	SUD, BP, Pulse
10:30	SUD, BP, Pulse
11:00	SUD, BP, Pulse
11:30	SUD, BP, Pulse
12:00	SUD, BP, Pulse
13:00	SUD, BP, Pulse
14:00	SUD, BP, Pulse
Approximately 5-6 hours after drug administration	C-SSRS, General Wellbeing, BP, Pulse, Temp, SUD

Participants will be encouraged to lie comfortably in bed wearing eye shades during the first few hours of the experience and to listen to pre-selected music chosen by the study staff. Two team members will remain with the participants the entire time, and be available for any processing of intrapsychic material made manifest by the treatment. In addition, the continued need for conventional medications (e.g. non-opioid analgesics such as ibuprofen) to alleviate pain will be monitored in a systematized, ongoing manner. Participants will be asked about any residual side effects of other adverse events (AEs) and any appropriate referrals for treatment will be made as necessary. They will also have their vitals taken. Participants will be debriefed by the PI and/or research staff

Participants will be asked to remain at CMHC overnight on the evening of drug administration for monitoring and study assessments. They will have the option of being

discharged the following day after examined and medically cleared by the PI or Dr. Pittenger, or another medical doctor. However, if a participant has traveled from out of state (or from a distance that is inconvenient to return the following day for an fMRI scan), he/she will be offered an option to stay overnight at CMHC. Driving may be performed by a family member or friend, or the participant once they have been cleared by the PI, Dr. Pittenger, or another medical doctor. Alternatively, a taxi can be provided to the participant.

If participants experience or report on any adverse effects or if the research staff feels that at the end of testing, that the participant has any adverse effects, participants will be asked / required to remain until effects wear off and medically cleared by the PI or Dr. Pittenger. Medical assistance will be offered. The investigators will query participants about suicidal ideation or intent during screening, and prior to each psilocybin session. Participants who evidence suicidal ideation or intent will be withdrawn from the study and referred to appropriate psychiatric care.

In the event that participants experience distressing anxious symptoms during the drug session, the clinical personnel in attendance (the principal investigator and team member) will initiate verbal communication designed to reorient and reassure that participant. The occurrence and intensity of anxiety or panic responses can be reduced through providing participants with information on potential drug effects, supervision and monitoring of participants for the duration of drug effects, and using ascending dose designs. The goal in this study is to treat participants undergoing anxiety or panic reactions first by verbal and psychological interventions, and using anxiolytic medication only after verbal and psychological interventions have failed, and if participants are endangering themselves or others. In case of insomnia or an overly anxious reaction, the investigator may prescribe a benzodiazepine or zolpidem as a “rescue medication” for the day or night after drug administration. Residual symptoms will be addressed during the frequent follow-up psychotherapy visits with the investigators.

Rescue Medications, Treatments, and Procedures: The PI may prescribe a designated rescue medication in the event of symptoms that require it during or after the experimental session. Rescue medications may be a benzodiazepine, zolpidem, or other anxiolytic or sedative according to the physician's clinical judgment.

Should a longer psychiatric hospitalization be necessary, then participants will remain admitted to the study unit. The hospital will be informed in advance about the study to arrange for patient registration. Participants will be free to withdraw from the study whenever they wish, but they will have to be medically cleared before being discharged to home. In addition, if any participant presents with an adverse reaction to the psychopharmacological agent as reported by them or assessed by a member of the research team, we will discontinue the study and call for medical assistance. Finally, the participant may be withdrawn from the study if his/her withdrawal is in the best interests of either the participant or of the research (e.g., due to a medical condition making the procedures unsafe or any condition making interpretation of the results difficult).

Visit 6, Inpatient 24 hours post-drug administration / possible discharge- Participants will complete some additional assessments, including an A-YBOCS examining specific OCD symptoms over the past 24 hours (Bloch et al. 2012), will be followed-up with the PI, Co-I, and/or key personnel (v6), and reminded to present for the second fmri appointment the next day. Then the participant may be discharged from the inpatient stay once they are

medically cleared by the PI, Dr. Pittenger, or another medical doctor. After participants return home, the researchers will check at study visits or by telephone each day to inquire about how the participant is feeling, until the one week post administration visit (V8).

Visit 7 Outpatient 48 hours post dose - Evaluation, fMRI, Unblinding: If they have been discharged from the inpatient unit following the completion of Visit 6, participants must have someone drive them to and from this visit. Participants will present to the CMHC for the second MRI scan and complete clinical assessments, A-YBOCS (see Table 1 B).

The participant will be debriefed again and given the chance to discuss his/her experience with the study. The participant will continue to receive follow-up support and ratings 1 week and 2 weeks, 4 weeks. 8 weeks. and 12 weeks with the PI, Co-I, and/or key study personnel. During non-drug and experimental sessions, participants will be asked to think about and discuss their thoughts and emotions about carrying a diagnosis of OCD, including anxiety and the impact the OCD has had on their lives. They may experience emotional responses to speaking about these thoughts, feelings and concerns.

The blind will be broken (48 hours post administration - the primary endpoint) at this visit. Afterwards, the participants who were randomized to receive the active-placebo-control agent, will be offered the option to receive open-label psilocybin (see Open Label Table 2). After participants return home, the researchers will check at study visits or telephone subjects every day for a week to inquire about how the participants are feeling. They will be re-screened not later than a week after the blind is broken to make sure they still meet study criteria~~.~~ The open-label phase of the study will include optional MRI scans.

Outpatient Visits 8 to 12 (Table 1C): Participants will be followed (to 12 weeks Post administration):

Outpatient follow-up support and ratings for the randomized phase will continue for 3 months at designated times (v8, v9, v10, v11, v12). Community observer ratings ~~will~~ may be obtained at week one and week 12. Assessments will continue as outlined, Post weeks 1 to 12.

The study schedule for the Open Label phase is as follows:

Open Label Psilocybin Phase (v8 to 17, Table 2)- The participants who choose to receive open-label psilocybin will be re-screened after the blind is broken during the experimental phase (d 10) to make sure they still meet study criteria. If they are eligible and still choose to enroll in the open-label continuation, they may do so, undergoing a psilocybin-assisted session occurring within another seven to 14-day period.

Table 2 - Time and Events Schedule for Open-Label Phase+B2:L49

Time and Events	Baseline			Dosing & Evaluation 1			Follow-up Evaluation			
Visit #	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17
Type of Visit	Med Screening	Neuropsychiatric Evaluation & Education	Questionnaires, Overnight & Education	Drug Admin.	Evaluation (48 hrs post)	Evaluation Follow-Up	Evaluation Follow-Up	Evaluation Follow-Up	Evaluation Follow-Up	Evaluation Follow-Up
Approximate Study Day	d 10 to d16			17	19	7 days post	2 weeks post	4 weeks post	8 weeks post	12 weeks post
Medical Examination (15-20 min)	X									
Caregivers / contacts (3-min)										
Drug Screen (5 min)			X							
~~Immunological Panel~~					~~X~~		~~X~~			~~X~~
Pregnancy Screen				X						
Psychiatric Evaluation (40-60 min)		X			X					
Clinician Administered										
Y-BOCS * (5-10 min)		X				X	X	X	X	X
MADRS (6-8 min)		X		X	X	X	X	X	X	X
A-YBOCS (5 min)				X	X					
MINI 7 */ SCID-II/Psychosis (60 min)										X - ocd
CGI - Clinician (2 min)					X					
YGTSS - Clinician (5-10 min)										
C-SSRS (5 min)	X	X	X	X	X	X	X	X	X	X

The open-label phase of the study will follow nearly identical procedures to those used in the randomized phase. Participants will be re-assessed on all study measures following the same schedule of the randomized phase.

Table 2 - Time and Events Schedule for Open-Label Phase+B2:L49

Time and Events	Baseline			Dosing & Evaluation 1			Follow-up Evaluation			
Visit #	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17
Type of Visit	Med Screening	Neuropsychiatric Evaluation & Education	Questionnaires, Overnight & Education	Drug Admin.	Evaluation (48 hrs post)	Evaluation Follow-Up	Evaluation Follow-Up	Evaluation Follow-Up	Evaluation Follow-Up	Evaluation Follow-Up
Approximate Study Day	d 10 to d16			17	19	7 days post	2 weeks post	4 weeks post	8 weeks post	12 weeks post
Self-Report Scales										
BDI-1 * (5 min)			X		X		X			X
BFAS (10 min)			X							
OBQ-44 * (5-10 min)			X				X			X
OCI-R (5 min)			X				X			X
OC-TCDQ-R2 (3-5 min)			X				X			X
TAF * (3-5 min)			X				X			X
Q-LES-Q-SF * (3 min)			X				X			X
RAS (5 min)								X		X
5D-ASC (10-15 min)				X						
STAI (5 min)			X		X	X	X	X		X
JRICA (3 min)			X		X			X	X	X
PANAS-X (10-15 min)			X				X			
RRPQ (3 min)				X						
PEQ (10 min)					X	X				X
SMiLE (10 min)					X		X			X
CEQ (5 min)				X						
EQ (10 min)					X	X				X
MEQ (5 min)				X			X			
NRS (3 min)			X				X			
PEBS (3 min)			X				X			
IDAQ (3 min)			X				X			
MBDS (3 min)			X				X			
IOS (1 min)			X				X			
EPQ (3 min)			X				X			
AUDIT (3 min)			X							X
UFEC (3 min)			X							X
DUDIT (3 min)			X							X
SRNU (3 min)			X							X
PSQI (3 min)			X		X			X		X
MIS (3 min)			X			X				
BIF (3 min)			X			X				
VAS (3 min)			X		X	X				
DS (2 min)			X							X
OT-R (2 min)			X							X
adua (5 min)			X							X
GI- Patient (2 min)			X							X
COM-R (5-10 min)						X				X
Adverse Events (PI or Co-I)				X	X	X	X			
Overnight Stay (2 nights)			X	X						
Pre-Session fMRI (optional)			X							
Administration (OPEN LABEL)				X						
Post-Session fMRI					X					
Post-Drug Followup support					X	X	X			
Blood Pressure			X	X	X					
Pulse			X	X	X					
Discharge					X					

Like the first phase, participants in the open label phase will be offered MRI Safety Questionnaires and fMRI scans on the day before drug administration and 48 hours post drug administration.
Participants need not complete any portion of the open-label phase or the several follow up support appointments for their participation in the study to be considered completed.

Data will be collected from all subjects after open-label treatment for descriptive purposes, and will be viewed not as part of our primary analysis plan but as part of a secondary analysis examining the pharmacological effects on OCD symptomatology.

Justification for Sensitive Procedures

The significance of this study lays primarily in the potential of producing results that may shed light on the neurobiological mechanisms of the clinical effect of psilocybin in the treatment of OCD, and more generally, contribute to the accumulating evidence for the value of drug-facilitated psychotherapy in OCD.

Rescue Medications, Treatments, and Procedures

The PI may prescribe a designated rescue medication in the event of symptoms that require it during or after the experimental session. Rescue medications may be a benzodiazepine, zolpidem, or other anxiolytic or sedative according to the physician's clinical judgment.

If participants experience or report on any adverse effects or if the research staff feels that at the end of testing, that the participant has any adverse effects, participants will be asked to remain until effects wear off (likely only for a short period) and medical assistance will be offered. Participants will be free to withdraw from the study whenever they wish. In addition, if any participant presents with an adverse reaction to the psychopharmacological agent as reported by them or assessed by a member of the research team, we will discontinue the study and call for medical assistance. Finally, the participant may be withdrawn from the study if his/her withdrawal is in the best interests of either the participant or of the research (e.g., due to a medical condition making the procedures unsafe or any condition making interpretation of the results difficult).

Should a longer psychiatric hospitalization be necessary, then participants will remain admitted to the study unit. The hospital will be informed in advance about the study to arrange for patient registration. Participants will be free to withdraw from the study whenever they wish, but they will have to be medically cleared before being discharged to home. In addition, if any participant presents with an adverse reaction to the psychopharmacological agent as reported by them or assessed by a member of the research team, we will discontinue the study and call for medical assistance. Finally, the participant may be withdrawn from the study if his/her withdrawal is in the best interests of either the participant or of the research (e.g., due to a medical condition making the procedures unsafe or any condition making interpretation of the results difficult).

Safety Plan for Suicidality:

During all study visits a Masters or Doctoral level clinician will assess the participant's well- being – responses, intent, plan, etc. while administering the C-SSRS (Columbia Suicidality Severity Response Scale) – which all clinicians have received CMHC training on) and if there is a serious concern they will either ask the participant to meet with or call the PI, or report to the clinic (if the study visit is being done remotely), or go to the nearest ER, or will call 911. If necessary, they will also call the participant's treating clinician and/or their emergency contact. As part of the consent, participants are required to designate an emergency contact person and provide their treating clinician's contact information. We will ask the treating clinician for their local plan for such emergencies so the study team can follow this plan should an emergency situation arise.

Payments for Participation (Economic Considerations):

Patients will be paid for participation from $350 randomized phase, and up to $250 for completing Open-Label phase of the study. All subject payments may be made using the Bank of America reloadable pre-paid card system through OnCore and the consent form specifies that certain subject information will be shared with Bank of America, namely the subject's name, address, and telephone number. The card will be mailed to participants and they will need to activate it. At the PI's discretion, subject payment may be through a petty cash system, by Yale check request, or an E-gift card.

For the randomization phase, payments will include: $50 for the screening, $100 for the 4 day / 3 night inpatient stay with study medication, $30 for each fMRI scan, and $20 for each of the six follow-up visits. With the participant's completion of the whole protocol, $20 bonus will be added, and so up to $350 may be paid for the randomized phase (less any advance amounts paid).

For the open-label phase: $120 for 2 day/ 1 night inpatient stay with study medication (v10-11), $30 for each fMRI scan completed and $70 for completing the follow-up visits (v12-17) and so up to $250 may be paid for the open-label phase (less any advance amounts paid).

At the principal investigator's discretion on a case by case basis and when arranged in advance, additional subject payment may be offered for travel, parking, lodging, food or transportation to ease participation expenses.

Assessment of Safety

Specification of Safety Parameters

Definition of Adverse Events (AE)

Adverse events (AEs) are defined any untoward, physical, social, economic or psychological occurrence affecting human subjects in research. An AE can be any unfavorable or unintended event including abnormal laboratory finding, symptom, reaction, or disease. An

AE does not necessarily have a causal relationship with the research, or any risk associated with the research, the research intervention, or the assessment. Adverse events involve subjects only.

Definition of Serious Adverse Events (SAE)

In addition to grading the adverse event, adverse events are evaluated to determine whether they meet the criteria for a Serious Adverse Event (SAE). An SAE is defined as death; a life threatening experience; inpatient hospitalization (for a person not already hospitalized); prolongation of hospitalization (for a patient already hospitalized); persistent or significant disability or incapacity; congenital anomaly and/or birth defects; or an event that jeopardizes the participant and may require medical, surgical or other intervention to prevent one of the preceding conditions (FDA, 21 CFR Part 312). An adverse event is considered serious if it:

1. is life-threatening
2. results in in-patient hospitalization or prolongation of existing hospitalization
3. results in persistent or significant disability or incapacity
4. results in a congenital anomaly or birth defect OR
5. results in death
6. based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition, or
7. adversely affects the risk/benefit ratio of the study

An adverse event may be graded as severe but still not meet the criteria for a Serious Adverse Event. Similarly, an adverse event may be graded as moderate but still meet the criteria for an SAE. It is important for the PI to consider the grade of the event as well as its "seriousness" when determining whether reporting to the IRBs and the data safety monitoring board is necessary.

Definition of Unanticipated Problems (UP)

An unexpected adverse event is one that is not listed in the current Investigators Brochure for Psilocybin, assisted psychotherapy produced by MAPS or an event that is by nature more specific or more severe than a listed event.

Such an event is unlikely because as of 01 December 2016, with over 1000 individuals exposed to Psilocybin in controlled research settings, there have been no unexpected drug-related SAEs to date, and expected SAEs have been rare and non-life threatening.

Classification of an Adverse Event

The following scale will be used in grading the severity of adverse events noted during the study:

1. Mild adverse event (does not affect patient activity)
2. Moderate adverse event (mild disruption in usual activity)
3. Severe (major disruption in usual activity)

Time Period and Frequency for Event Assessment and Follow-Up

Adverse events or unanticipated problems involving risks to subjects or others will be reported to the HIC or HSC within 48 hours of it becoming known to the investigator, using the appropriate forms found on the website.

Reporting Procedure (Adverse Events)
The investigator will report the following types of adverse events to the HIC:

1. serious and unanticipated and possibly, probably or definitely related events;
2. anticipated adverse events occurring with a greater frequency than expected;
3. other unanticipated problems involving risks to subjects or others.

Study Halting Rules
The HIC, Medical Monitor or the Principal Investigator has the right to discontinue this study at any time. If the trial is prematurely terminated, the Primary Investigator is to promptly inform the study participants and will assure appropriate therapy and follow-up. If the trial or study is prematurely discontinued, all procedures and requirements pertaining to retention and storage of documents will be observed. All other study materials will be treated in accordance with federal and state regulations.

Attribution of Adverse Events: Adverse events will be monitored for each subject participating in the study and attributed to the study procedures / design by the principal investigator (Benjamin Kelmendi, M.D.) according to the following categories:

a.) Definite: Adverse event is clearly related to investigational procedures(s)/agent(s).
b.) Probable: Adverse event is likely related to investigational procedures(s)/agent(s).
c.) Possible: Adverse event may be related to investigational procedures(s)/agent(s).
d.) Unlikely: Adverse event is likely not to be related to the investigational procedures(s)/agent(s).
e.) Unrelated: Adverse event is clearly not related to investigational procedures(s)/agent(s).

Plan for Grading Adverse Events: The following scale will be used in grading the severity of adverse events noted during the study:

1. Mild adverse event
2. Moderate adverse event
3. Severe

Plan for Determining Seriousness of Adverse Events:

Serious Adverse Events: In addition to grading the adverse event, the PI will determine whether the adverse event meets the criteria for a Serious Adverse Event (SAE). An adverse event is considered serious if it results in any of the following outcomes:

1. Death;
2. A life-threatening experience in-patient hospitalization or prolongation of existing hospitalization;
3. A persistent or significant disability or incapacity;
4. A congenital anomaly or birth defect; OR

5. Any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

An adverse event may be graded as severe but still not meet the criteria for a Serious Adverse Event. Similarly, an adverse event may be graded as moderate but still meet the criteria for an SAE. It is important for the PI to consider the grade of the event as well as its "seriousness" when determining whether reporting to the IRB is necessary.

Plan for reporting UPIRSOs (including Adverse Events) to the IRB - The principal investigator will report the following types of events to the IRB: Any incident, experience or outcome that meets ALL 3 of the following criteria:

1. Is unexpected (in terms of nature, specificity, severity, or frequency) given (a) the research procedures described in the protocol-related documents, such as the IRB-approved protocol and informed consent document and (b) the characteristics of the subject population being studied; AND
2. Is related or possibly related to participation in the research (*possibly related* means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); AND
3. Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, legal, or social harm) than was previously known or recognized.

Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs) may be medical or non-medical in nature, and include – but are not limited to – *serious, unexpected, and related adverse events* and *unanticipated adverse device effects*. ***Please note*** that adverse events are reportable to the IRB as UPIRSOs **only** if they meet all 3 criteria listed above.

These UPIRSOs/SAEs will be reported to the IRB in accordance with IRB Policy 710, using the appropriate forms found on the website (UPIRSO Reporting Form, 710 FR 4). In the event that such events occur, Reportable Events (which are serious or life-threatening and unanticipated, or anticipated but occurring with a greater frequency than expected, and possibly, probably, or definitely related) or Unanticipated Problems Involving Risks to Subjects or Others that may require a temporary or permanent interruption of study activities will be reported immediately (if possible), followed by a written report to the IRB within 5 calendar days (in accordance with IRB Policy 710) of the Principal Investigator becoming aware of the event (using the appropriate forms) and to any appropriate funding and regulatory agencies.

All related events involving risk but not meeting the *prompt* reporting requirements described in IRB Policy 710 should be reported to the IRB in summary form at the time of continuing review. If appropriate, such summary may be a simple brief statement that events have occurred at the expected frequency and level of severity as previously documented.

Plan for reporting adverse events to co-investigators on the study, research monitor(s), e.g., Protocol Review Committee (PRC), study sponsors, funding and regulatory agencies, and regulatory and decision-making bodies.

For the current study, the following individuals, funding, and/or regulatory agencies will be notified:

□ All Co-Investigators listed on the protocol.
□ Food and Drug Administration (Physician IND # 134406)
□ Study Funding and Sponsors

The investigator will apprise fellow investigators and study personnel of all UPIRSOs and adverse events that occur during the conduct of this research project through regular study meetings, or via email as they are reviewed by the principal investigator.

The protocol's research study sponsors, funding and regulatory agencies, and regulatory and decision-making bodies will be informed of any Serious, Unanticipated and Related adverse events within 5 days (or within any contract or policy designated time period) of the event becoming known to the principal investigator.

The principal investigator (Benjamin Kelmendi, M.D.) will conduct a review of all adverse events upon completion of every study subject. The principal investigator will evaluate the frequency and severity of the adverse events and determine if modifications to the protocol or consent form are required.

Safety Oversight

The principal investigator in conjunction with the Medical Monitor (Gustavo Angarita, MD) will be responsible for monitoring the data, assuring protocol compliance, and conducting the safety reviews at the specified frequency, which must be conducted at a minimum of every 6 months (including when reapproval of the protocol is sought). During the review process, the principal investigator (in collaboration with the Medical Monitor) will evaluate whether the study should continue unchanged, require modification or amendment, continue or close to enrollment. Either the principal investigator, the HIC, or the Medical Monitor have the authority to stop or suspend the study or require modifications. Likewise, the principal investigator will periodically review the collection, storage, and distribution practices associated with clinical data bank, and determine whether changes to enhance confidentiality and privacy are required. The research team will follow the Yale HIC's guidelines for attribution of adverse events and grading the severity of adverse events (including determining whether the adverse event meets criteria for a Serious Adverse Event).

A certificate of confidentiality for this study has been obtained from the FDA. The OCD Research Clinic operates within organizations (Yale University, State of Connecticut/CMHC) which are fully bound by and compliant with HIPAA policies and strict research requirements.

Clinical Monitoring

After administration of Psilocybin/placebo, participants will be checked regularly. A research team member will accompany the participants and be available at all times to call for medical assistance if required. Procedures will be immediately s topped if

participants request to stop or exhibit any sign of significant distress. The study medical doctors and nursing staff who are trained in dealing with drug challenge studies (such as ketamine, psilocybin, yohimbine, and various cannabis compounds) will remain in attendance during the entire session, from the administration of the drug, throughout symptom assessment, to clearance for discharge from the research facility. To ensure close monitoring, participants will spend overnight at CNRU – an inpatient unit that provides a 24/7 skilled nursing staff to field patient questions or issues at off hours provide support, including hospitalization if necessary, for any emergent issues such as acute suicidality.

2. Statistical Considerations

Statistical and Analytical Plans and Description of Statistical Methods

Analysis of the clinical effects of psilocybin will be analyzed using a strategy very similar to that used in a previous trial testing the effects of ketamine on OCD symptoms [52]. SPSS software will be used to conduct linear mixed modeling using restricted maximum likelihood estimates. Treatment (psilocybin 25 mg vs. placebo), time, and all interactions will be modeled as fixed effects. Subjects will be modeled as a random effect. The time factor will be analyzed in a piecewise manner in 3 separate equations: (i) Day 1, hours 0 (baseline) to 4; (ii) Baseline to Day 2 (24 hours); (iii) Days 3-7; and 4) Days 7-30. The mixed model assessing change from Baseline to Day 2 will be the primary analysis, given our primary hypothesis that psilocybin will reduce acute OCD symptoms (OCD-VAS and A-YBOCS) 24 hours after administration. Alpha-corrected (FDR) [53] t-tests will be used to probe interaction effects.

We used Optimal Design [54] to conservatively calculate power for a repeated-measures mixed model with 2 groups, 6 time points, alpha of .05, power of .80, and a standardized effect size (*d*) of 1.5, which indicated that a total sample of 30 subjects would be needed to detect a significant group effect across the three groups. While $d = 1.5$ is quite large, we believe it is a reasonable estimate given the magnitude of the effect sizes reported for psilocybin for depression one day after ingestion ($d = 2.01$) [55] and open-label study data for psilocybin for OCD. We should therefore be adequately powered to detect the predicted effect for Aim 1. Primary aims will be tested with an unadjusted alpha level of 0.05. Post-hoc analyses and analyses with multiple comparisons will be adjusted for multiple testing.

fMRI data will be analyzed using signal processing and multivariate statistical techniques within a combination of commercially available (Brain Voyager QX, Analyze) and in-house software. Group differences will be evaluated using standard regression and general linear modeling approaches in a general-purpose MRI analysis package, BioImage Suite (www.bioimagesuite.org). For the secondary hypothesis, that psilocybin will modulate activation of mPFC, amygdala, putamen and anterior cingulate upon presentation of provoking stimuli, mixed effects regression models, with group, time, and group X time effects modeled to examine the effect of psilocybin on region of interests (ROI) activation.

Hypotheses concerning the effect of psilocybin on emotional information processing (i.e. OCD-relevant symptom provocation task) and clinical scores (i.e. YBOCS) will be tested using repeated ANOVA and ANCOVA, linear regression models, and correlational analysis. Secondary analyses of functional connectivity and neuronal responses to symptom

provocation task will be performed using standard approaches at which Dr. Abdallah is expert.

Statistical Hypotheses

We hypothesize that psilocybin will lead to greater symptom improvement than placebo at all assessment points, and (i) psilocybin will normalize abnormal fronto-striatal functional connectivity in patients with OCD; and (ii) psilocybin will decrease activation of anterior cingulate cortices, amygdala, and putamen in response to symptom-provoking stimul

Sample Size

There are no peer-reviewed published neuroimaging studies of psilocybin versus placebo in OCD samples, so power analysis was performed based on a previous double-blind, placebo-controlled study in healthy controls. The within-subject design maximizes statistical power. Conservatively assuming 10% variability in the measure of BOLD response, we will have 80% power to detect a difference as small as 7% in 30 subjects performing pre and post-psilocybin fMRI studies, assuming a two-tailed alpha = 0.05. Pearson correlation will examine the association between changes in ROIs activation and performance on tasks. All statistical tests will be two-tailed with appropriate correction for multiple comparisons. Whole brain type I error correction will be accomplished via threshold-free-cluster-enhancement implemented in FSL Randomize.

Measures to Minimize Bias

Enrollment/Randomization/Masking Procedures

The necessary strict exclusion criteria for psilocybin interventions and fMRI may limit generalizability of the findings. The influence of repeated testing in the crossover design will be minimized by modeling order effects in analyses, but some effects of practice may persist. Tolerability of multiple scans may be problematic; however, the research staff has extensive experience in studies with multiple visits and scans in this population.

Evaluation of Success of Blinding

At the end of the randomized treatment, participants will be asked to name the study arm that they believe they were assigned to and to identify their level of confidence in their designation.

Source Documents and Access to Source Data/Documents

Paper source documents and research case books will be housed in restricted access files. Personally-identified and protected information (PHI) will be restricted to name, address, phone number, birth-date, social security numbers, dates of care, and will be kept by investigators in a separate file from the research data which will be coded using a unique subject identification.

Quality Assurance and Quality Control

The principal investigator is responsible for monitoring the data, assuring protocol compliance, and conducting the safety reviews yearly. During the review process, the principal investigator will evaluate whether the study should continue unchanged, require modification/amendment, continue or close to enrollment. Either the principal investigator or the IRB have the authority to stop or suspend the study or

require modifications.

Ethics/Protection of Human Subjects

Ethical Standards

The research will be performed according to ethical principles and in compliance with all federal, state and local laws, as well as institutional regulations and policies regarding the protection of human subjects.

Informed Consent Process

After an initial phone screen to determine obvious exclusions from the study protocol, potential subjects will be invited for an in-office visit. During the visit, the study procedures will be described and the subject's questions will be answered prior to obtaining an informed consent. The person obtaining the consent will ask the participant to provide a brief summary of the study to ensure they understand what is being asked of them and any potential risks and benefits.

Participant and Data Confidentiality

Participant study identification numbers (which cannot be linked to participant), names, and other demographic information, contact information, and previous medical history will be kept in a locked filing cabinet located in a locked room. Secure research files will be used to store assessment and data forms derived from the research data collection. Each participant is assigned a numeric code to conceal identity. This coding will carefully safeguard confidentiality on encrypted computer hard disks used for analysis. No personal identifying data will appear in the computer files or other papers (e.g., questionnaires, laboratory raw data).

Care will be taken to conceal other possible sources of identification, including addresses or occupations. A list of participant numbers, names, and other demographic information will be kept in a locked cabinet located in a locked room. Cross-referenced names and code numbers will be included in a master list that will be stored in a locked file cabinet that will be accessible only to the research staff. The identities of participants will not be revealed in any description or publications resulting from this research. The granting agency, the research monitors, the PI's laboratory, and collaborators will have access to de-identified study data. All electronic data is double password-protected and is in compliance with Human Investigation Committee (HIC) regulations at Yale. Digital data will be stored on a secured server and on secured desktop computers.

In accordance with the minimum necessary HIPAA policies, protected health information will be restricted to only individuals essential to the research. This includes the principal investigator and specified research staff (only those approved by the PI). Only the Principal and Co- Investigators will be able to link samples and data to patient identifiers.

Research Use of Stored Human Data

The investigators understand the importance of communicating research findings from studies. Results from this study may be presented at conferences and meetings or published

in academic journals. All data would be deidentified and participant identity would never be disclosed when presenting results of the study.

Future Use of Stored Data
De-identified data may be stored indefinitely and used for publications, research presentations and meetings.

3. Data Handling and Record Keeping

Data Collection and Management Responsibilities
The principal investigator, Benjamin Kelmendi, M.D., will be responsible for monitoring the data, assuring protocol compliance, and conducting the safety reviews at the specified frequency, which must be conducted at a minimum of every 6 months (including when reapproval of the protocol is sought). Dr. Kelmendi (with Dr. Pittenger and his research team) will confer, discuss any issues have been brought to light, and will discuss what alterations might be needed if any, in weekly rounds meetings (as is the clinic standard research practice). Any adverse events will be reported in accordance with Yale policies. During the review process, the principal investigator and the Medical Monitor (Gustavo Angarita, MD) will evaluate whether the study should continue unchanged, require modification/amendment, or close to enrollment. Either the principal investigator, the IRB, the MRRC, or CMHC administrators have the authority to stop or suspend the study or require modifications.

Research personnel will collect research data via direct interview after potential subjects sign release of information for available informants. This data will be recorded in both written and/or electronic formats, and all confidential PHI will be separated and stored in locked and secured files.

Study Records Retention
All electronic PHI (ePHI) will continue to be encrypted and password-protected after subject participation. Both written and ePHI will be destroyed 10 years after the protocol is completed.

Publication and Data Sharing Policy
The identities of participants will not be revealed in any description or publications resulting from this research. The granting agency, the research monitors, the PI's laboratory, and collaborators will have access to de-identified study data.

Conflict of Interest Policy

There are no conflict of interest to report from any of the study staff.

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