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High dose psilocybin is associated with positive subjective effects in healthy volunteers

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Abstract

Aim: The aim of the current study was to investigate the relationship between escalating higher doses of psilocybin and the potential psilocybin occasioned positive subjective effects.

Methods: Healthy participants (n=12) were given three escalating doses of oral psilocybin (0.3 mg/kg; 0.45 mg/kg; 0.6 mg/kg) or (18.8–36.6 mg; 27.1–54.0 mg; 36.3–59.2 mg) a minimum of four weeks apart in a supervised setting. Blood and urine samples, vital signs, and electrocardiograms were obtained. Subjective effects were assessed using the Mystical Experience Questionnaire and Persisting Effects Questionnaire.

Results: There was a significant linear dose-related response in Mystical Experience Questionnaire total score and the transcendence of time and space subscale, but not in the rate of a complete mystical experience. There was also a significant difference between dose 3 compared to dose 1 on the transcendence of time and space subscale, while no dose-related differences were found for Mystical Experience Questionnaire total scores or rate of a mystical experience. Persisting Effects Questionnaire positive composite scores 30 days after completion of the last dose were significantly higher than negative composite scores. Persisting Effects Questionnaire results revealed a moderate increase in sense of well-being or life satisfaction on average that was associated with the maximum Mystical Experience Questionnaire total score. Pharmacokinetic

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measures were associated with dose but not with Mystical Experience Questionnaire total scores or rate of a mystical experience.

Conclusions: High doses of psilocybin elicited subjective effects at least as strong as the lower doses and resulted in positive persisting subjective effects 30 days after, indicating that a complete mystical experience was not a prerequisite for positive outcomes.

Keywords

Psilocybe; psilocybin; psilocin; hallucinogen; psychedelic; entheogen; mystical experience; altered states of consciousness

Introduction and background

Psilocybin (4-phosphoroyloxy-*N,N*-dimethyltryptamine) is a naturally-occurring tryptamine that was first isolated from *Psilocybe* mushrooms in 1958 (Hofmann et al., 1958b), followed by *de novo* synthesis the same year (Hofmann et al., 1958a). Psilocybin and drugs such as dimethyltryptamine (DMT), mescaline, and lysergic acid diethylamide (LSD) have been categorized as classical “psychedelics” or “hallucinogens" (Nichols, 2016). These agents produce psychoactive effects that have been characterized as forming an intense dream-like state with colorful visual illusions, changes in auditory, tactile, olfactory, gustatory, and kinesthetic perceptions, altered perceptions of time and space, changes in body image, and sensations including ego dissolution, and intense mood changes ranging from feelings of wonder and bliss to sadness and grief (Liechti, 2017; Nichols, 2016). Because these drugs are reported to facilitate a spiritual or mystical experience in some people, they have also been referred to as entheogens, which suggests an altered state of consciousness that "generates the divine within" (Ruck et al., 1979).

Although early research with psilocybin demonstrated its potentially useful effects, it was classified as a controlled substance, placed in Schedule I in 1970, and effectively removed from clinical use or scientific study. After a research hiatus lasting several decades in the USA, scientific interest has grown in the resumption of research exploring the clinical safety and efficacy of psilocybin. Early research suggested that psilocybin administered in an appropriately controlled and supportive setting can have long lasting positive psychological effects (Pahnke, 1963). This has led to the examination of the role of the “mystical experience” in mediating the positive psychological effects, the defining features of which include feelings of unity, sacredness, ineffability, peace and joy, and transcending time and space (Maclean et al., 2012). In healthy volunteers, the intensity of the mystical experience has been associated with the degree and duration of the meaningfulness generated from the psilocybin experience (Griffiths et al., 2006, 2008, 2011), and long-term increases in the personality trait of openness (MacLean et al., 2011). Similar long-term positive effects have been observed in clinical studies showing a decrease in depressive and anxiety symptoms (Carhart-Harris, et al., 2016; Griffiths et al., 2016; Grob et al., 2011; Ross et al., 2016) and abstinence from addictive substances (Bogenschutz et al., 2015; Johnson et al., 2014). While these studies provide evidence of the potential therapeutic application of psilocybin, little is known about the potential positive effects achieved beyond the 20–30 mg/70 kg (0.28–0.43 mg/ kg) dose range used in the majority of these studies. This may be particularly relevant

for non-naïve individuals and those with substance-use disorders who may require a higher dose to achieve a sufficient intensity and outcome (Bogenschutz et al., 2015).

Toward this aim, the University of Wisconsin-Madison completed a Phase I study to determine the pharmacokinetics and demonstrate the safety of escalating doses of psilocybin (Brown et al., 2017). The primary objective of this current paper was to investigate the relationship between these escalating higher doses of psilocybin and the potential psilocybin-occasioned positive subjective effects using the Mystical Experience Questionnaire (MEQ) and Persisting Effects Questionnaire (PEQ).

Methods

Participants

Details of eligibility criteria have been published elsewhere (Brown et al., 2017) but, in general, participants were required to be medically and psychologically healthy. They also had to have at least one self-reported prior positive or meaningful psychedelic drug experience. Participants were recruited by word of mouth and also learned of the study through ClinicalTrials.gov, a registry of clinical trials published by the United States National Library of Medicine (NCT02163707). One hundred and twenty-five interested individuals contacted the study team and completed a telephone screening. Ninety-five individuals did not meet phone screen eligibility or were not interested in participating after hearing more about the study. Thirty individuals passed the phone screen and were further screened in-person for entry into the study. All qualifying participants provided written informed consent at the screening visit. Participants were evaluated for general medical and psychological health, adequate venous access, and prior meaningful experience with psychedelics. General medical health was assessed at the Clinical Research Unit (CRU) at the University of Wisconsin Institute for Clinical and Translational Research (ICTR) by completing a physical examination with a nurse practitioner or study physician; drawing blood for a complete metabolic panel, creatine kinase, and complete blood count; obtaining a urine sample for urinalysis, drug screen and pregnancy test; and having an electrocardiogram (ECG). Venous access was assessed through placement of an intravenous (IV) catheter. General psychological health was assessed at the University of Wisconsin-Madison School of Pharmacy by a licensed psychologist using the Structured Clinical Interview for DSM-IV Axis I Disorders Non-patient Edition (SCID-I NP) First et al., 2010) rule out any psychiatric disorders or family history thereof (See Brown et al., 2017). Seventeen people were excluded due to inadequate venous access, lack of meaningful prior experience, staff clinical judgment, uncontrolled hypertension, positive psychiatric family history, abnormal ECG, inability to make time commitment, or having another disqualifying disorder. Thirteen qualifying participants were enrolled in the study and 12 participants were evaluated and included in the statistical analyses (Figure 1; see Supplementary Material Table 1 for CONSORT diagram.)

Human subjects and safety

The study was conducted in accordance with the protocol approved by the University of Wisconsin Health Sciences Institutional Review Board. To monitor safety and data integrity,

the study was monitored by an independent data monitoring committee on a biannual basis and study data were routinely audited by an independent study monitor.

Study design and overview

The data for the current analyses come from a recently published open-label study (Brown et al., 2017) with the primary objective of evaluating the pharmacokinetics of escalating doses of psilocybin as the base in healthy adult volunteers. Participants were each given up to three doses of psilocybin in a controlled and supervised setting at the University of Wisconsin-Madison School of Pharmacy. Psilocybin was administered as a capsule taken orally. The dose of psilocybin given was based on weight, and the amount of psilocybin was increased for each consecutive dose with a minimum of four weeks between each dose. Participants received 0.3 mg/kg (dose 1), 0.45 mg/kg (dose 2), and 0.60 mg/kg (dose 3) resulting in dose ranges of 18.8–36.6 mg, 27.1–54.0 mg, and 36.3–59.2 mg, respectively. The first two dose levels have been evaluated in previous research studies (Griffiths et al., 2006, 2011). The third and highest dose has not been previously reported in research. Participants were accompanied at all times by two study monitors, or guides, one male and one female, in the session room for eight hours after ingesting the psilocybin. Participants were then escorted to the ICTR CRU at University of Wisconsin Hospital for an overnight stay with discharge to a support person 24 h post-dose.

Drug synthesis and qualification

Pure psilocybin for use in this study was synthesized in the laboratory of NV Cozzi of the University of Wisconsin-Madison School of Medicine and Public Health. Confirmation of chemical structure and purity and potency assessments of this material were performed by the University of Wisconsin-Madison School of Pharmacy Zeeh Pharmaceutical Experiment Station. Capsules containing psilocybin were individually prepared at Zeeh Station for each participant based on bodyweight.

Preparation for drug sessions

The preparation of the participant is referred to as the “set,” and the environment the “setting.” It is hypothesized that the control of the set and setting is important for maximizing participant safety, especially psychologically, during, and after a psilocybin session (Griffiths et al., 2006; Johnson et al., 2008; Leary et al., 1963; Nichols, 2004; Studerus et al., 2012).

Preparing the environment (setting).

All psilocybin sessions took place in a room that was specifically designed for this study at the University of Wisconsin-Madison School of Pharmacy (see photograph in online Supplementary Material). The room was furnished with comfortable living room furniture, including a large sofa where the participant typically sat or reclined, two armchairs for the guides, and an adjacent restroom. Food and beverages were available during each session. The room was also equipped with an audio system connected to wireless headphones through which participants could listen to a pre-selected playlist of music arranged by the study team, and the content of which has been utilized in previous studies involving

supervised psilocybin administration. All participants were provided the same playlist which was played at each of the three visits. Participants could remove their headphones at any time, though this rarely occurred for any extended period. Video and audio recording capabilities were also used for reference, teaching, and security purposes. Eyeshades were provided to participants to minimize outward distractions and facilitate inward focus. Rescue medications were available on-site in a lock box with a physician on call at all times to direct administration of emergency medication if necessary. Emergency medications available included lorazepam, diazepam, haloperidol, nitroglycerin, and carvedilol; however, there was no indication for rescue medication use among the 12 participants during their psilocybin sessions.

Preparing the participant (set).

Each participant was paired with two trained guides, one male and one female. Participants completed approximately 6–8 h of preparatory counseling with her/his guides prior to the first dose of psilocybin. Preparatory counseling sessions were generally structured as four meetings of about two hours each, and were carried out in accordance with previously published guidelines for safety in human hallucinogen research (Johnson et al., 2008). The overall purpose of the preparatory sessions was to establish rapport and develop trust between the participant and guides in order to facilitate a safe psilocybin experience. During the preparatory phase, guides incorporated elements of life review and generous listening with unconditional positive regard (Maercker and Bachem, 2013; Remen, 1996; Richards, 2015). Preparatory sessions included discussion of past psychedelic experiences and any immediate or late adverse effects, which provided an opportunity for guides to educate participants on the common effects of psilocybin, specifically at high doses. Additionally, coping skills, such as breathing exercises, use of mantra, focusing techniques, and requesting physical or verbal support were discussed and practiced. The nursing staff at the CRU were provided with in-service education instruction on how to continue the atmosphere of established set and setting during the participant's post-dosing hospitalization. This allowed the CRU nurses to obtain additional pharmacokinetic data points (at 12, 18, and 24 h) while allowing the study participant to quietly reflect on their psilocybin experience during their overnight stay. Prior to the first psilocybin session, participants met all of the study personnel with whom they might have contact while experiencing the effects of psilocybin so as to avoid having to meet anyone new during the psilocybin experience. The morning after each dose, participants were required to attend an integration session with the guides, in which they could reflect on and talk about their experience, before being picked up by their support person and returning to their daily life. Following the first dose, participants met with guides for about two hours in preparation for the second dose, and likewise after the second dose in preparation for the third dose.

Drug sessions

On the morning of the psilocybin session day, participants met a study coordinator at the University of Wisconsin Hospital CRU where he/she was admitted for an inpatient stay. Upon arrival participants were offered a light breakfast which occurred at least an hour prior to the start of the psilocybin session. A nurse then obtained vital signs, collected a urine sample for pregnancy testing and drug screening, placed ECG electrode patches, and

inserted an IV catheter with saline lock extension. After the admission process, the study coordinator walked with the participant to the School of Pharmacy for the psilocybin session. During the session, participants were invited to lie down on the sofa with eye-shades and headphones through which they could listen to a pre-selected musical program. Participants were encouraged to focus their attention inward. During the psilocybin session, the guides maintained a mindful and attentive presence, provided reality orientation, and provided an interpersonally warm relationship with firm ethical boundaries to "minimize anxiety, dysphoria or overwhelming distress" (Richards, 2015). Participants were permitted to use the private adjacent restroom when needed, and were offered food and beverages. Final hours in the session room were generally quiet and spent in meditation or with minimal, light discussion. At the close of the session participants were assessed to ensure readiness for transfer to the hospital CRU. After a minimum of eight hours in the School of Pharmacy session room post-psilocybin ingestion, participants were walked back to the CRU for overnight sampling and observation. Upon arriving at the CRU in the evening, participants were seen by a nurse practitioner or study physician for a complete physical examination. Participants were discharged from the CRU the following morning, 24 h after ingesting the psilocybin. After discharge, participants were accompanied back to the session room to meet with the guides for an integration session prior to being picked up by their designated support person.

Measures assessed throughout the drug session

Blood pressure, pulse, temperature, and ECG monitoring were performed for the purposes of safety and pharmacodynamic analysis during each psilocybin session. Additionally, blood and urine samples were collected over a 24-hour period to be used for pharmacokinetic analysis not described in this paper (Brown et al., 2017).

Participant follow-up

Participants were contacted by telephone seven days after each psilocybin session and again 30 days post-dose. Participants completed a final end of study visit in person 30 days after completing the final psilocybin dose. At each follow-up participants were asked about any changes in medications or medical history and were monitored for adverse events (AEs). All adverse events experienced by participants were collected and recorded using National Institutes of Health (NIH) Department of Health and Human Services Common Terminology Criteria for Adverse Events (CTCAE).

Questionnaires

MEQ.—After each psilocybin dose, on the evening of the psilocybin session day, participants completed the States of Consciousness Questionnaire (SOCQ). The SOCQ is a 100-item assessment used to characterize the consciousness-altering effects of psilocybin. Each item is rated on a six-point scale (0=none, not at all; 1=so slight cannot decide; 2=slight; 3=moderate; 4=strong (equivalent in degree to any previous strong experience or expectation of this description); 5=extreme (more than ever before in my life and stronger than 4)). Thirty of the questions embedded within the SOCQ make up the 30-item revised Mystical Experience Questionnaire (MEQ30). The MEQ30 was derived from the Pahnke-

Richards mystical experience questionnaire (MEQ43) and has been shown to be sensitive to psilocybin (Griffiths et al., 2006a; Pahnke, 1963; Richards et al. 1977; Turek et al., 1974) and LSD (Liechti et al., 2017). The MEQ30, which has been recently validated in experimental sessions with psilocybin, contains four subscales: mystical, deeply felt positive mood (joy, peace, love), transcendence of time and space, and ineffability (claim of difficulty in describing the experience in words) (Barrett et al., 2015). The "mystical" subscale includes items from the internal unity (pure awareness and/or a merging with ultimate reality), external unity (unity of all things, all things are alive, all is one), noetic quality (claim of an encounter with the ultimate reality, more real than everyday reality), and sacredness scales of the MEQ43. Data from each of the four MEQ30 subscales were expressed as a percentage of the maximum possible score. A "complete" mystical experience was defined as scoring greater than or equal to 60% on each of the four subscales: mystical, transcendence of time and space, positive mood, and ineffability; the criteria used were determined based on previous studies (Griffiths et al., 2006, 2011; Pahnke, 1969).

PEQ.—Participants completed the PEQ 30 days after completion of the last psilocybin session at the end of study visit. The PEQ is a 143-item questionnaire that seeks information regarding changes in attitudes, mood, behavior, relationships, and spiritual experience. The items on the PEQ have been shown to be sensitive to the effects of psilocybin 14 months after the experience (Doblin, 1991; Griffiths et al., 2006, 2011; Pahnke, 1969) and to the effects of LSD one and 12 months after the experience (Schmid and Liechti, 2017). The questionnaire is divided into six categories (attitudes about life, attitudes about self, mood changes, relationships, behavioral changes, spirituality) and three additional questions. The items from the six categories are each rated on a six-point scale (0=none, not at all; 1=so slight cannot decide; 2=slight; 3=moderate; 4=strong; 5=extreme, more than ever before in your life and stronger than 4). Twelve scores result from the items contained within the six categories, with each category giving rise to two scores: a positive score and a negative score. Each score is expressed as a percentage of the maximum possible score within the positive or negative section of that category. A high positive score means that the participant reported significant positive changes in that area of his or her life, whereas a high negative score in a category means the participant has experienced significant negative changes in that area. The three additional questions at the end of the questionnaire were each scored separately:

1. How personally meaningful was the experience? (rated from 1–8, with 1=no more than routine everyday experiences; to 8=the single most meaningful experience of my life);
2. Indicate the degree to which the experience was spiritually significant to you? (rated from 1 to 6, with 1=not at all; to 6=the single most spiritually significant experience of my life);
3. Do you believe that the experience and your contemplation of that experience have led to change in your current sense of personal well-being or life satisfaction? (rated from + 3=increased very much; to −3=decreased very much).

We used the same methods as previous studies for calculating the PEQ scores (Griffiths et al., 2011).

Analysis

Calculation of drug concentration.—Psilocybin and psilocin concentrations were measured in plasma and urine using a validated assay incorporating high-performance liquid chromatography (HPLC) and mass spectrometry performed by Covance Laboratories (Madison, Wisconsin, USA). The lower limit of detection of psilocybin and its active metabolite psilocin in plasma and urine were 0.5 and 5.0 ng/ mL, respectively. As expected due to the rapid dephosphorylation to psilocin (Hasler et al., 1997; Horita and Weber, 1961), no psilocybin was detected in either plasma or urine. The maximum plasma concentration of psilocin (C_{max}) was determined by inspection. The trapezoidal method was used to calculate the area under the curve (AUC) for plasma concentration of psilocin. The AUC was determined through the 24 h of sample collection. Extrapolation of AUC beyond the 24-hour collection time was not utilized for this analysis, since the administration of the MEQ questionnaire was done within the 24 h after each dose. Measurable plasma psilocin concentrations were only detectable at 24 h in seven of the 33 psilocybin doses, and all of these concentrations were below 1 ng/mL.

Statistical analyses.—Continuous outcomes measured at each dose consisted of the four subscales of the MEQ (mystical, positive mood, transcendence of time and space, and ineffability), total MEQ score, rate of mystical experience, and pharmacokinetic AUC and C_{max} values. Dichotomous outcomes consisted of occurrence of headache, tachycardia or hypertension, and attainment of a full mystical experience. Continuous outcomes were compared between dose groups with repeated analysis of variance (ANOVA) models using dose group as a fixed effect and participant as a random effect. Incidence of the dichotomous variable between dose groups was compared with mixed-effects logistic-regression models with dose group as a fixed effect and participant as a random effect. If significant differences were found between dose groups then a post-hoc mixed effects analysis with Tukey adjusted *p*-values was used to determine differences between dose groups. Data from the PEQ were collected once per participant 30 days after each participant's last dose of psilocybin. Paired *t*-tests were used to determine if positive PEQ composite scores were significantly different than the analogous negative PEQ composite scores. Analyses were conducted using R for statistical computing (R Core Team, 2013) with packages nlme (Pinheiro et al., 2016), (Lenth, 2016), geepack (Højsgaard et al., 2016), ppcor (Kim, 2015). All tests were conducted at an *a-priori* 0.05 significance level.

Results

Participants

A summary of study participants' characteristics is presented in Table 1. Participants' median age (range) was 43 (24–61) years, and participants were predominately male (83.3%) and Caucasian (75.0%). Twelve participants completed dose 1, 11 completed dose 2, and 10 completed dose 3 (see Brown et al., 2017). There were no serious adverse events.

Mystical experience questionnaire

Estimated means (95% confidence interval (CI)) from the MEQ are summarized in Table 2. Total MEQ scores increased with each dose from dose 1 (mean: 0.58, 95% CI: 0.46–0.71), to dose 2 (0.64, 0.51–0.77), to dose 3 (0.70, 0.56–0.83), but this difference was not statistically significant (p=0.209). The transcendence of time and space subscale was significantly higher after dose 3 (0.73, 0.58–0.88) than after dose 1 (0.52, 0.40–0.68; $t(19)$= −3.36, p=0.009). There were no other significant differences in the MEQ subscale responses between doses; nor were there any differences in the rate of complete mystical experience among the three doses, with four out of 12 (33.3%) occurring after dose 1, five out of 11 (45.5%) after dose 2, and three out of 10 (30.0%) after dose 3 (p=0.547). Lastly, dose level (mg) was positively associated with total MEQ score ($t(20)$=2.38, p=0.002) and the transcendence of time and space subscale ($t(20)$=3.46, p=0.027). Dose was not associated with the rate of a mystical experience or any other subscale of the MEQ.

Pharmacokinetics

See Brown et al. (2017) for a full report of the pharmacokinetic analysis. Briefly, the AUC for drug concentration curve from 0–12 h was proportional to dose. The average (95% CI) AUC (0–12 h) for dose 3 was 151 ug*h/mL (127–174), which was significantly higher than dose 2 (124 ug*h/mL, 101–148, $t(19)$=−3.16, p=0.014) and dose 1 (77 ug*h/mL, 54–100, $t(19)$=−8.94, p<0.001). The AUC for dose 2 was significantly higher than dose 1 ($t(19)$= −5.97, p<0.001). C_{max} was significantly lower in dose 1 (16.9 ug/mL, 11.4–22.4) compared to dose 2 (28.1 ug/mL, 22.4–33.8, $t(19)$=−3.55, p=0.006) and compared to dose 3 (35.9 ug/mL, 29.9–41.9, $t(19)$=−5.85, p<0.001). C_{max} was not significantly different between dose 2 and dose 3 ($t(19)$=−2.36, p=0.071). The AUC was positively associated with the transcendence of space and time subscale (t(20)=3.07, p=0.006) but not associated with total MEQ score or incidence of a complete mystical experience. C_{max} was not associated with any MEQ variable. Lastly, dose was positively associated with AUC ($t(20)$=8.06, p<0.001) and C_{max} ($t(20)$=5.44, p<0.001).

Persisting effects questionnaire

The positive and negative PEQ composite scores are summarized for all of the categories of responses in Table 3. Average positive composite scores were significantly higher (range: 0.58–0.67) than the corresponding average negative composite scores (range: 0.03–0.7) in all response categories (all p<0.001). On the question, “How personally meaningful was the experience?,” two (16.67%) rated it as the single most meaningful experience and seven (58.33%) rated it as among the five most meaningful experiences. On the question, “How spiritually significant was the experience?,” four (33.3%) rated it as the single most spiritually significant and six (50%) rated it among the five most spiritually significant. The final question of the PEQ asks: “Do you believe that the experience led to change in your current sense of personal well-being or life satisfaction?” Possible responses range from −3=“Decreased very much,” to +3=“Increased very much,” with 0=No change. The average response was 2.1 (standard deviation (SD)=1.6), which was significantly greater than 0, p=0.001. Seven participants (58.3%) responded “Increased very much,” three participants (25.0%) responded “Increased moderately,” one responded, “No change,” and one

participant responded, “Decreased moderately.” A full summary of results is reported in Supplementary Material Figure 2. There was a significant association between the final question of the PEQ and the maximum MEQ score obtained across all three doses (p=0.05). This result was not significant upon controlling for the dose number (e.g. 1, 2, or 3) associated with maximum MEQ score (p<0.096), though it should be noted that dose number was not associated with maximum MEQ or the PEQ final question 3. No other PEQ variable was associated with the MEQ (minimum, maximum, or mean across all three doses).

Discussion

Psilocybin has been shown to produce dose-dependent positive subjective changes in mood, perception, and psychological states in healthy participants (Studerus et al., 2011). Results from the current study, in which the immediate and persisting subjective effects of psilocybin were evaluated, revealed a significant linear dose-related response in MEQ total score and the transcendence of time and space subscale, but not in the rate of a complete mystical experience. Comparisons between the three doses revealed a significant difference between dose 3 and dose 1 on the transcendence of time and space subscale, though there were no differences in MEQ total scores or rate of a mystical experience. PEQ positive composite scores 30 days after completion of the last dose were significantly higher than negative composite scores. PEQ results also revealed a moderate increase in sense of well-being or life satisfaction on average that was associated with the maximum MEQ total score. AUC and C_{max} were associated with dose; and with the exception of a positive association between AUC and the transcendence of time and space subscale, there were no other associations between pharmacokinetic and subjective measures. Results of the current study suggest that even without differential effects of dose on the rate of a “complete" mystical experience, positive persisting effects were achieved following these higher doses of psilocybin.

The results of the current study showed a slightly lower rate of complete mystical experiences compared with some previous studies using psilocybin (Griffiths et al., 2006, 2011, 2018) but are similar to those of LSD in healthy participants and patients (Liechti et al., 2017). A complete mystical experience was defined as scoring ≥60% on each of the four subscales: mystical, transcendence of time and space, positive mood, and ineffability. Only 36% of the doses (12 of 33) facilitated a complete mystical experience. There was no significant difference in the rate of complete mystical experience across the three high doses with four (33.3%) occurring after dose 1, five (45.5%) after dose 2, and three (30.0%) after dose 3 (p=0.547). A number of considerations for our findings are offered below.

It would be reasonable to infer from previous reports of dose-related mystical-type experiences (Griffiths et al., 2011; Studerus et al., 2012) that a similar pattern would have been observed in the current study. While we did observe a dose-related response on the MEQ total score, the rate of mystical experiences was not associated with dose, nor did it differ between doses. One possible explanation for these findings, particularly at 0.60 mg/kg, could be the result of a ceiling effect: for some participants, maximum subjective effects were achieved at the 0.30 mg/kg or 0.45 mg/kg doses. Specifically, three out of four

participants who had a mystical experience at 0.30 mg/kg achieved one at 0.45 mg/kg, however, only one of these participants had a mystical experience at 0.60 mg/kg (see Supplementary Material Table 1). This may also be the case for the two participants who only had one mystical experience at either 0.30 mg/kg. or 0.45 mg/kg, respectively. Participants were exposed to higher concentrations of psilocybin with each escalating dose, as shown by the significant positive linear increase in AUC and C_{max} of psilocin with increasing doses of psilocybin (Brown et al., 2017). Future research investigating underlying causes of a ceiling effect in psilocybin will be important, particularly when developing therapeutic protocols.

The requirements that each participant not only be non-naive to psychedelics, but also that at least one of their prior experiences was deemed to be meaningful could have also contributed to a lower rate of mystical experience. We speculate that while findings from the PEQ (see below) indicated that the majority of participants rated their psilocybin experience in the study to be highly positive and meaningful, it is possible that some of our participants were relatively less sensitized to the effects of psilocybin compared to psychedelic naïve individuals. This notion may be consistent with pooled data across 23 experimental psilocybin studies showing significantly increased visual changes, disembodiment, and changed meaning of percepts (Studerus et al, 2012) in psychedelic-naïve participants. In contrast, no difference in the acute effects of LSD was found between naïve participants and those with up to 10 previous experiences (Schmid et al., 2015). is also possible that the PEQ results were affected by their prior positive experience (e.g. expectancy; learned ability to achieve meaning). Thus, more direct comparisons between non-naive and naïve participants with regard to the intensity of the acute effects, expectations, and their subsequent ability and/or efforts to personally integrate their experience would be informative.

Another characteristic of our sample which could have affected the validity of their responses on the SOCQ and the embedded MEQ, is that several of the participants in our study were proclaimed atheists, had limited or no involvement in a spiritual practice, or had belief systems outside the Judeo-Christian traditions. The MEQ includes several items referring to Judeo-Christian phenomena. These include the “sacredness” dimension of the mystical factor (e.g. “sense of reverence;” “sacred and holy”) in addition to other SOCQ items not included in the MEQ (e.g. “visions of events in the life of Christ”) that may be incongruous to the belief system of some of our participants. While sensitivity analysis involving recalculation of the MEQ without the “sacredness” dimension did not change the rate of a mystical experience, it is possible that frustration when encountering some of these items affected their pattern of responding on these measures. Additionally, the fact that some of our participants did not engage in a spiritual practice also limits our comparisons to studies where engagement in a spiritual practice was part of their inclusion criteria (Griffiths et al., 2006, 2008, 2011).

Given the exploratory nature and novelty of progressing to a never-reported high dose of psilocybin (i.e. 0.60 mg/kg), an important methodological decision based on our cautious approach to the study design was to implement an escalating weight-based dose design without controlling for dose sequence effects through counterbalancing. Thus, it is unknown whether a first dose at 0.60 mg/kg would have been associated with different scores on

subjective measures. Griffiths, et al (2011), observed dose sequence effects on follow-up measures, though not acutely on the MEQ when participants were randomized to either an ascending or a decending dose sequence. Also, the highest dose in that study was equivalent to 0.45 mg/kg; and consistent with our study, did not find a significant difference from 0.30 mg/kg to 0.45 mg/kg in the total MEQ score, or on any of the subscales, except transcendence of time and space.

It also remains unknown if the interval between consecutive doses is associated the subjective effects of psilocybin. Consecutive doses were administered on average four weeks apart for each participant, thus a shorter or longer interval between doses may be important to consider in future studies. Another possibility was the invasive nature of our sampling procedure, including frequent blood sampling through an IV catheter or using venipuncture, blood pressure, and temperature measurements, urine collection, and intermittent use of a 12-lead ECG monitoring system. Anecdotally, however, participants reported that these measures were not explicitly disruptive, often welcoming these measurements as a tangible reminder of their contribution to science.

Consistent with Griffiths et al. (2011), the only MEQ subscale that showed a significant increased effect at dose 3 relative to dose 1 and positive association with AUC in our study, was transcendence of time and space. It is possible that the subjective effects of time were the only aspects of the psychedelic experience that became distinguishably stronger, relative to the remaining MEQ subscales (mystical, positive mood, ineffability). In addition to the reasons described above (ceiling effect, non-naïvety of the participants; not explicitly spiritual), this may be related to the transcendence of time and space subscale, which contains less religious and/or spiritual wording and thus may be less affected by any possible validity issue in our sample.

Despite the lower rate of a complete mystical experience, participants reported profound positive changes evidenced by the PEQ results and as similarly reported in a study using LSD (Schmid and Liechti, 2017). Average positive composite scores were significantly higher (range: 0.58–0.67) than the corresponding average negative composite scores (range: 0.03–0.7) in all response categories (all $p<0.001$). In addition, while the majority of PEQ variables did not correlate significantly with minimum, maximum, or mean MEQ, the PEQ Final Question 3 (“Did the experience change your sense of well-being or life satisfaction?”) was associated with maximum MEQ ($p=0.05$), in effect suggesting that it may not be solely the “complete” mystical experience itself that leads to important positive effects and outcomes (Liechti et al., 2017).

Additional limitations are worth considering. With only 12 volunteers and 33 evaluable sessions, we likely had limited statistical power to capture possible differences between doses and larger dose related effects on subjective measures. Also, given that the probability that difficult and challenging psychological experiences increase at higher doses (Griffiths et al., 2011; Studerus et al., 2012), it would be informative to measure these experiences (Barrett et al., 2016; Carbonaro et al., 2016) future studies to examine their impact on the rate of mystical experience.

In the current study, every dose was considered a “high dose” based on previous research, with dose 3 (0.60 mg/kg,) providing the highest dose of psilocybin recorded in a research setting. Studying high doses may be relevant for substance-use disorders (e.g. alcoholism and opioid addiction), in which these individuals may need higher doses of psilocybin to benefit from its effects (Bogenschutz et al., 2015). Importantly, the results of this study show that the 0.60 mg/kg dose elicited results at least as strong as the 0.30 and 0.45 mg/kg doses, and resulted in no serious adverse events despite the invasive nature of the pharmacokinetic sampling in this study. Notably, this study also continues to underscore how careful screening and spending adequate time to develop trust and rapport allowed for highly positive outcomes.

In conclusion, while there were no statistically significant differences in the rate of complete mystical experiences at 0.60 mg/ kg versus 0.45 mg/kg or 0.30 mg/kg doses of oral psilocybin, there were significant dose-related differences on the transcendence of time and space MEQ subscale. Multiple factors may have contributed to the lack of dose-related difference in rates of mystical experience including ceiling effects, sample characteristics, and limitations of the MEQ. Participants reported significant positive persisting effects 30 days after their final dose and an average moderate increase in their overall sense of well-being or life satisfaction, which suggests that the “complete” mystical experience may not necessarily be a prerequisite for positive outcomes in certain samples (Griffiths et al., 2006; Schmid and Liechti, 2017). Further research discerning the complex relationship between methodological and sample characteristics and the underlying mechanisms (e.g. neurochemical and biological, psychological, and psycho-spiritual) associated with the positive effects of psilocybin will be important, particularly when developing therapeutic protocols for clinical populations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Study demographics.

Gender	
Male	10
Female	2
Race/ethnicity	
White	9
Native American	2
Native Hawaiian/Pacific Islander	1
Age (years)[a]	43 (24–61)
Psilocybin dose given (mg)[b] (*n*=33)	
Dose 1 (0.30 mg/kg)	21.3 (18.8–36.6)
Dose 2 (0.45 mg/kg)	31.1 (27.1–54.0)
Dose 3 (0.60 mg/kg)	43.0 (36.3–59.2)

[a]Median years

[b]median mg; ranges included in parentheses.

Table 2.

Summary of results by dose.

	Dose 1 (*n*=12)	Dose 2 (*n*=11)	Dose 3 (*n*=10)	*F*(2, 19)	*p*-Value
MEQ subscales					
Mystical (unity, noetic, sacred)	0.53 (0.37–0.69)	0.60 (0.44–0.76)	0.65 (0.48–0.82)	1.10	0.354
Positive mood	0.68 (0.56–0.80)	0.64 (0.51–0.77)	0.72 (0.58–0.85)	0.60	0.56
Transcendence of time and space	0.54 (0.40–0.68)	0.65 (0.51–0.79)	0.73 (0.58–0.88)	5.73	**0.011**
Ineffability	0.73 (0.62–0.85)	0.78 (0.66–0.90)	0.81 (0.69–0.94)	0.38	0.38
MEQ total score	0.58 (0.46–0.71)	0.64 (0.51–0.77)	0.70 (0.56–0.83)	1.70	0.209
Rate of complete mystical experience	33.3% (*n*=4)	45.5% (*n*=5)	30.0% (*n*=3)		
Pharmacokinetics					
AUC 0–12 h	77 (54–100)	124 (101–148)	151 (127–174)	41.8	**<0.001**
Maximum concentration (ng/mL)	16.9 (11.4–22.4)	28.1 (22.4–33.8)	35.9 (29.9–41.9)	17.5	**<0.001**

ANOVA: analysis of variance; AUC: area under the curve; CI: confidence interval; MEQ: Mystical Experience Questionnaire.

Results reported as estimated mean (95% CI) percentage of the maximum total score from the repeated measures ANOVA (RM-ANOVA).

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Table 3.

Summary of Persisting Effects Questionnaire (PEQ) composite scores.

PEQ category	Positive questions mean (SD)	Negative questions mean (SD)	*t*-Value (DF=11)	*p*-Value
Attitude toward life	0.64 (0.25)	0.07 (0.08)	7.87	**<0.001**
Attitude toward self	0.61 (0.25)	0.07 (0.09)	7.48	**<0.001**
Mood changes	0.61 (0.28)	0.03 (0.05)	6.79	**<0.001**
Relationships	0.58 (0.25)	0.04 (0.07)	7.18	**<0.001**
Behavioral changes	0.67 (0.31)	0.05 (0.12)	7.10	**<0.001**
Spirituality	0.61 (0.23)	0.03 (0.04)	8.82	**<0.001**

DF: degrees of freedom; SD: standard deviation.