Psychedelic Agents as Potential Therapeutics for Obsessive-Compulsive Disorder

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Obsessive-Compulsive Disorder (OCD) is a chronic psychiatric anxiety disorder distinguished by obsessive thoughts and repetitious actions. Current therapies for OCD are not very effective and have many possible side-effects. Psychedelics are a class of Schedule I substances that are re-emerging as novel therapeutics for a variety of psychiatric conditions. These substances cause a variety of psychological and physical effects, most notably, hallucinations and out-of-body experiences. Serotonergic psychedelics may provide a novel mechanism for alleviation of OCD symptomology through anti-inflammatory effects, modulation of neurotransmitters like serotonin, dopamine, norepinephrine, glutamate, gamma-aminobutyric acid, and oxytocin, and downstream systemic neural changes. Clinical studies have demonstrated lasting remission and a decrease in symptom severity in patients suffering from OCD after three doses of psilocybin. While they may provide symptom relief, psychedelics have risks. These include cardiovascular complications, psychosis in predisposed patients, and Hallucinogen persisting perception disorder. Psychedelic substances remain under tight control by the Federal government, creating a barrier for clinical research.

Abbreviations:  OCD – Obsessive-Compulsive Disorder; CSTC – cortico-striatal-thalamo-cortical; SSRIs – Selective Serotonin Reuptake Inhibitors

Keywords:  OCD; Obsessive-Compulsive Disorder; Psychedelics; CSTC; DMN; Neurotransmitter Modulation; Psychedelic Treatment

Introduction

Obsessive-Compulsive Disorder is a disabling psychiatric anxiety disorder that causes unwanted obsession and thoughts that usually manifest in repeated involuntary actions. Current therapies for OCD include selective serotonin reuptake inhibitors (SSRIs), talk therapy, and more invasive interventions like deep brain stimulation and surgery. Serotonergic psychedelics have long been used by indigenous peoples in many parts of the world for religious or cultural reasons. These substances mainly act on the serotonin system causing downstream effects: most notably, hallucinations and out-of-body experiences. More recently, psychedelics have been investigated as possible pharmacological interventions for mood disorders, addiction, and other psychiatric illnesses. These interventions have proven relatively successful in patients who do not achieve remission with first-line treatments. Current research surrounding OCD treatment with psychedelics is lacking, but there are several possible mechanisms by which these substances might prove to be therapeutic. This paper investigates how psychedelics might cause a decrease in OCD symptom severity through an anti-inflammatory response and neurotransmitter modulation, along with changes in activity in systems like the cortico-striatal-thalamo-cortical (CSTC) circuit. Given these neurological effects, psychedelics may be useful in treating OCD.

History of Psychedelics

Humphrey Osmond first used the term psychedelic in 1957 to define a type of drug that caused changes in mood, thought, and perception
Psychedelic Agents as Potential Therapeutics for Obsessive-Compulsive Disorder (Osmond, 1957). Various types of psychedelic drugs have been used for centuries. Indigenous peoples of the Americas have used psychedelics, particularly Mescaline and Ayahuasca, for religious ceremonies for hundreds of years (Sessa, 2016). Basic psychedelic research was conducted by medical researchers in the 1960s and 1970s with some success. A meta-analysis of studies on mood disorders published between 1949 and 1973 reported that 79% of participants showed ‘clinically judged improvement’ with psychedelic-assisted treatment (Rucker et al., 2016). Unfortunately, these studies were not double-blind and usually did not include a control group, weakening their findings. The research was halted when the federal government classified psychedelic drugs as Schedule I in 1970. Schedule I drugs are substances that lack any currently accepted medical use and have a high potential for abuse (Lopez and Tadi, 2021). This was because of both a fear of psychedelic substances, a rise in the recreational use of psychedelics, and a general fear of drugs in American society.

While the federal government tightly controls who is allowed to distribute and conduct research with psychedelic substances, some states and territories have moved towards legalization and now allow for recreational use. Preliminary studies have shown broad benefits from these substances in many psychiatric and neurological disorders. These same studies also report little to no side effects or addiction potential (Nichols, 2016).

Obsessive-Compulsive Disorder

Obsessive-compulsive disorder is a debilitating and chronic anxiety disorder with a population prevalence of 2-3% (Pallanti et al., 2011). Patients with OCD are characterized by the presence of obsessions and compulsions to alleviate chronic anxieties. OCD can manifest itself in many ways, with obsessions and compulsions ranging from germaphobia to a need for symmetry. These obsessions are involuntary and pair themselves with a compulsion that temporarily alleviates some anxiety. However, long-term, this compulsion becomes a coping method for the obsession, forming an unhealthy cycle. Patients suffering from OCD also have high comorbidity rates with other psychiatric conditions, for example, Generalized Anxiety Disorder, Major-Depressive Disorder, Social Anxiety Disorder, Post-Traumatic Stress Disorder, Body-Dysmorphic Disorder, and various eating disorders like Anorexia Nervosa and Bulimia (Pallanti et al., 2011).

Current Therapies for Obsessive-Compulsive Disorder

Pharmacological therapies for OCD came to prevalence in the 1980s with the discovery that the relatively selective serotonergic tricyclic antidepressant clomipramine had anti-obsessive effects (Volavka et al., 1985). Clomipramine inhibits the reuptake of serotonin but is not very selective as it has a high affinity for other receptors and reuptake sites (Pittenger and Bloch, 2014). Since then, serotonergic agents have been the main subject of investigation for clinical research on OCD. More specifically, selective serotonin reuptake inhibitors (SSRIs) have become the first-line treatment for patients with OCD (Skapinakis et al., 2016). SSRIs increase extracellular serotonin by binding to the serotonin transport protein and inhibiting reabsorption of the monoamine. The exact mechanism by which SSRIs reduce OCD symptomatology is not well understood, but neuroadaptive changes caused by an acute increase in serotonergic transmission may play a role (Blier and El Mansari, 2007). While SSRIs bind mainly to the serotonin transporter protein, they also have a weak binding affinity at other homologous transporter proteins sites (Tabsumi et al., 1997).

While somewhat effective, 40-60% of patients do not respond to SSRI treatment (Pallanti et al., 2002). It is not currently well understood why some patients respond to SSRIs, and others do not. It is thought that unique neurochemical environments may interact with SSRI efficacy (Penn and Tracy, 2012).

Mechanisms of Psychedelic Drugs

Normal brain function consists of a hierarchical compression and inhibition of sensory signals leading to an organized set of conscious outputs. This organizational function compresses and weighs sensory information to
process the most ‘normal’ and realistic outcome. In more familiar terms, the brain’s hierarchy of organization suppresses and inhibits certain signals from environmental stimuli deemed ‘out of the ordinary’ before producing consciousness. Through agonism at 5-HT2AR receptors, psychedelics seem to dysregulate this process, causing impairment in the hierarchical organization, leading to hallucinations (Carhart-Harris and Friston, 2019). Psilocybin, in particular, exerts binding at serotonin -1D, -2A, -2B, -2C, -5, -6, and -7 receptors and causes a deactivation of sodium-dependent serotonin transporters (Geiger et al., 2018). Antagonism at the 5-HT2A receptor inhibited hallucination in patients treated with psychedelics, pointing to the conclusion that the hallucinatory effects of these drugs are caused in at least some capacity by 5-HT2A agonism (Vollenweider et al., 1998).

While the exact mechanism is not entirely understood, these biochemical agonists seem to create a transient state of hyperconnectivity by decreasing default mode network (DMN) activity, a system in the brain that controls interregional communication. Once this entropic state fades, the brain may reset into a state of connectivity through cortical connections more associated with a healthy brain (Carhart-Harris et al., 2017). In sum, the brain may come out of psychedelic treatment reorganized, decreasing OCD symptomatology. This is discussed in further depth in the results section.

**Literature Review Methods**

2,008 articles resulted from a search on the database Web Of Science using the keyword “psychedelics”. From here, results were filtered by the database’s category of “Highly Cited Papers”, defined as articles that are in the top 1% of cited articles in their academic field. This filter left 28 articles. These were screened for relevance to the academic question and compiled into the category of the initial literature search. Any cited articles within this first group of papers were also screened for relevance to the academic question and included in the knowledge base accordingly.

Any lingering definitions or unexplained mechanisms were researched separately using the PubMed/Medline search engine.

**Results of Literature Review**

**Psychedelics and Inflammation**

Inflammation is medically defined as an “internal and endogenous process that assists repair and healing in response to an insult to the biological system” (Medzhitov, 2008). Inflammation is part of normal disease response and serves as a primary defense for biological systems. However, inflammation can sometimes become harmful if it is too global, intense, or chronic. Neuronal inflammation is now understood to play a role in neuropsychiatric disorders.

While the mechanisms are poorly understood, OCD may also be associated with increased inflammation in the brain. Patients with psychiatric disorders such as major depressive disorder have exhibited increased levels of pro-inflammatory cytokines TNF-a and IL-1b (Furtado and Katzman, 2015). Similarly, injections of TNF-a and IL-1b in animal models have shown induced behavioral changes such as social withdrawal (Najjar et al., 2013). Antidepressants also seem to decrease IL-6 levels in patients with depression (Strawbridge et al., 2015).

Studies investigating 5-HT2A agonism on rat aortic smooth muscle cells have shown that the 5-HT2A agonist (R)-2,4-dimethoxy-4-idoamphetamine [(R)-DOI] exhibits potent anti-inflammatory effects (Yu et al., 2008). (R)-DOI inhibited TNF-a-based expression of genetic pro-inflammatory cytokines and molecules. Even when TNF-a was added hours prior to adding (R)-DOI, the inflammatory response was attenuated, pointing to both a possible preventative and therapeutic mechanism for chronic or temporal inflammation (Pelletier and Siegel, 2009). Later, the effects of psychedelic attenuation of inflammation were tested in vivo. Similar anti-inflammatory responses were observed, with effects primarily mediated through similar TNF-a pathways (Jr et al., 2013). The psychedelic induced anti-inflammatory
response is hypothesized to be mediated primarily by functional selectivity, the process by which a bioactive molecule leads to a different binding conformation than another agonist, leading to a different response (Kenakin, 2011). For example, serotonin binding leads to a pro-inflammatory response, while psychedelic functionally selective binding causes an anti-inflammatory response (Flanagan and Nichols, 2018).

While studies of psychedelic induced anti-inflammatory response in relation to Obsessive-Compulsive Disorder are lacking, a possible therapeutic connection of great scientific value exists. Furthermore, given that many psychiatric disorders are associated with varying levels of chronic inflammation, it may prove helpful to explore mechanisms to systematically decrease this inflammation.

Psychedelics and Neurotransmitter Modulation

**Serotonin** The primary neurotransmitter associated with psychedelics is serotonin or 5-hydroxytryptophan. Serotonin is responsible for many different biological processes within both the brain and other parts of the body. Serotonin receptors in the body are categorized into 14 different types, controlling mood, sleep, appetite, anxiety, stress, social dominance, sexual behaviors, mobility, and gastrointestinal movements (Beattie and Smith, 2008). Serotonin levels are partly controlled by the rate-limiting catabolism of the enzyme indoleamine 2,3-dioxygenase. Chronically elevated states of this enzyme cause lower levels of serotonin which are associated with the pathogenesis of many psychiatric disorders (Messaoud et al., 2019). Most of the first-line treatments for OCD currently focus on the modulation of the serotonin system.

In a mechanism similar to classic SSRIs, psychedelics acutely decrease the firing of Dorsal Raphe Nucleus serotonergic neurons through activation of the 5-HT1A receptor. However, after chronic psychedelic administration, Raphe Nuclei serotonergic firing increases via dopaminergic, 5-HT1A, and Trace amine-associated receptors (De Gregorio et al., 2016).

Although psychedelic modulation of SERT protein function remains under investigation, particularly with LSD, SERT inactive mice showed lower levels of reaction to LSD treatment, pointing to a possible in vivo mechanism (Krall et al., 2008). Psilocybin, on the other hand, has been shown to decrease 5-HT reuptake by inhibiting SERT protein (Rickli et al., 2016).

Most notably, psychedelics are agonists of varying capacities at many of the 5-HT receptor subtypes. For example, psilocin, the active metabolite of the psilocybin, exerts binding agonism at 72% of 5-HT2A receptors at clinically relevant doses (Vollenweider et al., 1998).

**Dopamine** The dopaminergic and serotonergic systems are closely linked, and therefore, psychedelics exert potent effects on dopamine transmission. Selective lesion studies have indicated that serotonergic transmission has an inhibitory effect on DRN dopamine neurons (Guiard et al., 2008). LSD presents a possibly biphasic effect on dopamine transmission, decreasing it at lower levels, but increasing it at higher doses (De Gregorio et al., 2016). Action on dopaminergic neurons is more associated with LSD than psilocybin; however, studies have shown that psilocin also increased 5-HT and dopamine extracellular concentrations in the mesoaccumbens and mesocortical pathways (Sakashita et al., 2015).

**Glutamate** is the primary excitatory neurotransmitter in the nervous system (Meldrum, 2000). Glutamate projection neurons are present in most cortical and subcortical brain areas. Glutamate ionotropic receptors include AMPA, NMDA, and kainate receptors. When activated by glutamate, these receptors open calcium cation channels. Glutamate, at high levels, exhibits excitotoxicity and is therefore highly regulated by transport proteins, astrocytes, glial cells, and other neurons. The glutamate system is involved in many cognitive processes, including memory, learning, and cognition. Abnormalities in the glutamate system are implicated in OCD (Karthik et al., 2020). Specifically, glutamate plays a prominent role in the CSTC, or cortico-striato-thalamo-cortical, circuit (Wu et al., 2012). This system is often implicated in psychiatric pathology, and over-
activation of the CSTC is thought to be part of the cause of OCD. The CSTC links fronto-cortical and subcortical areas with many ‘side loops’ regulating its processes (Karthik et al., 2020).

While a complete description of the CSTC is out of the scope of this paper, a brief overview of the pathophysiology of OCD associated with the glutamatergic system of this circuit points to why psychedelics may offer a possible solution to treatment-resistant patients. While the exact mechanism is unknown, MRS studies have indicated that glutamate receptors in the PSD, or postsynaptic density, are involved in the pathogenesis of OCD symptoms. Sapap3 knockout mice present excessive grooming and anxiety-like behaviors (Welch et al., 2007). The Sapap3 gene encodes necessary components of the glutamatergic system in the CSTC (Bienvenu et al., 2009).

NMDA receptors also play a role in neurogenesis and synaptic plasticity, pointing to another target of psychedelic agents that might prove useful in OCD treatment (Malenka and Nicoll, 1993).

Psychedelics, more specifically LSD and psilocybin, elevate glutamate levels in the prefrontal-limbic system, with effects attenuated by using 5-HT2A antagonists (Aghajanian and Marek, 1997). This points to a serotonergic modulation of the glutamate systems in these areas. Thus, it seems possible that psychedelics, through their modulatory effect on glutamate in areas implicated in the pathogenesis of OCD, might provide protective and therapeutic effects.

**GABA** dysfunction is heavily associated with psychiatric disorders (Petty, 1995). SSRIs are thought to normalize hypoactive GABAergic circuits, leading to the possibility that psychedelics, through different mechanisms, could have similar or more favorable effects (Sanacora et al., 2002). DOI, a potent psychedelic, was shown to increase cortical levels of GABA through modulation of GABAergic interneurons (Abi-Saab et al., 1999). Decreases in neuronal activity after administration of psychedelics, especially in relevant areas of the brain to OCD pathologies like the CSTC and DMN, may increase GABAergic activity and subsequently local inhibitory control (Carhart-Harris et al., 2017).

**Oxytocin** Through downfield activity, SSRIs are thought to increase oxytocin levels which play a part in the antidepressant and anxiolytic effects of the drug (Keating et al., 2013). In addition, 5-HT1A/2A receptor stimulation caused by LSD leads to a transient increase in oxytocin levels, highlighting a possible novel therapeutic mechanism for anxiety disorders like OCD (Dolder et al., 2016).

**Structural Changes and Neurotransmitters**

It is essential to acknowledge that while changes in neurotransmitters may be associated with temporary changes in mood or OCD symptomatology, long-term structural and pathway-focused changes associated with chronic changes in neurotransmitters are more clinically relevant. The classic theory of simple increased or decreased neurotransmitter release in patients with OCD lacks the proper complexity and nuance of the disease. Growing evidence points to a more holistic and connected model of the brain, with the downstream effects of neurotransmitter modulation causing an increase or decrease in OCD symptomatology.

**Clinical Studies**

There has only been one relevant clinical study conducted so far concerning psychedelics and Obsessive-Compulsive Disorder. Conducted at the University of Arizona, the study recruited nine patients with moderate and severe symptoms of OCD. The participants were administered three doses of psilocybin one week apart. Each administration had an increased dosage of psilocybin from the week prior. One randomly assigned very low dose was administered at any time after the first dose. Each session lasted 8-hours in a controlled environment. The Yale-Brown Obsessive-Compulsive Scale (YBOCS) and a visual analog scale measuring overall obsessive-compulsive symptom severity were used to assess symptomatology at 0, 1-, 4-, 8-, and 24-hours post-dose administration. There was only one patient who experienced transient hypertension, and no other adverse events occurred. 23%-100% decreases in YBOCS scores were observed during at least one of the testing sessions in all patients. There was a significant Wilks-lambda score relating to time,
but no significant results from only dose or both time and dose. Long-term effects were less profound but still meaningful. Two subjects reported relief for up to a week, and one patient reported remission from symptoms at a follow-up six months later (Moreno et al., 2006).

These results are incredibly encouraging and warrant additional research. Psychedelics may not only provide more relief than current therapeutics but might also lead to a higher rate of long-term remission. In addition, this trial serves as a proof of concept for psychedelics as potential therapeutics for obsessive-compulsive disorder.

Moreno and colleagues are currently running a more rigorous placebo-controlled trial involving eight doses of psilocybin with brain imaging and long-term follow-ups (Moreno, 2021).

Discussion/Conclusion

Difficulties and Challenges

Currently, in the United States, psychedelic substances are classified as Schedule 1 substances with "no accepted medical use and a high potential for abuse" (Lopez and Tadi, 2021). This means that researchers do not have clearance to study the compounds further, and more importantly, patients do not have access to potentially life-saving treatment.

There also is a lack of sourcing capabilities for scientific research of the group of substances. While some organizations provide psychedelics to researchers, they are far and few in-between. Moreover, psychedelics have an uphill battle to gain acceptance among the general population. An estimated 32 million (95% confidence interval (CI): 30 to 33 million) individuals had lifetime use of psychedelics in 2010 (Krebs and Johansen, 2013). Psychedelics have the stigma of being drugs of abuse by members of the counterculture. Therefore, many in the general population and the scientific community believe that these substances have no place in an academic environment.

Benefits and Risks

Although it is widely believed that psychedelic drugs are addictive, an overwhelming amount of research has been conducted that states that psychedelics are physiologically safe and pose little addictive potential (Lüscher and Ungless, 2006). While the drugs are incredibly mentally and psychologically disorienting, they are physically surprisingly safe. There were no reported deaths due to overdose of LSD or psilocybin as of a study conducted in 2016 (Nichols, 2016). As mentioned prior in this paper, psychedelics present themselves as possible lifesaving and breakthrough therapeutics for various psychiatric and psychological disorders. Psychedelics have shown incredibly therapeutic properties in diseases that lack any current effective treatments. Psychedelics have even shown therapeutic effects in inflammatory disorders such as cardiovascular disease, diabetes, and asthma (Nau et al., 2015; Flanagan et al., 2019).

Psychedelics do not present themselves without risks. LSD has been shown to acutely increase heart rate and blood pressure. Patients with cardiovascular conditions may be at a heightened risk for adverse events after the administration of psychedelics. In addition, psilocybin may cause headaches in a dose-dependent manner.

Psychedelics may prematurely cause psychosis in patients who are already predisposed to psychotic conditions (Johnson et al., 2008). However, larger survey studies have weakened this hypothesis, reporting that users of psychedelics were no more likely to have a mental health condition than those who did not use the class of substances (Johansen and Krebs, 2015). The substances may also exacerbate bipolar depression symptoms (Gard et al., 2021).

There is also the risk of hallucinogen persisting perception disorder (HPPD), a rare condition categorized by intense flashbacks to psychedelic experiences (Hermle et al., 2012).

Overall, while the risks of psychedelics are not completely understood, they present a barrier to clinical application and warrant additional research.
Conclusion

While psychedelic research is rather novel and not very well understood, recent findings emphasize that these agents may prove to be powerful treatment options for patients suffering from OCD who have lacked a response to current therapies. Psychedelics may reduce neural inflammation and alter neurotransmitter circuits, ultimately leading to a reorganization of faulty neural circuits that contribute to OCD. Current therapies like SSRIs are not very effective and have relatively intolerable side effect profiles. Though they may be a breakthrough therapy, psychedelics are largely unstudied, and possible risks and contraindications are poorly understood. In all, future research studies on the exact mechanisms of psychedelic substances and larger placebo-controlled double blinded clinical trials are warranted.

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