Safety, Tolerability, and Efficacy of Psilocybin in 9 Patients With Obsessive-Compulsive Disorder

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Background: Anecdotal reports suggest that psychedelic agents may relieve symptoms of obsessive-compulsive disorder (OCD). This modified double-blind study investigated the safety, tolerability, and clinical effects of psilocybin, a potent 5-HT_{1A} and 5-$HT_{2A/2C}$ agonist, in patients with OCD.

Method: Nine subjects with DSM-IV–defined OCD and no other current major psychiatric disorder participated in up to 4 single-dose exposures to psilocybin in doses ranging from subhallucinogenic to frankly hallucinogenic. Low (100 μg/kg), medium (200 μg/kg), and high (300 μg/kg) doses were assigned in that order, and a very low dose (25 μg/kg) was inserted randomly and in double-blind fashion at any time after the first dose. Testing days were separated by at least 1 week. Each session was conducted over an 8-hour period in a controlled environment in an outpatient clinic; subjects were then transferred to a psychiatric inpatient unit for overnight observation. The Yale-Brown Obsessive Compulsive Scale (YBOCS) and a visual analog scale measuring overall obsessive-compulsive symptom severity were administered at 0, 4, 8, and 24 hours postingestion. The Hallucinogen Rating Scale was administered at 8 hours, and vital signs were recorded at 0, 1, 4, 8, and 24 hours after ingestion. The study was conducted from November 2001 to November 2004.

Results: Nine subjects were administered a total of 29 psilocybin doses. One subject experienced transient hypertension without relation to anxiety or somatic symptoms, but no other significant adverse effects were observed. Marked decreases in OCD symptoms of variable degrees were observed in all subjects during 1 or more of the testing sessions (23%–100% decrease in YBOCS score). Repeated-measures analysis of variance for all YBOCS values revealed a significant main effect of time on Wilks lambda ($F = 9.86$, $df = 3,3$; $p = .046$), but no significant effect of dose ($F = 2.25$, $df = 3,3$; $p = .261$) or interaction of time and dose ($F = 0.923$, $df = 9,45$; $p = .515$). Improvement generally lasted past the 24-hour timepoint.

Conclusions: In a controlled clinical environment, psilocybin was safely used in subjects with OCD and was associated with acute reductions in core OCD symptoms in several subjects.

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Obsessive-compulsive disorder (OCD) is a chronic and debilitating condition with a lifetime prevalence of 2% to 3%, which makes it the fourth most common psychiatric diagnosis[1,2] and one with a very high disease burden.[3] Furthermore, OCD is commonly complicated by the presence of comorbid delusions, suicidality, panic, substance abuse, depression, and interpersonal difficulties. Many patients with OCD delay or altogether avoid pursuing care, and of those who seek help, many remain unrecognized and untreated.

It is now well established that serotonin (5-HT) reuptake inhibitors (SRIs), such as the selective serotonin reuptake inhibitors (SSRIs) and clomipramine, are among the most effective pharmacologic treatments for OCD, although these treatments generally reduce symptoms by only 30% to 50%.[4,5] Some SRI-treated patients who receive the 5-HT_2 antagonist metergoline experience a resurgence of OCD symptoms.[6] Supporting the central role of 5-HT in the efficacy of SRIs, drugs such as desipramine and bupropion, which may act primarily by blocking reuptake of norepinephrine and/or dopamine, are not effective treatments for OCD.[7,8]

In spite of the greater efficacy of potent SRIs compared with other agents in the treatment of OCD, they are still suboptimal. The length of time required for improve-

ment of patients undergoing treatment with SRIs is quite extensive, the rates of remission are minimal, and many patients considered responders have residual symptoms that continue to cause dysfunction and may increase vulnerability to complications and exacerbations.[9] In addition to SRIs, other effective treatments include cognitive behavioral psychotherapy (CBT), combination of SRIs and CBT, and the use of polypharmacy.[5,9] It is estimated that as many as 40% to 60% of those who are adequately treated will fail to respond to standard therapies.[9] For these reasons, identifying new options for treatments has become a high priority.

There are several reported cases concerning the beneficial effects of hallucinogenic drugs (psilocybin and lysergic acid diethylamide [LSD]) in patients with OCD and related disorders.[10–14] For example, a 34-year-old man had suffered from OCD symptoms (checking and counting compulsions, performing actions a specific number of times, and a variety of other rituals) since age 14. However, he began using freeze-dried psilocybe mushrooms recreationally at age 18 and observed consistently that during the psilocybe mushroom intoxication, he was free of obsessions or compulsions. Repeated use induced tolerance to the psychedelic effects, but the subject continued to experience relief of his OCD symptoms despite the lack of a "high." Chronic use of this hallucinogen led to a symptomatic remission, which lasted for several months after discontinuing use.[15]

Psilocybin (4-phosphoryloxy-*N*,*N*-dimethyltryptamine), an indolealkylamine, is the main active compound of many species of the genus *Psilocybe,* commonly known as "magic mushrooms." Psilocybin binds potently as an agonist to the 5-HT_{1A}, 5-HT_{2A}, and 5-HT_{2C} receptors.[16,17] Behavioral pharmacology and electrophysiologic research show that agonist activity at 5-HT_2 receptors strongly correlates with a stimulus effect in animals and a hallucinogenic effect in humans.[18,19] Oral doses ranging from 8 to 20 mg p.o. or 100 to 315 μg/kg are considered safe and able to induce a quantifiable psychedelic experience that lasts, depending on the dose, from 3 to 8 hours.[20,21] Given a large first-pass metabolism in which psilocybin is converted primarily to psilocin, the latter may actually be responsible for the psychotropic effects observed after psilocybin administration.

Given the large body of clinical data suggesting that pharmacologic potency in increasing synaptic 5-HT may underlie the therapeutic effects of some drugs in the treatment of OCD and the anecdotal reports of acute reduction in OCD symptoms with hallucinogens, we hypothesized that agonist activity at 5-HT_{1A}, 5-HT_{2A}, and/or 5-HT_{2C} receptors might underlie the efficacy of drug treatments for OCD. The present study sought to evaluate the safety, tolerability, and potential therapeutic effect of psilocybin administration in OCD patients who had failed to respond to at least 1 adequate treatment trial with SRI agents. Additionally, we sought to explore the relationship between the intensity of psychedelic experience and the severity of obsessions and compulsions during testing.

METHOD

Safety and Ethical Considerations

This project was approved by the University of Arizona Human Subjects Committee and the U.S. Food and Drug Administration (FDA). All participants signed informed consent statements, which included a detailed discussion of potential somatic and mental effects of psilocybin. The subject selection and study design were the result of extensive discussions with members of the Human Subjects Committee at the University of Arizona and representatives of the FDA, who had a number of comments geared toward improving the safety of research subjects. The study was conducted from November 2001 to November 2004.

Subjects

Nine subjects (7 male, 2 female) who met criteria for current OCD based on the Structured Clinical Interview[22] for the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV)[23] were recruited through word-of-mouth, Internet postings, and local advertisement. Their ages ranged from 26 to 62 years (mean ± SD = 40.9 ± 13.2 years); 3 of the subjects were employed, 1 was a housewife, and 5 were unable to work because of their OCD symptomatology. Six of 9 participants lived alone, 2 were living with a significant other, and 1 was married.

Subjects were required to have at least 1 "treatment failure," defined as lack of significant improvement after an adequate treatment course with an SRI for at least 12 weeks (based on dose range recommendations published in the Expert Consensus Guidelines for OCD[5]). Subjects had a mean ± SD of 3.4 ± 1.9 treatment failures. Subjects were required to be symptomatic at the time of enrollment and had a baseline Yale-Brown Obsessive Compulsive Scale (YBOCS)[24] score ranging from 18 to 36 (mean ± SD = 24.1 ± 5.9) on the first test day. None of the subjects met criteria for current major psychiatric disorders other than OCD, including current substance abuse/dependence, and none of the subjects had a personal or family history of psychosis. Due to safety concerns over potential adverse reaction to psychedelic drugs, subjects were required to have tolerated well at least 1 prior exposure to indole-based psychedelics. Two of the subjects (1 and 4) reported a history of clinical benefit with use of psychedelics.

Subjects were free of general medical or neurologic conditions based on the clinical history and review of systems; physical examination; electrocardiogram; routine laboratory blood, urine, and pregnancy screenings; and urine testing for drugs of abuse. Subjects were required to

abstain from use of antidepressants for at least 2 weeks (6 weeks for fluoxetine) and any pharmaceutical or nutritional supplement for at least 1 week before testing. Additionally, subjects were free of any other prescription or over-the-counter medication or drug of abuse.

Procedure

Testing was performed in the Department of Psychiatry at the University of Arizona Health Sciences Center. Psilocybin sessions were conducted in the outpatient offices of the Psychopharmacology Research Program. As a cautionary measure, subjects were then transferred to the psychiatric inpatient unit of the same hospital for overnight observation and were discharged the next morning. When a bed was not available in the psychiatric unit, subjects were admitted to the medical-surgical units under the care of the psychiatric service and remained under constant supervision by a staff member. Subjects had an opportunity to develop rapport with the study team during screening. All subjects met with the principal investigator (F.A.M.) and whenever possible with the sitters the day before testing. During the initial visit, further rapport was established, the procedure was again discussed, and the testing room and the psychiatric inpatient unit were shown to the subjects.

Subjects reported for testing at 8:00 a.m., after having had a light snack. Testing for drugs of abuse and pregnancy (when applicable) was conducted prior to each session. Subjects were escorted to the testing room, where they remained for the next 8 hours. Subjects were allowed to use a nearby restroom, but no other outings were allowed. A light snack was again made available for subjects at about 1:00 p.m. Study drug was ingested at about 8:30 a.m. Subjects received up to 4 different doses, 1 dose per test session, in a modified dose escalation blinded protocol. Doses were 25 (very low dose [VLD]), 100 (low dose [LD]), 200 (medium dose [MD]), and 300 (high dose [HD]) μg/kg of body weight. LD, MD, and HD were assigned in that order, and VLD was inserted randomly and in double-blind fashion at any time after the first dose (LD). Testing days were separated by at least 1 week. Subjects were asked to wear eyeshades, listen to a standardized set of music, and minimize interactions during the sessions. Trained sitters were present at all times and included at least 1 of the investigators; whenever possible, a male and a female sitter were present simultaneously. Toward the end of the 8-hour test, subjects were allowed to modify the music selection, have more conversation, discontinue use of the eyeshades, and gradually debrief with the principal investigator regarding aspects of their experience.

Measurements

The YBOCS and a visual analog scale (VAS) for overall obsessive-compulsive symptom severity were administered immediately before psilocybin ingestion (baseline) and at 4, 8, and 24 hours postingestion. The Hallucinogen Rating Scale (HRS)[25] was administered at 8 hours post ingestion. The HRS is a non-theoretically constructed scale, and its item selection is based on reported observations from experienced hallucinogen users who could experience a full range of effects. It measures 6 aspects of the hallucinogenic experience, including the following subscales: somaesthesia, affect, volition, cognition, perception, and intensity. Volition and intensity subscales are compounded by a small number of items and lack the established validity of the other mentioned subscales. Vital signs were monitored at baseline and 1, 4, 8, and 24 hours after psilocybin ingestion.

Data Analysis

Change in YBOCS and VAS scores was assessed by multivariate analysis of variance (ANOVA) in a repeated-measures design. This allowed for an assessment of the main effect of time, dose, and time-by-dose interaction. ANOVA within-subjects linear contrast was utilized to test for dose-response relationship in the HRS intensity subscale. Pearson correlation was used to assess the relationship between HRS intensity score and change in YBOCS score.

Results were considered significant when $p \leq .05$. Trends are also reported when $p \leq .1$. All tests were 2-tailed. Data analysis and graphic presentation utilized SPSS[26] and SYSTAT[27] software programs.

RESULTS

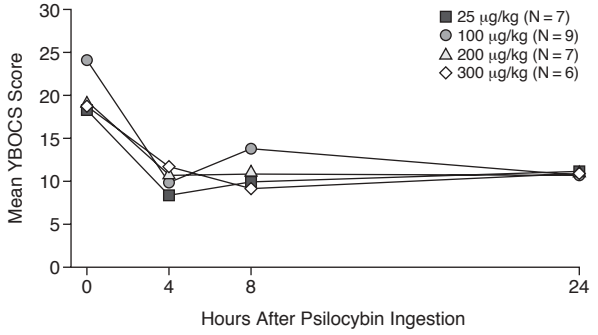
Safety and Tolerability

Subjects generally tolerated the procedure well. One subject experienced transient hypertension (132/90, 135/90, 142/105, 142/95, and 116/78 mm Hg at 0, 1, 4, 8, and 24 hours, respectively, after ingestion of a medium dose of psilocybin), which was not associated with psychic anxiety or somatic symptoms. Two subjects declined further participation after the first testing session due to discomfort with hospitalization. No other adverse reactions were observed. All 9 subjects received LD, 7 of them also received VLD and MD, and 6 of them received all 4 doses.

Effect on OCD Symptoms

Repeated-measures ANOVA for all YBOCS values revealed a significant main effect of time on Wilks lambda ($F = 9.86$, $df = 3,3$; $p = .046$), but no significant effect of dose ($F = 2.25$, $df = 3,3$; $p = .261$) or interaction of time and dose ($F = 0.923$, $df = 9,45$; $p = .515$). Marked decreases in OCD symptoms of variable degree were observed in all subjects during 1 or more sessions (23%–100% reduction in YBOCS score). Contrast comparison of baseline versus postingestion YBOCS scores for all doses combined was also statistically significant ($F = 9.37$, $df = 1,5$; $p = .028$); see Figures 1 and 2.

Figure 1. Effects of Psilocybin on Obsessive-Compulsive Symptom Severity[a]



[a]Mean YBOCS scores immediately prior to ingesting psilocybin (T-0) and 24 hours after ingesting psilocybin (T-24) for each dose were as follows: 25 μg/kg, T-0 = 18.29, T-24 = 11.14; 100 μg/kg, T-0 = 24.11, T-24 = 10.67; 200 μg/kg, T-0 = 19.57, T-24 = 11.00; 300 μg/kg, T-0 = 18.83, T-24 = 11.33.
Abbreviation: YBOCS = Yale-Brown Obsessive Compulsive Scale.

Repeated-measures ANOVA for effects of individual doses on YBOCS scores found a significant effect of time for LD (p = .004) and MD (p = .006), but not for VLD (p = .128) or HD (p = .406). Changes in obsessions and compulsions were comparable. ANOVA of baseline to 24 hours YBOCS score also showed a significant effect of time (F = 7.89, df = 1,5; p = .038), but no effect of dose or time-by-dose interaction.

VAS scores for all doses combined showed no significant effect of time (F = 3.05, df = 3,3; p = .192) or dose (F = 2.7, df = 3,3; p = .218). Repeated-measures ANOVA for effect of individual doses on VAS scores found a significant effect of time for LD (p = .010), but not for VLD (p = .307), MD (p = .182), or HD (p = .25). Contrast comparison of baseline versus postingestion VAS scores for all doses combined was also statistically significant (F = 11.41, df = 1,5; p = .020). ANOVA of baseline to 24 hours revealed a significant main effect of time (F = 5.38, df = 1,5; p = .068), a nonsignificant effect of dose (F = 1.83, df = 3,3; p = .316), and a significant interaction of time and dose (F = 183.1, df = 3,3; p = .001).

The HRS intensity subscale showed a significant linear main effect of dose (F = 12.36, df = 1,5; p = .017) (Figure 3). Total HRS score and every subscale with the exception of volition also showed a statistically significant linear main effect of dose. There were no significant correlations between HRS total or subscale scores and changes in OCD severity based on YBOCS or VAS scores.

OCD measurements were only obtained for up to 24 hours following psilocybin ingestion prior to the next session, and the duration of symptomatic improvement was not prospectively measured; however, 88.9% of subjects maintained a ≥ 25% decrease and 66.7% maintained a ≥ 50% decrease in YBOCS score at 24 hours with at least 1 of the testing doses. Two of the subjects reported that their symptomatic improvement lasted most of the following week after testing. Although there was a numerical difference between baseline scores at test 1 versus other test times, there was no statistically significant order effect when ANOVA with repeated measures was used (p = .133). One subject achieved long-term remission at the end of the 4 test sessions, as measured at 6-month follow-up.

Post hoc pairwise t test analysis comparing YBOCS scores during screening (25.2 ± 8.6) and baseline scores (24.1 ± 6.3) on test day 1 showed no statistical difference (p = .673), suggesting stability of YBOCS scores prior to psilocybin testing and the lack of anxiety-induced increase in YBOCS score prior to testing.

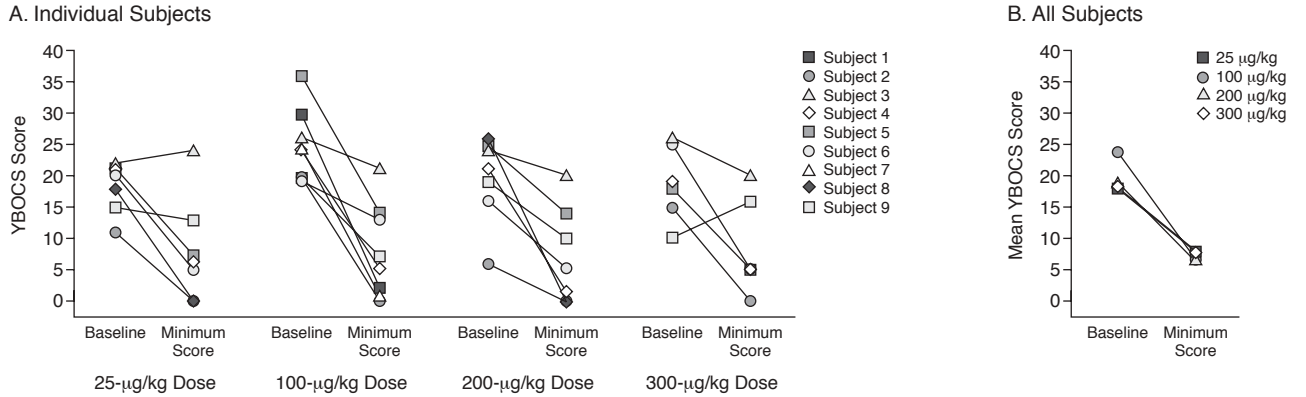
CONCLUSIONS

When administered in a supportive clinical environment, psilocybin appears to be safe and well tolerated. Psilocybin was associated with transient symptomatic reduction of OCD symptoms in subjects with treatment-resistant OCD.

These data result from a small proof-of-concept, phase I study designed to explore the safety for human consumption of 4 doses of psilocybin in a small sample of symptomatic OCD patients. The escalating dosing scheme was selected to allow exposure to increasingly higher doses only to individuals who had tolerated previous exposures. A smaller dose (VLD) was hypothesized to have negligible psychedelic effects and was introduced randomly at any time after the first dose. Subjects experienced stronger than anticipated response to this dose, as shown in Figure 3, and its clinical effects were also greater than anticipated. This response to VLD impedes the use of VLD as a placebo comparator, which clearly represents a major obstacle in our ability to explore clinical effects. Another methodological concern is the fact that the order of the doses was escalating, with the exception of VLD, which was inserted randomly and in double-blind fashion. This modified blind may have influenced expectations in both subjects and raters. Despite the obvious limitations from design and sample size, the data are suggestive of an acute benefit, worth exploring further.

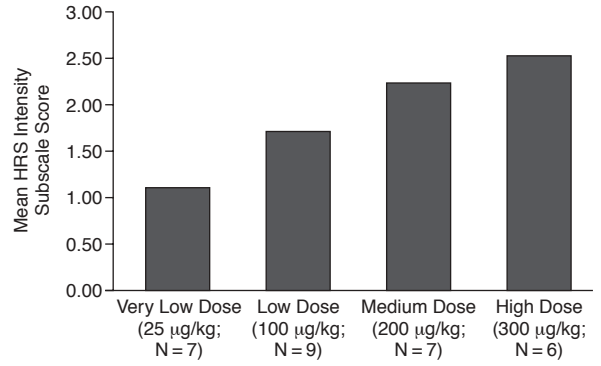
Although we understand the psychedelic mechanism of action of psilocybin, it is not clear which specific receptors or pathways may mediate antiobsessional responses. It may be possible for subjects to experience a decrease in symptoms by the mere artifact of mindset and setting, which are known to affect the psychedelic experience in itself; by the contextual expectation of improvement; or just by the distracting psychedelic effects or a "pleasurable experience." It should be noted that to some of the patients the exposure to a psychedelic agent was perceived as a stressful event; for others, testing repre-

Figure 2. Comparison of Baseline to Minimum YBOCS Score During Testing[a]



[a]Baseline = score obtained immediately prior to ingesting psilocybin, minimum = lowest score observed (4, 8, or 24 hours) after ingestion of psilocybin.
Abbreviation: YBOCS = Yale-Brown Obsessive Compulsive Scale.

Figure 3. Relationship Between Psilocybin Dose and Intensity of Hallucinogenic Experience



Abbreviation: HRS = Hallucinogen Rating Scale.

sented a time without access to the usual distractions that help reduce their obsessions; and for most, the overnight stay in the hospital represented a significant stressor. Therefore, the setting was ideal not for reduction of stress and obsessions, but rather for safety and monitoring purposes. This issue may have introduced selection bias by allowing participation by only those subjects who tolerated travel and overnight hospitalization.

There was, however, no clear dose-response relationship to the change in YBOCS score and no correlation of YBOCS score reduction to the perceived psychedelic intensity based on HRS total score or intensity subscale score.

Although the intent of this study was not to conduct psychedelic-facilitated therapy during testing, 5 of the subjects readily described their experiences as very psychologically and spiritually enriching. Four subjects reported during HD profound positive transcendental experiences such as exploration of other planets, visiting past-life reincarnations, and interacting with deities.

Most subjects reporting symptom reduction experienced a period of relief that extended beyond the pharmacologically expected life of the drug and beyond the 24-hour rating (see Figure 1). This lingering effect, which extends clearly beyond the "high" or psychedelic state, raises a number of intriguing mechanistic questions. For example, does the effect result from a residual feeling of well-being due to the experience of temporary symptom distraction or "pleasure," from the psychological insights described above, or from changes in working memory and attention as reported previously, or is the effect directly pharmacologically mediated? Although the explanation is highly speculative, if these are prolonged pharmacologic effects, they may be related to a rapid adaptive cascade of events such as postsynaptic 5-HT receptor down-regulation or early gene expression.

A large body of evidence supports the down-regulation of 5-HT_{2A} receptors in response to hallucinogen administration in animal models and human subjects.[28] LSD has been reported to induce intracellular signal transduction changes that are different from endogenous 5-HT despite binding to the same receptor site.[29] In fact, LSD is reported to decrease gene expression in rat brain after single-dose administration, while no changes in expression of 5-HT_{1A}, 5-HT_{2A}, or 5-HT_{2C} were observed.[30] These changes in gene expression, although reported with a similar compound rather than with psilocybin, may result in physiologic alterations that explain the delayed effect described above. It is also possible that the early changes in gene expression may be different after repeated administration of LSD or similar compounds, leading to the known down-regulation of 5-HT_{2A}.[28]

Ingestion of psilocybin and similar substances will facilitate subjects' experiencing of altered states of consciousness and may lead to the development of powerful insights and profound existential and spiritual questions. Administration of these substances therefore should be approached with caution to minimize exposure to individuals who are vulnerable to psychosis or overvalued ideas. Researchers should carefully consider the subject's mindset prior to exposure, address concerns developed during the psychedelic experience through careful debriefing, and secure a source of supportive continuity afterward. In spite of these concerns, given that OCD is associated with a great deal of human suffering and societal burden, and that treatment-resistant OCD represents a valid indication for irreversible brain surgery, it may be reasonable to consider psilocybin, with its potential benefit, a less burdensome alternative and one worth investigating further.

In summary, this study confirms and extends anecdotal reports of acute reduction in OCD symptoms with exposure to psilocybin. Given the chronicity and disease burden of OCD and the high rate of insufficient response to currently approved treatments, future studies involving traditional blinded, randomized, placebo-controlled methodology should explore the efficacy of and duration of therapeutic benefit from a more prolonged exposure to repeated doses of psilocybin in patients with OCD.

Drug names: bupropion (Wellbutrin and others), clomipramine (Anafranil and others), desipramine (Norpramin and others), fluoxetine (Prozac and others).

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