Psilocybin for the Treatment of Obsessive-Compulsive Disorders

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Contents

Abstract Obsessive-compulsive disorder (OCD) is a highly prevalent and disabling condition for which currently available treatments are insufficiently effective and alternatives merit priority attention. Psilocybin may represent a safe and effective avenue for treatment of individuals affected by this condition. In this chapter we briefly introduce OCD symptoms, epidemiology, as well as relevant hypotheses on the mechanism of disease that may inform treatment interventions. We briefly describe currently available treatments, mechanisms of action, and efficacy limitations, as preamble to the potential use of psilocybin and perhaps similar compounds in the treatment of OCD and related conditions. Although much is reviewed throughout this book about the mechanisms of action of psychedelic agents, a

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focused discussion of psilocybin effects as they pertain to OCD is also included. Our experience with incidental observation, prospective research, and current explorations of psilocybin in OCD are also described.

Keywords Compulsions · Obsessions · Obsessive-compulsive disorder · OCD · Psilocybin · Psychedelics

1 OCD Defined

The American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders 5th Edition (DSM-5) and the International Classification of Diseases 11th Edition (ICD-11) describe OCD as a mental condition characterized by the presence of either obsessions and/or compulsions that are usually recognized as excessive, unreasonable, and a product of the individual's own mind. These symptoms are time consuming (lasting at least 1 h per day and ranging to nearly constant) and cause marked distress and/or significant interference in the person's ability to function.

2 OCD Hypothesized Mechanisms of Disease

OCD is a heterogenous condition (Raines et al. 2018) with proposed clinical subtypes, some of which have been associated with biological, psychological, developmental, and environmental risk factors, and with distinct course of disease and treatment response. It is safe to assume that no single mechanism of disease explains OCD, and the complexity of the OCD phenotype may explain at least in part the variability of findings from pharmacological, psychotherapeutic, imaging, genetic, epidemiologic, and other study approaches.

2.1 Psychological Theories

Traditional psychoanalytic theories postulate that obsessional neurosis, a term that preceded the modern OCD diagnosis, results from unresolved fixations or regressions to primitive stages of psychosexual development, specifically the "Anal Phase." In the anal phase, aggressive and sexual impulses conflict with a rigid superego and certain ego defenses that attempt to keep such impulses out of consciousness, as they are unacceptable to personal imperatives as conscience and cultural development occur (Freud 1966). More recent formulations informed by *object relations theory* focus on the development of a fragmented or ambivalent self.

Patients feel threatened by thoughts that they are bad, imperfect, unreliable, uncontrollable, or immoral, and are unable to integrate these attributions into a coherent self-image. Cognitive Behavioral Theories have supported the development of current psychological best practices for OCD. Learning theory maintains that a neutral event stimulus (i.e., perception, thought) comes to elicit fear when it is repeatedly presented together with an event that causes pain/distress (obsession formation). Subsequently, escape or avoidance behaviors (i.e., compulsions) are developed and maintained to reduce the anxiety. OCD has been characterized by the following erroneous cognitions: (1) Assigning a high probability of danger to situations that are relatively safe; (2) Exaggerating the severity of anticipated negative outcomes; (3) Assuming dangerous qualities of an event or object in the absence of evidence of safety (Foa and Kozak 1985; Foa 2010).

Traditional analytical and modern cognitive-behavioral formulations overlap in that they emphasize contradictory and poorly integrated attributions of self and other (Chlebowski and Gregory 2009). Regardless of the particular psychodynamic formulation, obsessions and compulsions can serve the function to keep patients' attention away from longstanding conflicts, some of which may be brought to awareness during the psilocybin experience and which may be an important target for the support and integration that occurs in the context of psilocybin sessions.

2.2 Biological Theories

It is known that OCD is heritable, with estimates from twin studies that 27–65% of the variance in symptoms may be attributable to genetic variance. OCD also runs in families, and it is observed four times more frequently in relatives of people with OCD than in the general population. Certain subtypes of OCD are clearly more heritable, including early onset OCD (Mahjani et al. 2021), and the heterogeneity of ascertainment methods used in studies may explain the variability of results. Several neurotransmitters, neurohormones, and immunological alterations have been proposed as explanations for symptom generation, and treatment response, including specific elements of the serotoninergic, glutamatergic, GABAergic, and dopaminergic systems. Molecular genetic studies suggest a higher representation of certain genes related to serotonin function in patients with OCD, particularly the serotonin transporter and the serotonin 2a receptor gene (Taylor et al. 2016). Candidate gene association studies now available suggest the role of glutamatergic transmission, involving genes related to glutamatergic transport (SLC1A1), receptor regulation (DLGAP1), receptor and subunit synthesis (GRID2 and GRIN2B). The role of glutamate in OCD neurobiology and pathophysiology is also well supported, although treatments involving this neurochemical are in need of further research (Pittenger et al. 2011).

The serotonergic system, however, is among the most broadly supported given the seemingly selective pharmacological response to serotonin acting agents, the reports of serotonin related changes in the central nervous system, and other

alterations in peripheral markers of serotonin function in OCD patients (Delgado and Moreno 1998). Intriguingly, laboratory-induced reductions in brain serotonin availability in patients recovered from OCD do not lead to a worsening of obsessive-compulsive symptoms. In contrast, specific blockade of serotonin subtype-2 receptors (5HT2) in patients recently improved and receiving treatment with serotonin enhancing medications causes an acute return of OCD symptoms. Furthermore, 5HT2 blockers used in practice such as atypical neuroleptics and mirtazapine appear to be beneficial in the treatment of OCD. These findings suggest that response to OCD is not only related to activity at a specific receptor, but rather the complex postsynaptic functional and structural changes that may involve the function of various neurochemicals and/or regions and circuits.

2.3 Brain Basis of OCD

Data from animal models as well as functional and structural human brain imaging studies point to the involvement of parallel and partially-segregated circuits that play a role in initiation and termination of thoughts and behaviors. The so-called Cortico-Striato-Thalamo-Cortical (CSTC) circuit refers to interconnectivity of the orbitofrontal cortex, the caudate nucleus, and the thalamus, however a larger number of regions frequently interacting with CSTC have been implicated in OCD (Tang et al. 2013). Interestingly, specific-symptom dimensions of OCD appear to be associated with findings in different brain regions, further supporting the heterogeneity of OCD.

The proposed OCD cortico-striatal hyperactivity leads to a persistently high error signal, ultimately resulting in its characteristic psychopathology, including irrational fears or obsessions, or that an action was not completed correctly according to a set of internal unattainable rules, triggering repetitive, compensatory behaviors (i.e., compulsions). An index of this error signal is larger in OCD patients, its magnitude relates to the continuum of OCD symptom severity (Zambrano-Vazquez and Allen 2014).

Other neural systems that play a role in a number of disorders characterized by persistent negative thinking are thought to play a role in OCD as well. Primary among these is the default mode network (DMN), a system of brain regions that coactivate during spontaneous self-generated deliberate thought, and that appear to be highly coactivated during times of persistent negative self-focused thought (Andrews-Hanna et al. 2014). In OCD, one of the main characteristics is an extreme focus on internally generated unpleasant, unwanted thoughts or images thought to be generated in the DMN. It has been shown that this network is hyperactive in patients with OCD during cognitive tasks, reflecting a failure in the normal process of DMN suppression to engage in externally-focused task-relevant activity. This lack of disengagement in OCD patients compared to healthy controls indicates a difference in communication between the DMN (posterior cingular cortex, medial frontal cortex, posterior inferior parietal lobule and parahippocampus) and frontal areas of

the brain, leaving OCD patients less able to focus their attention on external cues, and thus the task at hand (Stern et al. 2012). This is even true for emotion provoking stimuli, especially pleasant stimuli. OCD patients, compared to healthy controls, have difficulties deactivating the DMN (Gonçalves et al. 2017) leaving them more engaged with internally generated negative thought content than with external information that has potential to elicit positive mood or thoughts.

3 OCD Treatments

Modern treatment guidelines support the use of Cognitive Behavioral Therapy (CBT) for OCD with emphasis on the value of Exposure and Response Prevention (ERP), and/or pharmacotherapy with serotonin reuptake inhibitor medications.

3.1 Pharmacotherapy

The U.S. Food and Drug Administration (FDA) has approved a small number of agents to treat this disorder. They are all potent serotonin reuptake inhibitors that lead to an increase in serotonin function and include: clomipramine (Anafranil® and others), fluoxetine (Prozac® and others), fluvoxamine (Luvox®), sertraline (Zoloft®), paroxetine (Paxil® and others). In spite of their established efficacy (Gosmann et al. 2021), a number of shortcomings limit their ability to improve a patient's function. For example, in spite of OCD medications being frequently prescribed at higher doses and for longer periods than for other disorders, only about half of the patients receiving adequate treatment-trials will reach a satisfactory response, while most patients that do improve only have a one third to one half decrease in severity ratings. Their residual symptoms continue to cause dysfunction and increase vulnerability to complications and exacerbations.

Drugs such as desipramine and bupropion, which may act primarily by enhancing function of norepinephrine and/or dopamine, have been found to be ineffective at treating OCD (Vulink et al. 2005). The apparent selectivity of treatment response to medication that acts on the serotonin system, and the finding that serotonin blockers cause a relapse of OCD symptoms further justifies pursuing options related to serotonin actions in this population.

3.2 Psychotherapy

CBT has been the mainstay of non-analytic therapy and a first-choice treatment for OCD. CBT comprises two components: cognitive reappraisal of distorted beliefs and a behavioral intervention to prevent symptom engagement. The treatment of choice

for OCD is ERP, which involves gradual and prolonged exposure to fear-provoking stimuli combined with instructions to abstain from the compulsive behavior (Foa and Goldstein 1978; Öst et al. 2015). The integration of ERP with cognitive components, such as the discussion of feared consequences and other dysfunctional beliefs, can enhance the acceptability and effectiveness of ERP, particularly for patients with limited insight or those that may find exposure treatments difficult to tolerate (Stein et al. 2019).

3.3 Treatment Strategies for Poor Responders

Although both pharmacotherapy and psychotherapy can be useful alone, the most effective outcomes typically occur through a combination of these treatment forms (pharmacology and CBT) (March et al. 1997). When these treatments fail due to intolerance or lack of benefit after adequate trials of evidence supported first line interventions, an increasingly complex series of alternatives is possible, often with the goal of diminishing symptom severity rather than anticipating symptom remission. These include: alternative drug trials, augmentations and combination strategies, and the use of repeated transcranial magnetic stimulation (TMS), electroshock treatment, deep brain stimulation (DBS) in the anterior cingulate cortex and other targets, and surgical ablation such as cingulotomy and other lesion-based treatments. Surgical options may be tried only after other avenues have been exhausted in highly treatment-resistant cases. Given that a significant portion of individuals remain symptomatic and impaired in spite of escalation of treatment strategies with increasing associated morbidity and decreased likelihood of benefit, identifying new options for treatments of patients with severe and treatment resistant OCD has become a high priority.

4 Background of Psilocybin in OCD

4.1 Incidental Findings

A quarter century ago, we met a 34 year-old male patient in clinic who had suffered from severe OCD symptoms for nearly 30 years. His symptoms included upsetting obsessions of contamination and disgust with body secretions, and preoccupations with order, and his compulsions included excessive and ritualistic washing and cleaning, checking, arranging, and counting. This person reported having used multiple substances recreationally. Alcohol and marijuana relieved his anxiety but not his OCD, while stimulants made his OCD worse. He noticed that if he used 2 g of freeze-dried psilocybin mushrooms his symptoms would disappear during the time that he was intoxicated, and he would remain symptom free for several days before gradually returning. He then began chronic use of hallucinogens and found that the

obsessions and compulsions actually went into remission for periods of several months after he stopped using them. The use of unspecified doses of peyote also improved his symptoms (Moreno and Delgado 1997). While reviewing the literature at the time we encountered previous similar reports, and a number of similar instances have been added to the literature documenting a suggested benefit of psilocybin use including lasting benefits with repeated use (Wilcox 2014), and in at least one case using psilocybin in combination with high dose SSRIs (Lugo-Radillo and Cortes-Lopez 2021), a practice currently discouraged based on concerns for increased risk of serotonin syndrome and concerns about potential decreased effects in people who take antidepressants chronically.

4.2 Rationale for Psilocybin Use in OCD

Psilocybin, LSD, and mescaline are known to bind to a large number of receptors, transporters, and other proteins; however, they are extremely potent agonists at 5-$HT_{1A,}$ 5-HT_{2A}, and 5-HT_{2C} receptors and their binding potency to these receptors is correlated with their human potency as hallucinogens (Pokorny et al. 2016). It is possible that involvement of other sites of action may explain the acute improvement in symptoms described in the published case reports, however it is likely that interactions with 5-$HT_{1A,}$ 5-HT_{2A}, and 5-HT_{2C} receptors may be an important component of anti-OCD drug action. SSRIs lead to increases in activation of postsynaptic 5-$HT_{1A,}$ and chronic downregulation of 5-$HT_{2A.}$ Additionally, the observations that administration of the non-selective 5-HT antagonists metergoline or ritanserin exacerbates OCD symptoms in patients recently remitted with SSRI treatment add complexity to the interpretation of a receptor specific effect. Knockout mice who lack 5-HT_{2A} receptors lack the behavioral and cellular responses to psychedelics compared to wild type animals who have their natural 5-HT_{2A} receptor expression.

Important questions arise from the reports above, including: why are the anti-obsessional effects so immediate with psilocybin, while potent serotonin enhancing agents like clomipramine and the SSRIs take weeks to months to show beneficial responses? Why do some 5HT2 blockers actually help treat OCD symptoms (atypical neuroleptic medications, mirtazapine), while experimental 5HT2 blockers ritanserin, ketanserin, and MDL-100,907 do not cause any effect? Delgado and Moreno (Delgado and Moreno 1998) published a mechanistic paper that reviews some of these topics offering an early theoretical foundation to support exploration of psilocybin and indole-based psychedelics in the treatment of OCD.

Advances in our understanding of OCD, psychedelic mechanisms, and brain circuitry in the last two decades suggest a more complex mechanism may be in play than initially proposed, involving a variety of postsynaptic effects, interactions with other neurochemical systems, and brain circuits in the anti-obsessional response. Considering specific receptors within the serotonergic system, Carhart-Harris and Nutt (Carhart-Harris and Nutt 2017) have proposed that serotonin

neurotransmission enhances two distinct adaptive responses to adversity, in which postsynaptic 5-HT_{1A} signaling mediates passive coping characterized by stress moderation (SSRI treatments), whereas 5-HT_{2A} signaling facilitated by psychedelics mediates active coping and further enhances plasticity. In terms of interactions with other neurochemical systems, knockout mice who do not express the metabotropic glutamate receptor-2 (mGluR2) also fail to have the cellular and behavioral responses to LSD similar to 5-HT_{2A} knockouts, suggesting that the interaction of mGluR2 and 5-HT_{2A} is necessary for certain neuro-behavioral effects to take place (Moreno et al. 2011).

Successful treatments, both pharmacological and psychological therapies, show a normalization of CSTC circuits in patients with OCD (Van der Straten et al. 2017), indicating that a disruption of the CSTC circuits might be a good target for the treatment of OCD with psychedelics. Patients with OCD show higher functional connectivity and ventral striatal activity in sensorimotor and ventral cognitive circuits, while at the same time showing lower functional connectivity followed by disinhibition of dorsal striatal circuits (Stein et al. 2019).

The 5-HT_{2A} agonism of psychedelics is thought to disrupt the CSTC circuits. It has been proposed that this disruption lessens the sensory input filtering of the thalamus, thus allowing an increase of information in the cortex (Nichols 2004).

Providing another perspective on its potential therapeutic benefits, a single dose of psilocybin has been associated with a change in neocortical 5-HT_{2A} receptor binding followed by long-term increased mindfulness (Madsen et al. 2020). Furthermore, it has been shown that 5-HT_{2A} signaling can enhance neural plasticity (Lugo-Radillo and Cortes-Lopez 2021) and low-level learning as well as extinction learning (Vaidya et al. 1997), which is a key component of ERP and CBTs in OCD.

Psychedelics may also prompt neuroplasticity within the DMN (Carhart-Harris 2019). With the assumption that the DMN is controlling how information is integrated, it can be reasoned that incongruent or dissonant information deriving from perceptual anomalies and ambiguities will be dismissed by existing narratives, which in the case of OCD can be described as rigid and overlearned thought patterns and beliefs. Psychedelics are thought to interfere with this restrictive process. Excessive self-referential cognitive activity that is characteristic for OCD can be loosened by disrupting and "resetting" the DMN, allowing a healthier engagement with the patients' environment, by disengaging rigid top-down information processing patterns (Carhart-Harris and Friston 2019).

Thus multiple levels of analysis prompt optimism about the use of psychedelics to disrupt rigid patterns, both neural and psychological, in OCD. Independent of what level of analysis one prefers to describe the potential mechanism of action, there is sufficient support for the psychedelic class of drug as a tool to rapidly reduce OCD symptoms with the clinical benefit lasting significantly more than the subjective effects of the drug paving the way for important explorations of therapeutic potential.

5 Previous and Prospective Research

Near the turn of the century, we begun collaborations with the Multidisciplinary Association for Psychedelic Studies (MAPS) and the Heffter Research Institute to pursue the first clinical trial in psychiatric disorders in the USA in three decades. After overcoming multiple challenges, the University of Arizona, the Food and Drug Administration, and the Drug Enforcement Agency approved a proof-of-concept study to give psilocybin in a controlled research environment to individuals with OCD who had failed to improve with standard treatments.

5.1 Initial Study Design and Participants Characteristics

Seven men and two women, adults under the age of 65 years, with symptomatic OCD and previous experience using psychedelic drugs were treated with repeated escalating doses of psilocybin. They were free from antidepressants or other anti-OCD treatment for at least 2 weeks, and free of symptomatic relief medications such as anxiolytics or hypnotics, or any other prescription or over-the-counter medication, nutritional supplements or drugs of abuse, for at least 1 week as it is customary in all Phase I studies. OCD diagnosis was confirmed with the Structure Clinical Interview for DSM-IV.

Participants had failed to improve after an average of 3.4 adequate treatments with known anti-obsessional medications. Severity of symptoms was measured with the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS, range 0–40) as is commonly done in clinical trials of OCD. The participants had an average baseline Y-BOCS score of 24.1 (severe) ranging from 18 (moderate) to 36 (extreme) prior to study drug ingestion in the first test day.

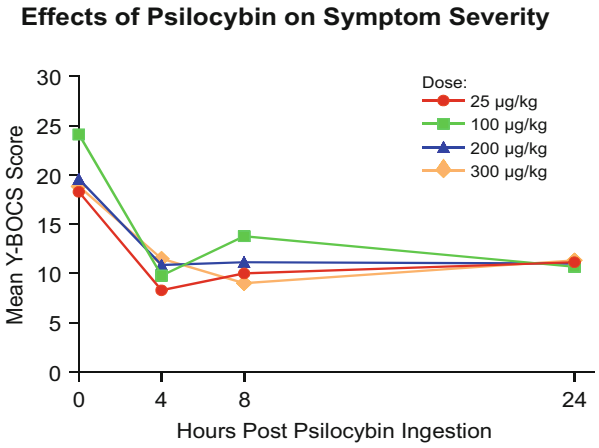
All participants signed written informed consent, which included a detailed discussion of potential physical and mental effects of psilocybin and risks of participation.

Psilocybin sessions were conducted in a specially adapted room (made to look as a home-like living room) in the outpatient offices of the Psychiatry Research Program, and subjects were subsequently housed overnight in the psychiatric unit to extend their monitoring. Special attention was given to the development of rapport and familiarization with the procedure and pertinent facilities. Psilocybin doses were selected to allow a range from non-hallucinogenic to frankly hallucinogenic. The low (100 μg/kg), medium (200 μg/kg), and high doses (300 μg/kg) were assigned in that order to secure escalating tolerability. A very low dose (25 μg/kg) thought to be almost inactive was assigned randomly as a control condition in a double-blind fashion during testing sessions 2, 3, or 4. The testing days were separated by at least 1 week. Trained sitters were present at all times. Subjects listened to a standardized set of music and wore eyeshades as they laid on a couch. They were advised to try to keep their experience focused internally, to avoid external distractions, and to

engage with the theme of their experience (thoughts, emotions, perceptions, etc.) as they arose without avoidance or intentionally pursuing specific topics. Subjects were asked to follow these directions for 5–8 h. The duration of this phase coincided with the duration and intensity of their psychedelic experience, generally wearing off sooner for the very low dose and lasting as long as 8 h as the doses escalated. Within each dose session, participants were gradually allowed to modify the above-described routine, changing music to familiar or preferred content, take off their shades, engage in interesting activities like drawing, writing, and started debriefing with the principal investigator (FM) regarding aspects of their experience. At the end of 8 h, the participants went into our inpatient psychiatric unit for an overnight stay.

5.2 *Study Findings*

Psilocybin was clearly able to induce a psychedelic experience in a dose-dependent fashion. Some patients experienced altered states of consciousness similar to the classic descriptions of LSD effects. Subjects generally tolerated the procedure well, none of the participants experienced psychotic symptoms, or mood complications, and did not exhibit any threatening or dangerous behaviors. One individual experienced a transient asymptomatic elevation of blood pressure, which was not associated with nervousness, or the content of his psychedelic experience. Some of the subjects were uncomfortable with the overnight stay in the psychiatric unit and two decided not to continue primarily for this reason. Clinically, the most remarkable finding was the acute decrease in OCD symptoms of variable degree observed in every study participant during one or more of their test sessions. Improvement ranged from a modest reduction (23%) to a complete (100%) but temporary resolution of symptoms.



Interestingly as well, although the psychedelic effect had clearly worn off, the decreases in Y-BOCS scores generally lasted for at least 24 h.

Surprisingly, the very low dose (0.025 μg/kg) was found to have stronger psychedelic and anti-OCD effects than anticipated. For the group as a whole, psilocybin led to acute improvement of obsessive and compulsive symptoms comparable to higher doses (Moreno et al. 2006).

5.3 Important Implications

When administered in a supportive clinical environment, psilocybin is tolerated well and leads to a transient reduction of OCD symptoms. This protocol was developed in the year 2000, prior to the recent wave of psychedelic research experience, and the generalization of lay knowledge derived from self-experimentation that is currently available. Our very small dose was anticipated to be mostly inactive and serve as a placebo, however we now know that we were micro-dosing our subjects, which may have facilitated both a partial psychedelic-like experience and clinical symptom improvement. The draconian safety precaution to keep participants hospitalized in an inpatient psychiatric unit overnight significantly limited our ability to recruit and retain subjects in this protocol. Interestingly, although subjects were challenged by an overnight stay at a psychiatric facility that was generally perceived as an unpleasant setting, they reported continuation of OCD symptom relief overnight in ratings obtained at 24 h following study drug ingestion. Testing took place 1 week apart or a few days longer, and ratings of OCD severity were obtained prior to each session. Individuals consistently reported that their symptoms remain well controlled for several days after psilocybin ingestion. Unfortunately, a number of factors limit the interpretation of these preliminary data and are being addressed in ongoing studies, namely: (a) Prospective measurement after the last session is consistently obtained by collecting standardized data (Y-BOCS and various self-report symptom measures) for 6 months; (b) rather than using a psilocybin very low dose, the ongoing study includes an alternative active placebo (lorazepam 1 mg), which is anticipated to facilitate relaxation but not to lead to significant or lasting OCD symptom reduction; (c) our new protocol explores the effects of blinded and repeated psilocybin administration on lasting symptom reductions.

Furthermore, in this ongoing study, we are including psychedelic-naïve as well as experienced study participants. Moreover, we are gathering information that may inform our understanding of the potential psilocybin mechanisms of anti-OCD action by exploring brain imaging, and electrophysiological data, and their relations to the subjective experience.

6 Conclusion

As explained in detail in other chapters in this book. Psychedelic substances like psilocybin hold promise as a future treatment option for a broad spectrum of mental disorders, and in particular for individuals with disorders that include the transdiagnostic symptoms of rigid and repetitive negative thinking, and the inability to inhibit unhelpful and unwanted behaviors.

Preliminary data suggest that psilocybin may be an important agent to pursue as we explore alternative treatment options for OCD. Moreover, the current research base concerning brain chemistry and network function in OCD and how patients respond to the administration of psychedelics further motivates the promise of using psychedelics as a part of an intervention package for those with treatment-resistant OCD.

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