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ORIGINAL INVESTIGATION

Subjective features of the psilocybin experience that may account for its self-administration by humans: a double-blind comparison of psilocybin and dextromethorphan

Theresa M. Carbonaro[1] · Matthew W. Johnson[1] · Roland R. Griffiths[1,2]

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Abstract

Rationale Although both psilocybin and dextromethorphan (DXM) produce psychedelic-like subjective effects, rates of non-medical use of psilocybin are consistently greater than DXM.

Objective New data are presented from a study of psilocybin and DXM relevant to understanding the features of psilocybin subjective effects that may account for its higher rates of non-medical use.

Methods Single, acute oral doses of psilocybin (10, 20, 30 mg/70 kg), DXM (400 mg/70 kg), and placebo were administered under double-blind conditions to 20 healthy participants with histories of hallucinogen use.

Results High doses of both drugs produced similar time courses and increases in participant ratings of peak overall drug effect strength. Nine subjective effect domains are proposed to be related to the reinforcing effects of psilocybin: liking, visual effects, positive mood, insight, positive social effects, increased awareness of beauty (both visual and music), awe/amazement, meaningfulness, and mystical experience. For most ratings, (1) psilocybin and DXM both produced effects significantly greater than placebo; (2) psilocybin showed dose-related increases; 3, DXM was never significantly higher than psilocybin; (4) the two highest psilocybin doses were significantly greater than DXM. These differences were consistent with two measures of desire to take the drug condition again.

Conclusions This analysis provides new information about domains of psilocybin subjective effects proposed to be related to its reinforcing effects (alternatively described as the "motivation" to use). Observed differences on these domains between psilocybin and DXM are consistent with the relative rates of non-medical use of psilocybin and DXM.

Keywords Psilocybin · Dextromethorphan · Hallucinogen · Psychedelic · Abuse liability · Reinforcing effects · Mood · Insight · Subjective experience · Mystical experience · Insightful experience · Humans

Introduction

Psilocybin and other classic psychedelic drugs have been used for their psychoactive effects for centuries if not millennia across various cultures (Wasson 1980; Metzner 2004). Epidemiological survey data in the USA for persons 12 or older indicates that lifetime use of psilocybin has been relatively modest and stable from 2002 to 2017 (mean 8.2%, range 7.8–8.6%; SAMHSA 2019). Anthropological and anecdotal reports indicate that some individuals may use psilocybin and other classic psychedelics repeatedly, but at low frequency (e.g., monthly or a few times a year), often in religious or spiritual ceremonial settings or in settings with therapeutic, religious, spiritual, or psychological insight intent (Metzner 2004; Labate et al. 2016; Pollan 2018).

The National Institute on Drug Abuse does not consider psilocybin to be addictive because it does not cause uncontrollable drug-seeking behavior (NIDA 2019 – Internet DrugFacts). In human studies, psilocybin does not reliably increase ratings on a classic measure of euphoria (MBG scale of the Addiction Research Center Inventory (ARCI) that has been used to predict drug abuse liability; however, psilocybin does increase ratings on a measure of dysphoria (LSD scale of the ARCI) that has been used to predict absence of abuse

✉ Roland R. Griffiths
rgriff@jhmi.edu

[1] Center for Psychedelic and Consciousness Research, Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, 5510 Nathan Shock Drive, Baltimore, MD 21224-6823, USA

[2] Department of Neuroscience, Johns Hopkins University School of Medicine, 5510 Nathan Shock Drive, Baltimore, MD 21224-6823, USA

potential (Martin 1973; Griffiths et al. 2006, 2011). Furthermore, psilocybin is not reliably self-administered by monkeys in a standard model used to assess drug abuse potential (Fantegrossi et al. 2004). Although psilocybin can produce tolerance in humans and animals, there is no evidence for withdrawal syndrome after termination of chronic administration (Martin 1973; Johnson et al. 2018). Psilocybin does not produce cross-generalization to classic drugs of abuse in animal drug discrimination models used to assess drug abuse potential (Johnson et al. 2018). Finally, although the actions of most drugs of addiction are mediated through an increase in dopaminergic brain activity (Adinoff 2004), this is not the case for psilocybin and most other classic psychedelics (Nichols 2016; Volkow et al. 2019).

Dextromethorphan (DXM) is sometimes used non-medically as a hallucinogen at high doses and, in a blinded study in participants with histories of hallucinogen use, was often mistakenly identified as psilocybin (Reissig et al. 2012). However, DXM, whose primary mechanism of action is blockade of excitatory amino acid *N*-methyl-D-aspartate (NMDA) receptors, is mechanistically different from classic psychedelics such as psilocybin whose actions are mediated at serotonin 2A receptors (Church 1990; Church et al. 1994; Nichols 2016). Epidemiological survey data in the USA for persons 12 or older indicates that lifetime use of DXM has been low from 2002 to 2017 (mean 0.05%, range 0.02–0.08%; SAMHSA 2019). Thus, non-medical lifetime use of DXM is only a small fraction of that of psilocybin.

The purpose of the present study was to examine aspects of the subjective effects of the psilocybin that might account for the seeming contradiction that psilocybin is used at modest rates non-medically while lacking features that typically are used to predict the non-medical use (i.e., abuse) of drugs. More specifically, this report presents new data from a previously conducted rigorously blinded comparison of the effects of placebo, three doses of psilocybin, and a high dose of DXM in participants with histories of use of classic psychedelics (Carbonaro et al. 2018; Barrett et al. 2018). The rationale for this approach was that comparison of a range of different qualitative subjective effects of psilocybin and DXM at doses that produce comparable effects on ratings of overall magnitude of drug effects would provide unique insight into the domains of subjective effects of psilocybin that might account for its non-medical use.

Methods

Participants

The participant population has been described in more detail previously (Carbonaro et al. 2018). Briefly, the 20 participants (11 females) had a mean age of 29 years (range = 22–43 years). All were medically and psychologically healthy and had a history of psychedelic drug use: use of both classic hallucinogens (mean = 61 uses; range 16–183) and dissociative anesthetic hallucinogens (mean = 19; range = 1–154). Nineteen participants were Caucasian (95%) and one was Asian American. All had a high school degree or higher with 50% having a Bachelor's degree or higher.

General procedures

General procedures have been described in more detail previously (Carbonaro et al. 2018). Briefly, the study was approved by the Institutional Review Board of the Johns Hopkins University School of Medicine. Sessions took place in an esthetic, living room–like environment. For most of the time during the sessions, participants were instructed to lie down on a couch while wearing eyeshades and using headphones through which a program of classical and world music was played. Participants were encouraged to focus their attention on their inner experiences when they were not engaged in experimental tasks.

After completing screening, eligible individuals participated in 5 experimental sessions lasting about 7 h each and follow-up assessments 1 week and 1 month after the last session. Experimental sessions were separated by at least 48 h, but usually by about a week.

To minimize expectancy effects, participants were informed both verbally and in the consent form that during the study they could receive placebo or doses of 38 psychoactive drugs from a variety of drug classes. Psilocybin and DXM were among the drugs listed. Participants were told that in at least one session they would receive a hallucinogen from the list, either a classic hallucinogen or a dissociative anesthetic hallucinogen. Staff monitoring drug sessions received identical instructions, with the only exception being that one of the 10 monitors was not blind to the drug conditions to be administered; however, this monitor remained blinded to the order of drug conditions.

Each participant met with their session monitors on two occasions before the first drug session, 1 to 2 days after each experimental session, and at 1 week and 1 month after the last session.

Various measures were assessed before capsule administration, repeatedly after administration, about 7 h after capsule administration when acute drug effects had resolved (end of session), 1 week after the last session, and 1 month after the last session.

During the study, participants received psilocybin (10, 20, and 30 mg/70 kg), dextromethorphan HBr (400 mg/70 kg expressed as the base), and placebo (lactose or microcrystalline cellulose) using a complete crossover experimental design. Drug and placebo doses were prepared in identically appearing opaque, size 0 gelatin capsules, with lactose or

microcrystalline cellulose as the inactive capsule filler. On each session, two capsules were administered with approximately 100 ml water.

After each session, participants were instructed to write a brief description of their session experience (e.g., ranging from a few sentences to several pages), which they gave to their session monitors at the meeting 1 to 2 days after the session.

Measures assessed during the session

Subjective Effects Questionnaire (within session) Participants completed this questionnaire before capsule administration and 60, 120, 180, 240, 300, 360, and approximately 500 min after capsule administration. Participants were instructed to rate overall drug effect and liking based on how they felt at the current time on a scale from 0 (none) to 10 (strongest imaginable), expressed as a percent of maximum possible score.

Measures assessed at the end of the session, approximately 7 h after capsule administration

Altered States of Consciousness (5D-ASC) This standardized questionnaire assesses drug and non-drug-altered states of consciousness (Dittrich 1998; Studerus et al. 2010 with English translation by Hasler and Cahn). Ninety-four items were rated using a visual analogue scale from 0 to 100.

States of Consciousness Questionnaire (SOCQ) This 100-item questionnaire assesses possible hallucinogen experience content (Griffiths et al. 2006). Data from individual items and mean data from the 15 items comprising Mystical Subscale of the Mystical Experience Questionnaire (MEQ30) (MacLean et al. 2012) were expressed as a percentage of the maximum possible score.

Hallucinogen Rating Scale (HRS) This is a 100-item questionnaire (Strassman et al. 1994) on which both psilocybin and DXM produce dose-related increases (Griffiths et al. 2011; Reissig et al. 2012). Scores on individual items were expressed as a percentage of a maximum possible score.

End of Session Subjective Effects Questionnaire Eight additional subjective effect ratings were assessed at the end of sessions. Participants rated the degree to which the session experience was personally meaningful, spiritually significant, psychologically insightful, and psychologically challenging. These items were rated on a scale from 1 to 8, with 1 = no more than routine, everyday experiences; 7 = among the five most (meaningful, spiritually significant, or psychologically insightful, or psychologically challenging experiences) of my life; and 8 = the single most (meaningful, spiritually significant, psychologically insightful, or psychologically challenging experience) of my life. Four items assessed liking, overall drug effect, joy or happiness, and peace or harmony. These items were rated on a 5-point scale with 0 = none; and 4 = extreme.

Measure assessed 1 week after the last session

Retrospective Comparative Effects Across Sessions Questionnaire For purposes of facilitating the differentiation of drug effects between the different drug conditions, participants completed a 202-item questionnaire comprised of selected items from the four questionnaires administered 7 h after capsule administration (5D-ASC, SOCQ, HRS, and the End of Day Subjective Effects Questionnaire). Before completing the questionnaire, the participant was given copies of their written descriptions of each session to review. The purpose of this was to facilitate their recall and differentiation between effects experienced in each of the five sessions. For each item, participants were instructed to rate the degree to which they experienced the specified phenomena during each session relative to the strongest experience of that phenomena that they ever had, or expected to be possible. Sessions were identified sequentially in their chronological order (i.e., session 1, session 2,…session 5). Each item was rated using a visual analogue scale from 0 to 100. Above the analogue scale, the following labels appeared at equally spaced intervals: none, not at all; so slight cannot decide; slight; moderate; strong (equivalent in degree to any previous strong experience or expectation of this description); and extreme. This questionnaire was completed after the second, third, fourth, and fifth sessions, but only data obtained 1 week after the fifth session were analyzed.

Measure assessed 1 month after the last session

One Month Retrospective Questionnaire Similar to the foregoing questionnaire, which was completed 1 week after the last session, participants were given copies of their written session descriptions to review for the purpose of facilitating their comparison between drug conditions. However, this questionnaire was completed 1 month after the last session. As in the previous questionnaire, sessions were identified sequentially in their chronological order. Participants were asked to rank the order of their session experiences in regard to preference for repeating the drug condition again, psychological insight, personal meaning, and spiritual significance.

Data analysis

Data were analyzed with IBM SPSS Statistics (IBM Corporation, Armonk, NY). For time-course data, planned

comparison *t* tests were conducted between placebo and active doses at each time point. For peak subjective effect ratings and subjective effect ratings completed 7 h after drug administration or at 1 week after the last session, repeated measures ANOVAs were used, with Fisher's LSD post hoc tests used to compare drug conditions. Scores for these ratings were expressed on a scale of 0 to 100. Peak ratings were defined as the maximum value after capsule administration observed for each participant. For analysis of questions assessed 1 month after sessions in which participants rank ordered their responses across the five sessions, Friedman's ANOVA was used with the Wilcoxon signed-rank test for pairwise comparisons. For analysis of differences in percentages of participants endorsing wanting to repeat the drug condition within a month, Cochran's *Q*, a non-parametric, binary repeated measures test, was conducted with a factor of drug condition (placebo, 10, 20, and 30 mg/70 kg psilocybin, and DXM). Planned comparisons among placebo, 30 mg/70 kg psilocybin, and DXM were conducted using McNemar's test. Statistical tests were considered significant at $p \leq 0.05$. Missing data (2, 1, and 2 participants, respectively, from the liking rating time course, liking rating at end of session, and spiritual significance rating 1 week after the last session) are noted in the "Results."

Results

Subjective ratings of drug effect magnitude and liking

Psilocybin and DXM produced orderly time-related effects during the sessions. Figure 1 shows session time-course data for participant ratings of drug effect and drug liking. Psilocybin generally produced dose-related increases. As described previously (Carbonaro et al. 2018) on these and other measures of subjective effects assessed repeatedly during the session, the time course of DXM was similar to that of the high psilocybin doses, with maximal effects occurring at 2 to 4 h and effects decreasing at the 6-h time point.

Consistent with the within-session time-course data, the first column of Fig. 2 shows that peak ratings of drug effect and liking during the session also reflect dose-related increases with psilocybin and shows that effects of DXM were similar to the high dose of psilocybin. Figure 2 (top row, columns 2 and 3) show a similar pattern of ratings of drug effect at both the end of session and 1 week after the last session. However, the bottom row shows that ratings of liking of DXM were significantly lower than both 20 and 30 mg/70 kg psilocybin at these assessment times.

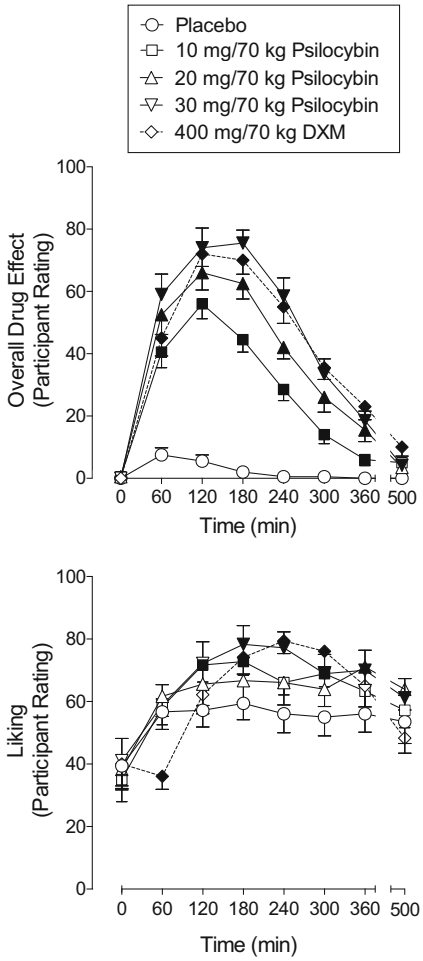

Fig. 1 Time course of effects of placebo, psilocybin (10, 20, and 30 mg/70 kg), and dextromethorphan (DXM, 400 mg/70 kg) on participant ratings of overall drug effect ($N = 20$, top panel) and liking ($N = 18$, bottom panel) assessed repeatedly across the session. *Y-axes*: participant-rated effect expressed as a percentage of the maximum possible rating. *X-axes*: time after capsule administration in minutes; 0 = before capsule administration. Data points show means and brackets show 1 SEM. *Filled symbols* indicate values that are significantly different from the corresponding placebo value at the same time point ($p < 0.05$, planned comparisons)

Ratings of subjective domains proposed to be related to reinforcing effects

Ratings assessed at end of session Table 1 shows participant ratings of drug session experiences assessed retrospectively 7 h after drug administration (at the end of the session). Data show results from 36 individual questionnaire items and 1 questionnaire subscale arranged under 9 labels reflecting different domains of subjective experience proposed to be predictive of the self-administration (i.e., reinforcing effects) of classic psychedelic drugs. These domains are descriptive and were not empirically derived. For psilocybin on 36 of the 37 measures, all three doses were significantly greater than placebo. Psilocybin generally showed dose-related increases, often with the higher doses (20 and/or 30 mg/70 kg) being significantly greater than

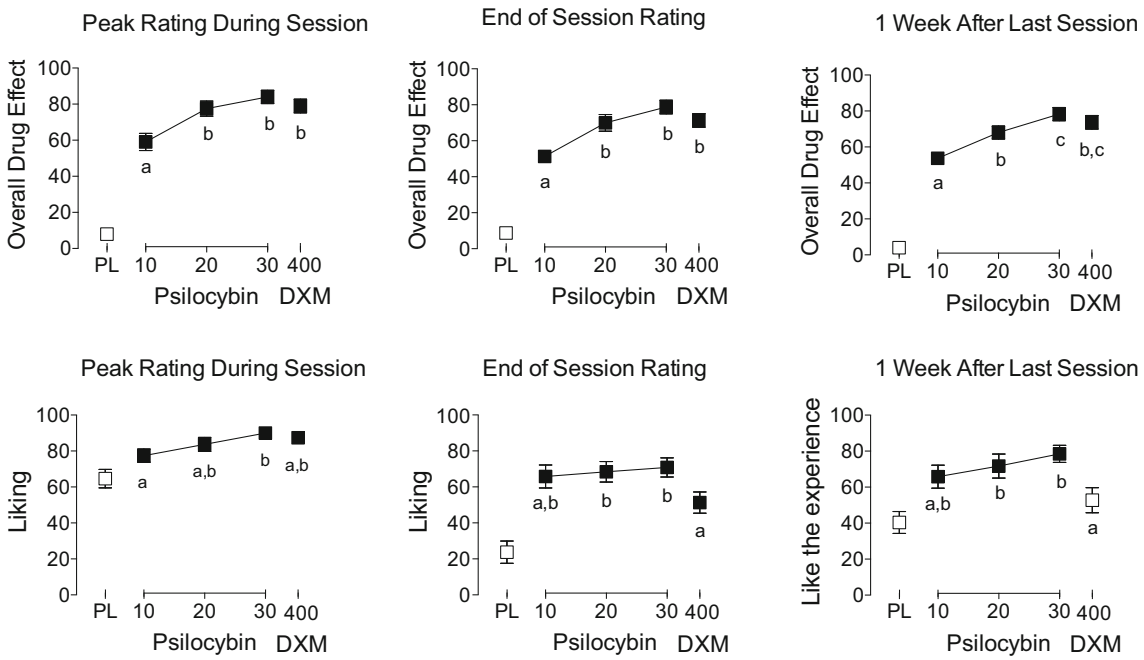

Fig. 2 Participant ratings of drug effect and liking of placebo, psilocybin (10, 20, and 30 mg/70 kg), and dextromethorphan (DXM, 400 mg/70 kg) on three assessment occasions. *Y-axes*: participant-rated effects expressed as a percentage of the maximum possible rating. *X-axes*: drug condition. Data points show means and brackets show 1 SEM. *Filled symbols* indicate values that are significantly different from the corresponding placebo value ($p < 0.05$, planned comparisons). $N = 20$ for each panel except $N = 18$ and 19 for bottom left and bottom center panels, respectively

the low dose (25 of 37 measures). DXM was significantly greater than placebo on most measures (25 of 37). Comparing all three doses of psilocybin to DXM, there were no instances in which DXM was significantly higher than psilocybin. Psilocybin was significantly higher than DXM on 9, 26, and 32 of the 37 measures at 10, 20, and 30 mg/70 kg, respectively. For those measures showing significant differences, the high dose of psilocybin was, on average, over 200% greater than DXM (range 131–474%). These significant differences between psilocybin and DXM occurred on measures within all nine domains indicative of subjective effects. Not shown in the table, after 30 mg/70 kg psilocybin, 45% of participants rated the experience as among the top 10 most meaningful and psychologically insightful of their lives, both of which were significantly higher than after placebo (0% and 0%, respectively) and DXM (10% and 0%, respectively).

An indirect measure of the reinforcing effects of psilocybin (i.e., an estimate of the future probability of self-administration) was the response to a question from the HRS assessed 7 h after drug administration asking participants how soon they would like to repeat the experience. The percentage of participants indicating that they would like to repeat the experience within a month or less was 50%, 80%, 80%, 75%, and 25%, for placebo; 10, 20, and 30 mg/70 kg psilocybin; and DXM, respectively. All three psilocybin doses were at least 3 times higher than DXM, and the planned comparison showed that the highest dose of psilocybin was significantly higher than DXM.

Ratings assessed 1 week after the last session Table 2 shows participant ratings of drug session experiences assessed retrospectively 1 week after the last drug session. To facilitate comparisons, the table layout is identical to that of Table 1 with em dashes indicating data not assessed 1 week after the last session. Data show results from 26 individual questionnaire items and 1 questionnaire subscale reflecting different domains indicative of possible reinforcing effects of classic psychedelic drugs that were assessed at this time point. On 26 of the 27 measures, psilocybin produced significantly greater effects than placebo. Psilocybin generally showed dose-related increases, often with the higher doses (20 and/or 30 mg/70 kg) being significantly greater than the low dose (18 of 27 measures). DXM was significantly greater than placebo on 14 of the 27 measures. Comparing all three doses of psilocybin to DXM, there were no instances in which DXM was significantly higher than psilocybin. Psilocybin was significantly higher than DXM on 8, 18, and 26 of the 27 measures at 10, 20, and 30 mg/70 kg, respectively. For those measures showing significant differences, the high dose of psilocybin was, on average, over 200% greater than that of DXM (range 139–335%).

Ratings assessed 1 month after the last session Table 3 shows participant retrospective ratings of the drug sessions assessed 1 month after the last session. On all four measures (rank order of preference for repeating the drug condition again, psychological insight, personal meaning, and spiritual significance),

Table 1 Participant ratings of 36 individual questionnaire items and 1 questionnaire subscale assessed retrospectively 7 h after drug administration representing subjective effect domains proposed to be predictive of subsequent self-administration

Item description	Placebo	Psilocybin dose (mg/70 kg)			Dextromethorphan dose (mg/70 kg)
	0	10	20	30	400
Classic drug abuse liability measures					
Liking‡ ($n = 19$)	23.68 (6.19)	**65.79 (6.40)**	**68.42 (5.68)***	**70.83 (5.44)***	**51.32 (5.88)**
Euphoria^	7.50 (2.63)	**36.25 (6.41)**[a]	**52.50 (8.09)**[a,b]	**65.00 (7.57)***[,b]	**35.00 (6.12)**
Like the experience^	42.50 (5.47)	**72.50 (5.99)***	**75.00 (6.28)***	**76.25 (6.66)***	50.00 (5.44)
Experience of ecstasy#	5.00 (1.99)	**33.00 (5.85)**[a]	**48.00 (6.71)**[a,b]	**61.00 (5.71)***[,b]	**43.00 (6.03)**
I experienced boundless pleasure+	0.30 (0.16)	**21.10 (6.83)**[a]	**34.80 (7.17)***[,a,b]	**44.25 (6.76)***[,b]	14.35 (5.50)
Satisfaction with the experience^	41.25 (5.81)	**68.75 (5.40)***	**81.25 (5.70)***	**82.50 (5.47)***	52.50 (5.99)
Bodily sensations were very enjoyable+	4.80 (1.91)	**32.40 (7.27)**	**38.45 (7.75)**	**45.30 (8.13)**	**38.20 (7.05)**
Visual effects					
Visual images, visions, hallucinations^	1.25 (1.25)	**36.25 (6.69)**[a]	**67.50 (6.56)***[,b]	**71.25 (7.32)***[,b]	**25.00 (7.69)**
Positive mood					
Greatest peace‡	30.00 (4.29)	**58.75 (6.09)**	**62.50 (6.15)**	**70.00 (5.90)**	**58.75 (4.89)**
Greatest joy‡	21.25 (4.17)	**50.00 (5.13)**[a]	**71.25 (5.52)***[,b]	**63.75 (6.14)***[,a,b]	**48.75 (5.28)**
Loving^	22.50 (5.10)	**58.75 (5.22)***[,a]	**72.50 (7.88)***[,a,b]	**77.50 (6.51)***[,b]	38.75 (5.58)
Feelings of peace and tranquility#	34.00 (5.05)	**59.00 (4.92)**	**64.00 (5.15)**	**66.00 (5.64)**	**57.00 (6.03)**
Feelings of universal or infinite love#	11.00 (3.69)	**46.00 (5.25)***[,a]	**55.0 (7.80)***[,a,b]	**67.00 (6.03)***[,b]	**28.00 (5.69)**
Feelings of joy#	16.00 (3.73)	**56.00 (4.00)**	**61.00 (6.07)**	**66.00 (5.64)***	**47.00 (6.03)**
Feelings of tenderness and gentleness#	22.00 (4.33)	**51.00 (5.12)***	**63.00 (6.20)***	**60.00 (6.16)***	35.00 (5.60)
I experienced profound inner peace+	5.00 (2.14)	**39.45 (6.83)**[a]	**47.35 (7.76)**[a,b]	**62.15 (6.79)***[,b]	**40.30 (7.74)**
I experienced an all-embracing love+	0.60 (0.33)	**33.30 (7.74)**[a]	**55.85 (9.53)***[,b]	**64.20 (7.86)***[,b]	18.50 (5.65)
Happy^	30.00 (5.90)	**52.50 (5.71)**[a]	**70.00 (5.00)**[b]	**65.00 (6.12)**[a,b]	**55.00 (4.66)**
Many things seemed incredibly funny to me+	0.20 (0.20)	**22.00 (6.44)**[a]	**45.30 (6.44)***[,b]	**55.90 (7.47)***[,b]	**19.75 (5.85)**
Feel like laughing^	3.75 (2.05)	**37.50 (6.41)**[a]	**61.25 (6.66)***[,b]	**72.50 (6.51)***[,b]	**32.50 (6.31)**
Insight					
Personally psychologically insightful‡	19.38 (2.48)	**45.63 (3.77)***[,a]	**57.50 (5.32)***[,b]	**65.63 (4.79)***[,b]	**33.75 (3.86)**
New thoughts or insights^	12.50 (3.85)	**45.00 (5.32)**[a]	**61.25 (6.66)***[,b]	**56.25 (5.40)***[,a,b]	**30.00 (5.62)**
Insights into personal or occupational concerns^	15.00 (4.21)	**42.50 (7.50)***[,a]	**62.50 (6.66)***[,b]	**55.00 (7.61)***[,a,b]	23.75 (6.41)
I had insights into connections that had previously puzzled me+	0.60 (0.41)	**26.85 (6.13)**	**41.75 (8.51)***	**36.90 (7.03)***	17.85 (6.33)
Positive social effects					
Feeling of emotional closeness with your guide or assistant guide#	44.00 (6.90)	38.00 (6.31)	33.00 (5.85)	40.00 (4.59)	47.00 (4.87)
Increased awareness of importance of interpersonal relationships#	18.00 (3.81)	**53.00 (4.87)***[,a]	**63.00 (7.00)***[,a,b]	**69.00 (3.97)***[,b]	30.00 (6.07)
Understanding others feelings^	11.25 (3.84)	**41.25 (5.52)**[a]	**57.50 (7.50)***[,a,b]	**63.75 (5.87)***[,b]	27.50 (6.76)
Increased awareness of beauty					
Many things appeared to me as breathtakingly beautiful+	0.30 (0.21)	**26.85 (7.17)**[a]	**44.70 (8.62)***[,a,b]	**62.80 (8.18)***[,b]	13.25 (4.90)
Experience of increase awareness of beauty#	9.00 (3.07)	**47.00 (5.48)***	**49.00 (6.72)***	**62.00 (5.96)***	**30.00 (4.70)**
Increase in the beauty and significance of music#	16.00 (4.72)	**51.00 (4.92)**[a]	**62.00 (5.21)***[,a,b]	**67.00 (5.29)***[,b]	**41.00 (5.33)**
Awe/amazement					
Sense of awe or awesomeness#	8.00 (2.68)	**46.00 (5.64)**[a]	**58.00 (7.80)**[a,b]	**70.00 (4.23)***[,b]	**45.00 (6.79)**
Awe, amazement^	7.50 (3.19)	**48.75 (6.41)**[a]	**68.75 (6.76)***[,b]	**73.75 (6.41)***[,b]	**46.25 (5.81)**
I experienced a kind of awe+	3.50 (2.45)	**36.60 (7.16)**[a]	**63.35 (7.57)***[,b]	**73.90 (7.04)***[,b]	**41.55 (8.25)**
Experience of amazement#	10.00 (3.97)	**51.00 (4.70)**[a]	**69.00 (4.92)***[,b]	**75.00 (3.52)***[,b]	**51.00 (6.57)**

Table 1 (continued)

Item description	Placebo	Psilocybin dose (mg/70 kg)			Dextromethorphan dose (mg/70 kg)
	0	10	20	30	400
Meaningfulness					
Personally meaningful‡	21.25 (1.84)	**48.13 (3.54)**[a]	**58.75 (4.98)***,[b]	**66.88 (3.54)***,[b]	**45.00 (3.99)**
Spiritually significant‡	19.38 (1.92)	**45.00 (4.20)**	**48.13 (5.61)**	**56.88 (4.49)***	**38.13 (4.58)**
Mystical					
Mystical Subscale of MEQ30 (unity, sacredness, noetic)#	6.53 (2.08)	**34.80 (4.42)**[a]	**48.47 (6.28)***,[b]	**61.27 (4.81)***,[b]	**29.67 (4.82)**

Data are expressed as percentages of maximum possible score; data are mean scores with 1 SEM shown in parentheses ($N = 20$, except where noted); within a row, bold font indicates significant difference from 0 mg/70 kg; * indicates significant difference from 400 mg/70 kg dextromethorphan; for psilocybin doses, values not sharing a common letter are significantly different (Fisher's LSD $p < 0.05$)

^ Items from Hallucinogen Rating Scale

Items from States of Consciousness Questionnaire

+ Items from 5-Dimension Altered States of Consciousness Questionnaire

‡ Items from the End of Session Subjective Effects Questionnaire

the four active dose conditions were significantly higher than placebo, psilocybin produced dose-related increases, and the 20 and 30 mg/70 kg psilocybin doses were significantly higher than DXM.

Ratings of nausea, physical distress, and psychological challenge

At 1 week after the last session, participants provided separate ratings of the relative degree of "nausea" and "physical distress (e.g., nausea, vomiting, sweating, rapid heartbeat)" associated with the sessions. All four active drug conditions were significantly higher than placebo. Psilocybin produced numerically and statistically dose-related increases. DXM was significantly higher than all three doses of psilocybin. For placebo; 10, 20, and 30 mg/70 kg psilocybin; and DXM, respectively, means (SEMs) for ratings on a 0 to 100 scale of nausea were 0.95 (0.68), 19.45 (5.28), 27.15 (5.51), 37.05 (5.35), and 53.50 (7.14), and ratings of physical distress were 1.10 (0.62), 20.75 (5.18), 29.05 (6.13), 35.40 (5.74), and 54.00 (6.06).

Participants also rated another item indicating the relative degree to which they found the session experience to be psychologically challenging at the end of each session and retrospectively 1 week and 1 month after the last session. Participants also completed the Challenging Effects Questionnaire 1 week after the last session. For all of these assessments, all four active drug conditions were significantly higher than placebo. Psilocybin produced numerically and often statistically dose-related increases. DXM was not statistically different from any dose of psilocybin.

Discussion

The present report was undertaken to shed light on the conundrum that psilocybin has been used non-medically for centuries in various cultures and recently at stable, quite modest rates in the USA, while lacking many of the usual features that have been used to predict the repeated taking of psychoactive drugs by humans (i.e., drug abuse liability, see "Introduction"). In this double-blind study, a variety of subjective effects of three doses of psilocybin were compared to a high dose of DXM in participants with histories of non-medical use of various hallucinogens. DXM was chosen as a comparator to psilocybin because, although it is a hallucinogen with some effects similar to psilocybin (Reissig et al. 2012; Carbonaro et al. 2018; Barrett et al. 2018), it is associated with a substantially lower rate of non-medical use despite its widespread availability (see "Introduction").

Important to a meaningful comparison of psilocybin and DXM, participant ratings during the session, at the end of the session, and 1 week after the last session showed that the magnitude of drug effect for DXM was similar and not significantly different from that for the two highest doses of psilocybin. Also important to the examination of subjective effects domains proposed to predict differences in non-medical use or subsequent drug self-administration, the present study assessed two participant-rated measures assessing participants' disposition to take the drug condition again in the future. At 7 h after drug administration, 75 to 80% of participants receiving 10, 20, or 30 mg/70 kg psilocybin endorsed wanting to repeat the experience within a month, which was higher than the 25% making that endorsement after receiving DXM. Furthermore, at 1 month after the last session, ratings of relative preference for repeating

Table 2 Participant ratings assessed retrospectively 1 week after the last session representing subjective effect domains proposed to be predictive of subsequent self-administration

Item description	Placebo	Psilocybin dose (mg/70 kg)			Dextromethorphan dose (mg/70 kg)
	0	10	20	30	400
Classic drug abuse liability measures					
Liking‡	—	—	—	—	—
Euphoria^	8.65 (3.46)	**43.20 (6.92)**[a]	**50.00 (7.36)**[a,b]	**66.80 (6.10)***[,b]	**34.80 (6.19)**
Like the experience^	40.40 (6.11)	**65.80 (6.36)**	**71.65 (6.66)***	**78.45 (4.77)***	52.80 (6.96)
Experience of ecstasy#	1.10 (1.10)	**32.35 (7.08)**[a]	**43.05 (7.35)***[,a]	**60.00 (6.59)***[,b]	**20.90 (5.43)**
I experienced boundless pleasure+	—	—	—	—	—
Satisfaction with the experience^	38.85 (6.61)	**65.80 (6.18)**	**73.30 (6.22)**	**79.65 (3.53)***	**57.15 (6.09)**
Bodily sensations were very enjoyable+	—	—	—	—	—
Visual effects					
Visual images, visions, hallucinations^	0.15 (0.15)	**48.70 (6.53)**[a]	**64.55 (5.03)***[,b]	**75.35 (3.61)***[,b]	**44.20 (7.86)**
Positive mood					
Greatest peace‡	30.45 (4.97)	**53.30 (6.00)**	**59.45 (6.53)**	**64.80 (5.68)***	43.30 (5.79)
Greatest joy‡	15.25 (3.95)	**48.15 (6.41)**[a]	**62.10 (6.82)***[,a,b]	**67.10 (5.81)***[,b]	**36.85 (5.61)**
Loving^	23.10 (4.32)	**49.70 (6.18)***[,a]	**61.10 (7.94)***[,a,b]	**68.65 (5.12)***[,b]	31.45 (5.82)
Feelings of peace and tranquility#	27.05 (5.46)	**53.00 (6.69)**	**57.30 (7.10)**	**63.65 (6.12)***	44.70 (6.44)
Feelings of universal or infinite love#	5.80 (2.12)	**39.70 (6.62)***[,a]	**54.65 (8.23)***[,a,b]	**63.20 (6.94)***[,b]	18.85 (5.36)
Feelings of joy#	10.05 (3.58)	**43.65 (7.31)***[,a]	**54.45 (7.04)***[,a,b]	**63.70 (6.32)***[,b]	22.95 (5.76)
Feelings of tenderness and gentleness#	7.80 (2.81)	**47.60 (6.36)***	**56.45 (7.07)***	**58.95 (6.24)***	22.65 (5.63)
I experienced profound inner peace+	—	—	—	—	—
I experienced an all-embracing love+	—	—	—	—	—
Happy^	33.90 (4.61)	49.40 (6.51)	**54.55 (7.64)***	**62.90 (5.30)***	34.20 (6.08)
Many things seemed incredibly funny to me+	—	—	—	—	—
Feel like laughing^	8.75 (2.95)	**31.30 (5.60)**[a]	**49.00 (6.72)***[,b]	**53.60 (5.80)***[,b]	**26.05 (5.97)**
Insight					
Personally psychologically insightful‡	18.05 (5.04)	**51.15 (5.43)**[a]	**67.30 (6.21)***[,b]	**70.80 (4.58)***[,b]	**37.95 (6.48)**
New thoughts or insights^	16.30 (4.58)	**50.05 (6.09)***[,a]	**64.55 (6.06)***[,a,b]	**71.00 (4.09)***[,b]	**33.35 (6.56)**
Insights into personal or occupational concerns^	17.65 (4.98)	**44.90 (6.78)***	**54.50 (5.23)***	**60.05 (6.64)***	27.20 (6.32)
I had insights into connections that had previously puzzled me+	—	—	—	—	—
Positive social effects					
Feeling of emotional closeness with your guide or assistant guide#	27.75 (5.82)	32.75 (5.58)	47.25 (6.36)	48.95 (6.52)	34.65 (6.57)
Increased awareness of importance of interpersonal relationships#	14.85 (4.62)	**38.65 (6.04)***[,a]	**60.85 (5.76)***[,b]	**62.50 (4.55)***[,b]	20.25 (5.57)
Understanding others feelings^	19.00 (3.97)	**43.00 (6.84)***[,a]	**59.75 (7.05)***[,b]	**55.10 (5.33)***[,a,b]	22.40 (5.15)
Increased awareness of beauty					
Many things appeared to me as breathtakingly beautiful+	—	—	—	—	—
Experience of increase awareness of beauty#	—	—	—	—	—
Increase in the beauty and significance of music#	12.90 (4.07)	**45.45 (5.71)**[a]	**53.30 (6.73)***[,b]	**65.80 (5.09)***[,a,b]	**30.20 (5.71)**
Awe/amazement					
Sense of awe or awesomeness#	4.45 (3.08)	**44.85 (7.47)**[a]	**56.50 (7.85)**[a,b]	**70.50 (5.80)***[,b]	**44.05 (6.40)**
Awe, amazement^	5.50 (3.20)	**41.25 (6.34)**[a]	**56.10 (7.05)**[a,b]	**71.45 (6.45)***[,b]	**44.65 (5.69)**
I experienced a kind of awe+	—	—	—	—	—
Experience of amazement#	4.90 (3.48)	**43.6 (7.22)**[a]	**59.2 (7.50)**[a,b]	**73.25 (5.17)***[,b]	**50.00 (6.04)**

Table 2 (continued)

Item description	Placebo	Psilocybin dose (mg/70 kg)			Dextromethorphan dose (mg/70 kg)
	0	10	20	30	400
Meaningfulness					
Personally meaningful‡	25.00 (5.65)	**56.90 (5.86)**[a]	**73.20 (6.27)***,[b]	**79.75 (4.44)***,[b]	**47.30 (6.36)**
Spiritually significant‡ ($n = 18$)	14.67 (5.04)	**48.11 (8.57)**	**58.89 (8.49)***	**65.67 (6.46)***	29.94 (7.28)
Mystical					
Mystical Subscale of MEQ30 (unity, sacredness, noetic)#	6.17 (1.74)	**35.62 (6.16)**[a]	**47.27 (7.13)**[a,b]	**60.01 (5.48)***,[b]	**27.10 (5.30)**

Table layout is identical to Table 1, with em dash (—) indicating data not assessed 1 week after last session

Data are expressed as percentages of maximum possible score; data are mean scores with 1 SEM shown in parentheses ($N = 20$, except where noted); within a row, bold font indicates significant difference from 0 mg/70 kg; * indicates significant difference from 400 mg/70 kg dextromethorphan; for psilocybin doses, values not sharing a common letter are significantly different (Fisher's LSD $p < 0.05$)

^ Items from Hallucinogen Rating Scale

Items from States of Consciousness Questionnaire

+ Items from 5-Dimension Altered States of Consciousness Questionnaire

‡ Items from End of Session Subjective Effects Questionnaire

all three doses of psilocybin were significantly higher than those for placebo and DXM. These findings are consistent epidemiological data showing that rates of non-medical use of psilocybin are consistently higher than those of DXM. Given the similarity of drug strength ratings for psilocybin and DXM and the differences in measures of disposition for future self-administration, the examination of differences between DXM and on other qualitative subjective drug effect measures may be informative to understanding domains of subjective experience that may be predictive non-medical use.

Data presented in Tables 1 and 2 show results from a range of subjective effect ratings obtained either 7 h after drug administration (Table 1) and 1 week after the last session (Table 2). Data are arranged under nine labels proposed to reflect different domains of subjective experience proposed to be predictive of the self-administration of classic psychedelic drugs: (1) classic abuse liability subjective effects (e.g., ratings of liking or euphoria); (2) visual effects (e.g., visual images); (3) positive mood (e.g., feelings of peace or loving); (4) insight (e.g., new perspectives into personal concerns); (5) positive social effects (e.g., increased empathy and importance of personal relationships); (6) increased awareness of beauty (e.g., beauty in visual appearance or music); (7) awe/amazement; (8) meaningfulness (e.g., personal meaning or spiritual significance); (9) mystical (i.e., a combination of unity, sacredness, and noetic). The specific questionnaire items used to define the 9 domains were drawn from four questionnaires (5D-ASC, SOCQ, HRS, and the End of Day Subjective Effects Questionnaire) that have been commonly used to assess a wide variety of subjective effects produced by psychedelic drugs (Strassman et al. 1994; Griffiths et al. 2006, 2011; Studerus et al. 2010; Bouso et al. 2016).

The present analysis shows that all nine of the subjective effect domains proposed to be predictive of subsequent self-administration do, in fact, differentiate psilocybin from placebo as well as psilocybin from DXM. These differences are

Table 3 Participant ratings assessed 1 month after the last session proposed to be predictive of the subsequent self-administration

Item description	Placebo	Psilocybin dose (mg/70 kg)			Dextromethorphan dose (mg/70 kg)
	0	10	20	30	400
Rating of preference for repeating the drug condition again	1.30 (0.11)	**3.15 (0.22)**[a]	**3.85 (0.25)***,[a,b]	**4.10 (0.24)***,[b]	**2.60 (0.28)**
Rating of psychological insight	1.35 (0.18)	**3.00 (0.19)**[a]	**3.90 (0.24)***,[b]	**4.25 (0.20)***,[b]	**2.50 (0.28)**
Rating of personal meaning	1.40 (0.15)	**2.90 (0.19)**[a]	**3.80 (0.29)***,[b]	**4.20 (0.22)***,[b]	**2.70 (0.29)**
Rating of spiritual significance	1.50 (0.17)	**2.95 (0.27)**[a]	**3.75 (0.26)***,[a,b]	**4.20 (0.20)***,[b]	**2.60 (0.29)**

For each measure, participants ranked the five conditions from 1 (least preferred or lowest) to 5 (most preferred or highest). Data are mean scores with 1 SEM shown in parentheses ($N = 20$); within a row, bold font indicates significant difference from 0 mg/70 kg; * indicates significant difference from 400 mg/70 kg dextromethorphan; for psilocybin doses, values not sharing a common letter are significantly different (Wilcoxon signed-rank test $p < 0.05$)

consistent with the relative rates of non-medical use of psilocybin and DXM (see "Introduction"). More specifically, for most of the ratings in all nine of the proposed dimensions, (1) all three doses of psilocybin and the single dose of DXM were significantly greater than those of placebo; (2) psilocybin generally showed dose-related increases, often with the higher doses being significantly greater than the low dose; (3) comparing all three doses of psilocybin to DXM, there were no instances in which DXM was significantly higher than psilocybin; (4) the two highest doses of psilocybin were significantly greater than those of DXM on most of the assessed measures. Other findings showed that almost half (45%) of participants rated the experience after the high psilocybin dose to be among the top most meaningful and psychologically insightful of their lives, both of which were significantly higher than both placebo and DXM.

An important limitation of this analysis is that the nine separate domains were intuitively rather than empirically derived. More specifically, the nine domains were based on the authors' judgment of seemingly different aspects of psychedelic experience based on observations with hundreds of psilocybin research participants at Johns Hopkins and thousands of written accounts of psilocybin experiences from several anonymous survey studies (e.g., MacLean et al. 2012; Barrett et al. 2015; Griffiths et al. 2019). These proposed domains are likely not completely independent. For example, it seems probable that a mystical-type experience would also be rated as being meaningful. Future research should determine the extent to which these domains are independent of each other as well as whether there are additional domains of psychedelic experience that are relevant to the predicting self-administration of psychedelic drugs.

The results from this study indicate that peak participant ratings of drug liking of psilocybin and DXM during the session time course do not correspond with retrospective ratings of liking after the drug session. More specifically, although DXM and all three doses of psilocybin produced similar peak ratings of drug liking during the session, retrospective ratings of liking at the end of sessions and 1 week after the last session showed that both 20 and 30 mg/70 kg psilocybin produced significantly higher ratings of liking than DXM. Notably, the post-session differences in liking between DXM and the high doses of psilocybin were observed across all nine domains proposed to reflect differences in subjective experience proposed to be predictive of the self-administration (Tables 1 and 2). These observations may have implications for laboratory assessment of drug abuse potential which often rely on ratings of peak liking. The data suggest that retrospective ratings of drug liking, either at the end of sessions or after exposure to all drug conditions, may provide a better estimate of the likelihood of future use of the drug than peak ratings of drug liking. The observation of no difference in peak liking yet a significant difference in retrospective liking is similar to observations in a study comparing sodium oxybate and ethanol (Johnson and Griffiths 2013).

The present analysis sought to examine domains of psychedelic experience that were proposed to be predictive of subsequent self-administration of psilocybin. It should be noted that this analysis did not include domains of experience that might be expected to be negatively related to subsequent self-administration. Previously published results from this same study (Carbonaro et al. 2018) showed that measures of psychologically challenging emotional experiences were similar or significantly greater after psilocybin than DXM. However, DXM generally produced significantly greater participant ratings than psilocybin on some likely aversive somatic symptoms (i.e., dizziness, nausea, and vomiting). Although increases in such somatic symptoms could plausibly result in decreases in measures such as overall drug liking and disposition to take again, the relationship between such somatic symptoms and the other subjective domains such as visual images, insight, awe, or meaningfulness is not clear.

The use of very low doses of psilocybin or lysergic acid diethylamide (LSD) (i.e., "micodosing") weekly or more frequently for alleged therapeutic, cognitive, and emotional benefits (Fadiman and Korb 2019; Hutten et al. 2019; Lea et al. 2019) has garnered considerable attention in the last several years, although little rigorously controlled research has been conducted (Bershad et al. 2019; Kuypers et al. 2019; Passie 2019). In the current study, the doses of psilocybin tested were much greater, the interval between doses was longer, and the total number of psilocybin doses was lower than those reported in typical microdosing protocols (Hutten et al. 2019). Thus, although the current study focused on possible subjective effects related to non-medical use of psilocybin at typical psychoactive doses, these findings can not meaningfully be applied to the newly emerging phenomenon of psilocybin microdosing.

The present study sought to contribute to an understanding of what effects of psilocybin might account for the observation that psilocybin is used at modest rates non-medically while lacking features that typically are used to predict the non-medical use (i.e., abuse) of drugs (e.g., ability to reliability produce euphoria in humans or reliably maintain self-administration in non-humans). Various conceptual descriptions could be appropriate for such an analysis such as motivation for drug use (Cohen 1971) or instrumental drug use (Müller and Schumann 2011). The conceptual description used to analyze and discuss the findings in the present study is that of the experimental analysis of behavior (Schuster and Thompson 1969) in which the observation that instances of drug taking increase the probability of future drug taking can be understood through the rigorous empirical framework of operant reinforcement. In its broadest application, the experimental analysis of drug-taking behavior does not assume that drug reinforcement is limited to activation of the same

neurobiological systems underlying reinforcement of various other so-called motivated behaviors such as food consumption and sexual behavior. Nor is this approach incompatible with explaining instances of drug self-administration that occur intermittently or at low rates because it is well established that a variety of factors including history, antecedent conditions, and current environmental circumstances can be important determinants of drug reinforcement (Schuster and Thompson 1969).

In conclusion, the present analysis of data from a double-blind study comparing psilocybin and DXM in non-medical users of hallucinogens was undertaken to assess euphoria and eight additional subjective effects domain factors proposed to reflect the reinforcing effects (i.e., the likelihood of future self-administration or non-medical use of classic psychedelic drugs: visual effects, positive mood, insight, positive social effects, increased awareness of beauty (visual and music), awe/amazement, meaningfulness, and mystical experience). The present analysis shows that all nine of the subjective effect domains differentiate psilocybin from placebo and from DXM. These differences were consistent with two measures of desire to take the drug condition again and with the relative rates of non-medical use of psilocybin and DXM. Future studies should determine the independence of these domains and whether there are additional domains of psychedelic experience that are relevant to predicting their non-medical use.

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Compliance with ethical standards The study was conducted in compliance with US laws.

Conflict of interest Roland Griffiths is on the Board of Directors of the Heffter Research Institute.

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