

Psilocybin-assisted treatment for alcohol dependence: A proof-of-concept study

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Abstract

Several lines of evidence suggest that classic (5HT_{2A} agonist) hallucinogens have clinically relevant effects in alcohol and drug addiction. Although recent studies have investigated the effects of psilocybin in various populations, there have been no studies on the efficacy of psilocybin for alcohol dependence. We conducted a single-group proof-of-concept study to quantify acute effects of psilocybin in alcohol-dependent participants and to provide preliminary outcome and safety data. Ten volunteers with DSM-IV alcohol dependence received orally administered psilocybin in one or two supervised sessions in addition to Motivational Enhancement Therapy and therapy sessions devoted to preparation for and debriefing from the psilocybin sessions. Participants' responses to psilocybin were qualitatively similar to those described in other populations. Abstinence did not increase significantly in the first 4 weeks of treatment (when participants had not yet received psilocybin), but increased significantly following psilocybin administration ($p < 0.05$). Gains were largely maintained at follow-up to 36 weeks. The intensity of effects in the first psilocybin session (at week 4) strongly predicted change in drinking during weeks 5–8 ($r = 0.76$ to $r = 0.89$) and also predicted decreases in craving and increases in abstinence self-efficacy during week 5. There were no significant treatment-related adverse events. These preliminary findings provide a strong rationale for controlled trials with larger samples to investigate efficacy and mechanisms.

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Keywords

Addiction treatment, alcoholism, hallucinogens, psilocybin, clinical trial, motivational interviewing

Introduction

In the 1950s through early 1970s there was extensive research on the use of LSD and other classic (5HT_{2A} agonist or partial agonist) hallucinogens in the treatment of addiction (Abuzzahab and Anderson, 1971; Dyck, 2006; Grinspoon and Balakar, 1997; Halpern, 1996; Mangini, 1998), existential distress in dying patients (Grof et al., 1973; Pahnke et al., 1969; Richards, 1975; Richards et al., 1977), pain (Kast, 1966; Kast and Collins, 1964), and other conditions (Grinspoon and Balakar, 1997; Grof, 2008). A recent meta-analysis (Krebs and Johansen, 2012) examined the six published randomized trials (Bowen et al., 1970; Hollister et al., 1969; Ludwig et al., 1969; Pahnke et al., 1970; Smart et al., 1966; Tomsovic and Edwards, 1970) of LSD treatment of alcoholism. A total of 325 participants received active treatment with LSD, and 211 received control treatment. At the first post-treatment follow-up (ranging from 1 month to 12 months) the odds ratio for improvement was 1.96, favoring LSD (95% confidence interval 1.36–2.84, $Z = 3.59$, $p = 0.0003$).

The past decade has seen a rapid growth of interest in potential clinical applications of the classic hallucinogen psilocybin (Bogenschutz, 2012; Burdick and Adinoff, 2013; Carhart-Harris et al., 2012, 2013; Garcia-Romeu et al., 2013; Grob et al., 2011; Kometer et al., 2012; Nichols, 2014). Using a double-blind, cross-over design, Grob et al. administered psilocybin 0.2 mg/kg vs. placebo to 12 patients with anxiety related to advanced cancer (Grob et al., 2011). Participants showed significant improvement with time, and there were statistical trends suggesting a positive effect of psilocybin on mood. Additional clinical trials in cancer patients are currently nearing completion at Johns Hopkins

University and New York University (Nichols, 2014). A recent pilot study of psilocybin as an adjunct in smoking cessation treatment resulted in remarkable rates of abstinence (80% point abstinence at 6-month follow-up) (Johnson et al., 2014). Extensive clinical research with the classic hallucinogens (LSD, psilocybin, DMT, mescaline) has established their relative safety within a clinical research setting when subjects are carefully screened, supervised, and followed up (Strassman, 1984). A number of articles and chapters have reviewed the literature on the use of hallucinogens in the treatment of addictions (Abuzzahab and Anderson, 1971; Dyck, 2006; Grinspoon and Balakar, 1997; Halpern, 1996; Mangini, 1998), with the recent addition of two reviews that incorporate current research on the effects of classic hallucinogens more generally and discuss possible mechanisms of action (Bogenschutz and Pommy, 2012; Ross, 2012).

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Biological mechanisms

Although classic hallucinogens bind to many serotonin receptor subtypes and other receptors (Ray, 2010), the psychoactive effects of all classic hallucinogens appear to depend primarily on their actions at 5HT_{2A} receptors (Nichols, 2004; Vollenweider and Kometer 2010; Vollenweider et al., 1998). Administration of classic hallucinogens in rat models has been shown to induce down-regulation of 5HT_{2A} receptors, particularly those in the anterior cingulate and frontomedial cortex, likely accounting for the rapid development and reversal of behavioral tolerance to most classic hallucinogens (Buckholtz et al., 1990; Gresch et al., 2005).

The behavioral correlates and effects of 5HT_{2A} receptor activity are complex. Increased 5HT_{2A} receptor binding has been found in relation to pathological conditions in humans including depression (Shelton et al., 2009), impulsive aggression (Rosell et al., 2010), neuroticism (Frokjaer et al., 2008), borderline personality disorder (Soloff et al., 2007), and suicide (Anisman et al., 2008). The relationship of 5HT_{2A} receptor binding/activity and alcoholism or alcohol exposure is less clear. Family history of alcoholism may be associated with lower 5HT_{2A} binding (Underwood et al., 2008), and alcoholism is not consistently associated with change in 5HT_{2A} receptor levels (Thompson et al., 2012; Underwood et al., 2008). Among alcoholics, one small post-mortem study reported that higher impulsivity was associated with increased 5HT_{2A} receptor binding (Thompson et al., 2012). In animal models, alcohol exposure has been associated with region-specific increases (Akash et al., 2008) and decreases (George et al., 2010) in 5HT_{2A} receptors binding. Studies indicate that increased activity in 5HT_{2A}-mediated pathways relative to 5HT_{2C} activity increases cue response and impulsivity in rat models of cocaine addiction (Cunningham and Anastasio, 2014). 5HT_{2A} antagonists suppress alcohol consumption in animal models (Johnson, 2008). However, two large trials of the 5HT_{2A} antagonist ritanserin failed to demonstrate beneficial effects in people with alcohol dependence (Johnson et al., 1996; Wiesbeck et al., 1999).

Animal studies suggest mechanisms by which acute activation of 5HT_{2A} receptors could activate intracellular signaling pathways resulting in persisting changes in cellular structure and synapses. The classic hallucinogen DOI increases expression of glial cell line-derived neurotrophic factor (GDNF) mRNA in glioblastoma cells by a 5HT_{2A}-dependent mechanism (Tsuchioka et al., 2008). Through its action on 5HT_{2A} receptors, DOI has also been shown to increase levels of mRNA for brain-derived neurotrophic factor (BDNF) in rat parietal cortex and other neocortical regions, with decreases in the hippocampus and no change in piriform cortex (Vaidya et al., 1997). These findings are relevant because levels of BDNF and GDNF are inversely related to alcohol consumption and conditioned place preference in animal models (Ghitza et al., 2010). DOI activates intracellular signaling cascades associated with dendritic spine remodeling on rat pyramidal cells, and transiently increases the size of dendritic spines on cortical neurons (Jones et al., 2009).

Psychological models of psychedelic treatment

Clinical work with classic hallucinogens has emphasized the central role of the altered state of consciousness experienced during the drug's acute effects (Grof, 2008; Hoffer, 1967; Masters and

Houston, 2000; Pahnke et al., 1970; Sherwood et al., 1962). The "psychoanalytic" model of treatment emphasized the use of classic hallucinogens to enhance the process of psychodynamic psychotherapy by making unconscious material more accessible (Leuner, 1967). The "psychedelic" treatment model on the other hand emphasized the use of relatively high doses of classic hallucinogens (usually LSD) to occasion a "peak-psychedelic" or mystical experience of ego loss, often likened to psychological death and rebirth (Kurland et al., 1967). The latter model was used in most of the clinical studies conducted in North America using LSD in the treatment of addiction or existential anxiety in the dying. The concept of a singular transformative experience leading to lasting behavior change is consistent with classic descriptions of religious conversion (James, 1902), "spiritual awakening" in the context of Alcoholics Anonymous (Forchimes, 2004), and spontaneous Quantum Change experiences (Miller and C'de Baca, 2001). Recent studies have demonstrated that the self-reported "mystical" dimension of the psilocybin experience (feelings of unity, sacredness, ultimate reality, transcendence of time and space, deeply felt positive mood, and ineffability (Pahnke, 1963)) significantly predicts the lasting personal significance of the experience (Griffiths et al., 2008) and personality change (Maclean et al., 2011) in normal volunteers receiving psilocybin.

The evidence summarized above provides a convincing rationale for investigating whether a classic hallucinogen can improve treatment response among patients with alcohol dependence. In spite of the accumulating evidence that psilocybin has clinically relevant effects and is safe under controlled conditions, there are no prior studies of psilocybin in the treatment of alcohol dependence. We therefore undertook a proof-of-concept study which aimed to quantify the psychoactive effects and tolerability of oral psilocybin in alcohol-dependent participants, and to evaluate outcomes during and after completion of treatment.

Methods

Study design

The study employed a single-group, within-subjects design. Participants received a 12-week, 14-session manualized intervention including two open-label psilocybin sessions in which psilocybin was administered: the first after 4 weeks of psychosocial treatment, the second after 8 weeks. Outcome data were collected for a total of 36 weeks.

Participants

Participants were recruited from the community using advertisements in local media and flyers. They were males and females age 25–65 with a diagnosis of active alcohol dependence, ascertained using the Structured Clinical Interview for DSM-IV (SCID) (First et al., 1996), and at least two heavy drinking days in the past 30 days, who were concerned about their drinking and not currently in treatment. Participants were excluded if screening showed them to have exclusionary medical or psychiatric conditions; family history of schizophrenia, bipolar disorder, or suicide; cocaine, psychostimulant, or opioid dependence; or history of using hallucinogens more than 10 times (or any use in the past 30 days). Participants were required to be abstinent and not in alcohol withdrawal at the time of the psilocybin sessions.

Participants provided written informed consent, and all study procedures were reviewed and approved by the IRB of the University of New Mexico Health Sciences Center.

Interventions

Psychosocial intervention. The psychosocial intervention comprised a total of 12 sessions: seven sessions of Motivational Enhancement Therapy (MET: a structured approach using the principles of motivational interviewing (Miller and Rolnick, 2013)), three preparation sessions, and two debriefing sessions. Four sessions occurred before the first psilocybin session, four sessions between the first and second psilocybin sessions, and four sessions after the second psilocybin session. The psychosocial intervention was conducted by a team of two therapists. One performed the seven MET sessions focused on changing drinking behavior, while the other was responsible for preparation before, support during, and debriefing after the psilocybin sessions. Both therapists were present for the preparation and debriefing sessions, as well as the psilocybin sessions. Three of the authors (MB, AF, CW) served as study therapists. Therapy sessions were audiorecorded. The first and third MET sessions were coded using the Motivational Interviewing Treatment Integrity (MITI 3.1) coding system (Moyers et al., 2005) by a rater trained to reliability.

Dosing and administration of study medications. On the morning of the psilocybin sessions, participants were required to be afebrile, non-hypertensive, non-tachycardic, abstinent from alcohol for at least 24 hours, and without evidence of alcohol withdrawal. Urine drug screens were negative for cocaine, psychostimulants, and opioids, and breath was negative for alcohol. The psilocybin sessions took place in a room that was specially prepared to provide a living-room-like environment for the sessions. Individualized doses of psilocybin (based on participant weight) were prepared by the study pharmacist on the morning of the session, and placed in a single gelatin capsule. Participants ingested the psilocybin capsule followed by 4 ounces of water. They were instructed to lie on a couch wearing eyeshades and headphones (providing a standardized program of music), and to direct their attention toward their internal experience. Participants remained under observation for at least 8 hours following psilocybin administration. Both therapists were present throughout the session. Interactions with the participants were supportive and non-directive. Medications were available for administration if needed to treat hypertension (sublingual nitroglycerin 0.4 mg), anxiety (lorazepam 1–2 mg PO/IM), or acute psychosis (ziprasidone 10–20 mg PO/IM). Beginning 7 hours after drug administration, participants completed questionnaires and assessments, and a brief clinical interview was performed, including mental status exam. Participants were escorted home at the end of the session by a family member or friend, who stayed with the participant overnight.

For the first psilocybin session, participants received a dose of 0.3 mg/kg. For the second session, the dose was increased to 0.4 mg/kg unless the participant (i) was unwilling to increase the dose; (ii) experienced adverse effects during the first session which suggested that a higher dose would pose significant risk; or (iii) reported a “complete” mystical experience during the first session (Griffiths et al., 2006), indicating very strong effects from 0.3 mg/kg.

Assessments

Medical evaluation. Medical screening consisted of medical history and physical examination, ECG, liver function tests, complete blood count, blood chemistries, urinalysis, serum pregnancy test, and body mass index. Women of childbearing potential completed a menstrual calendar at each assessment visit, and urine pregnancy tests were completed prior to each drug administration session. The Clinical Institute Withdrawal Scale—Alcohol, revised (CIWA-Ar) (Sullivan et al., 1989) was used to assess alcohol withdrawal at screening and before the psilocybin sessions.

Psychiatric and substance use disorder diagnoses. The SCID (First et al., 1997) was used to diagnose DSM-IV Axis I disorders including substance abuse and dependence diagnoses.

Acute hallucinogen effects. Self-report scales (administered 7 hours after drug administration) and monitor ratings (0–6 hours after drug administration) were used to quantify acute subjective effects. The Intensity subscale of the Hallucinogen Rating Scale (HRS) (Strassman et al., 1994) was used as a global measure of the intensity of the drug experience. The 5-Dimensional Altered States of Consciousness Scale (5D-ASC) (Dittrich, 1998) has 94 items using the visual analog scale format, yielding five primary dimensions: “Oceanic Boundlessness,” “Dread of Ego Dissolution,” “Visionary Restructuralization,” “Auditory Alterations,” and “Altered Vigilance.” The States of Consciousness Scale is a 100-item questionnaire which has been used extensively to measure states of consciousness in hallucinogen administration experiments (Griffiths et al., 2006; Pahnke, 1963, 1969; Richards et al., 1977; Turek et al., 1974). This scale contains the 43 items of the Pahnke–Richards Mystical Experience Questionnaire (MEQ) (Griffiths et al., 2006). The Addiction Research Center Inventory (ARCI), 49-item version (Martin et al., 1971) was also administered following each drug administration session. In addition, a Monitor Session Rating Form (Griffiths et al., 2006) was completed by both monitors at intervals during the psilocybin sessions to provide ratings of participants’ behavior and affect during the session.

Substance use and consequences. The Time-Line Follow-Back (TLFB) (Sobell and Sobell, 1992, 1995) procedure was used to assess drinking behavior at baseline (covering the 12 weeks preceding enrollment) and follow-up visits. Heavy drinking days were defined as days during which participants consumed five or more standard drinks if the participant was male, or four or more standard drinks if the participant was female, a standard drink being defined as 14 g of alcohol. Drinking days were defined as days during which participants consumed any amount (even a sip) of an alcoholic beverage. The Short Inventory of Problems (SIP) (Miller et al., 1995), past 3 month version, was used to measure consequences of alcohol use. Breath Alcohol Concentration (BAC) was measured at each visit, but was used to ensure safety of treatment and validity of assessments rather than as an outcome measure.

Psychological assessments. The Stages of Change Readiness and Treatment Eagerness Scale (SOCRATES 8A) (Miller and

Tonigan, 1996) was used as a measure of motivation. The Alcohol Abstinence Self-Efficacy Scale (AASE) (Diclemente et al., 1994) was used as a measure of self-efficacy to abstain from drinking. The Penn Alcohol Craving Scale (PACS) (Flannery et al., 1999) was used to assess craving. The Profile of Mood States (POMS) (Mcnaur et al., 1981) was used as a measure of mood. Additional measures of persisting psychological effects obtained but not discussed in this publication were the Hood Mysticism Scale (Hood et al., 2001), the Persisting Effects Questionnaire (Griffiths et al., 2006), the ASPIRES Spiritual Transcendence Scale (Piedmont, 1999), the Brief Multidimensional Measure of Religiousness/Spirituality (Fetzer Institute, 1999), the NEO Personality Inventory 3 (NEO-PI-3) (McCrae et al., 2005), and the Schwartz Value Survey (Schwartz, 1992, 2006).

Safety assessment. Vital signs were obtained at each visit and measured frequently during psilocybin sessions: every half hour for the first 2 hours, then hourly for the next 4 hours, with more frequent readings as needed. Adverse events (AEs), when present, were collected on an AE case report form at the end of the psilocybin sessions and at all subsequent visits, including assessment of clinical significance and relatedness to treatment.

Statistical analysis and power

Statistical analyses for this open-label pilot study were primarily descriptive, but two a priori hypotheses were tested. To test for changes in drinking behavior (percent heavy drinking days and percent drinking days), consequences of drinking, and psychological outcomes, scores at follow-up time points were contrasted with baseline and week 4 values using paired *t*-tests, and effect sizes (Cohen's *d*) (Cohen, 1988) were computed with correction for correlation between time points (Morris and Deshon, 2002). The primary drinking outcome was percent heavy drinking days, and the primary contrast was baseline vs. weeks 5–12. With a sample size of $n = 10$, the study had power of 0.803 to detect pre-post changes of effect size $d = 1.0$, with $\alpha = 0.05$ (2-tailed) prior to correction for multiple comparisons. For drinking outcomes, the Benjamini–Hochberg procedure (Benjamini and Hochberg, 1995) was used to control the false discovery rate at the 0.05 level.

Results

Participants

In total 70 individuals were screened for the study, of whom 10 were included in the study (Figure 1). Participants were four women and six men with DSM-IV alcohol dependence. Two participants were Native American/Alaska Native, one was African American, four were Hispanic, and three were white non-Hispanic. Four were single, three were married, and three were divorced. Four were working full-time, five part-time, and one was unemployed. Mean household income was \$47,023 (SD \$35,262). Participants averaged 15.1 (SD 3.7) years of education (12 years representing graduation from high school), and three were college graduates.

Mean age was 40.1 years (SD 10.3, range 25–56), and mean duration of alcohol dependence was 15.1 years (SD 11.5, range 4–32). Participants had a mean of 5.0 dependence criteria (SD

1.2, range 3–7). Eight out of 10 had evidence of physical dependence (tolerance or withdrawal), but none had alcohol withdrawal symptoms requiring treatment during the trial.

Treatment exposure and follow-up

Figure 1 summarizes participation in treatment and follow-up. Ten participants completed the first psilocybin session. Of the seven participants completing the second psilocybin session, six received psilocybin 0.4 mg/kg and are included in analysis of second session effects. One received psilocybin 0.3 mg/kg due to meeting criteria for “complete mystical experience” in the first session. Nine participants completed all follow-up assessments and are included in outcome analyses. One participant discontinued participation shortly after the first psilocybin session and did not provide usable outcome data. A total of 14 MET sessions were coded for fidelity using the MITI 3.1. Mean (SD) global scores ranged from 4.43 (0.76) to 5.00 (0.00), well above the proficiency benchmark of 4.0.

Acute effects

Figure 2 illustrates physiologic effects and monitor ratings during the first psilocybin session, in which all participants received psilocybin 0.3 mg/kg, and during the second psilocybin session for the six participants who received psilocybin 0.4 mg/kg. Systolic or diastolic blood pressure was modestly but significantly increased from 30 minutes to 180 minutes in one or both conditions. Heart rate (not shown) did not change significantly. Monitor ratings of global drug effect and “distance from ordinary reality” peaked between 120 and 180 minutes, and were significantly elevated at most time points. Differences in these measures between the two doses were not statistically significant (paired *t*-tests, $df = 5$).

Table 1 shows mean scores on self-report measures of subjective experience obtained 7 hours following administration of psilocybin 0.3 mg/kg in the first session and for the six participants who received psilocybin 0.4 mg/kg in the second session. Intensity of effects varied markedly from patient to patient. On average, acute effects on the MEQ and HRS are numerically lower in magnitude than those seen at comparable doses in normal volunteers (Griffiths et al., 2011). For the six participants who received psilocybin 0.4 mg/kg in the second session, subjective ratings were not significantly different between the two sessions (paired *t*-tests, $df = 5$), but were strongly correlated between the sessions for most of the scales intended to measure hallucinogen effects.

Clinical outcomes

Percent heavy drinking days decreased during weeks 5–12 relative to baseline (mean difference (SD) = 26.0 (22.4), 95% CI 8.7–43.2, $t(8) = 3.477$, $p = 0.008$), and also decreased relative to weeks 1–4 (during psychosocial treatment but prior to psilocybin) (mean difference (SD) = 18.2 (20.0), 95% CI 2.8–33.5, $t(8) = 2.723$, $p = 0.026$). Percent drinking days also decreased during weeks 5–12 relative to baseline (mean difference (SD) = 27.2 (23.7), 95% CI 9.0–45.4, $t(8) = 3.449$, $p = 0.009$) and relative to weeks 1–4 (mean difference (SD) = 21.9 (21.8), 95% CI 5.1–38.6, $t(8) = 3.010$, $p = 0.017$). Figure 3 illustrates change in

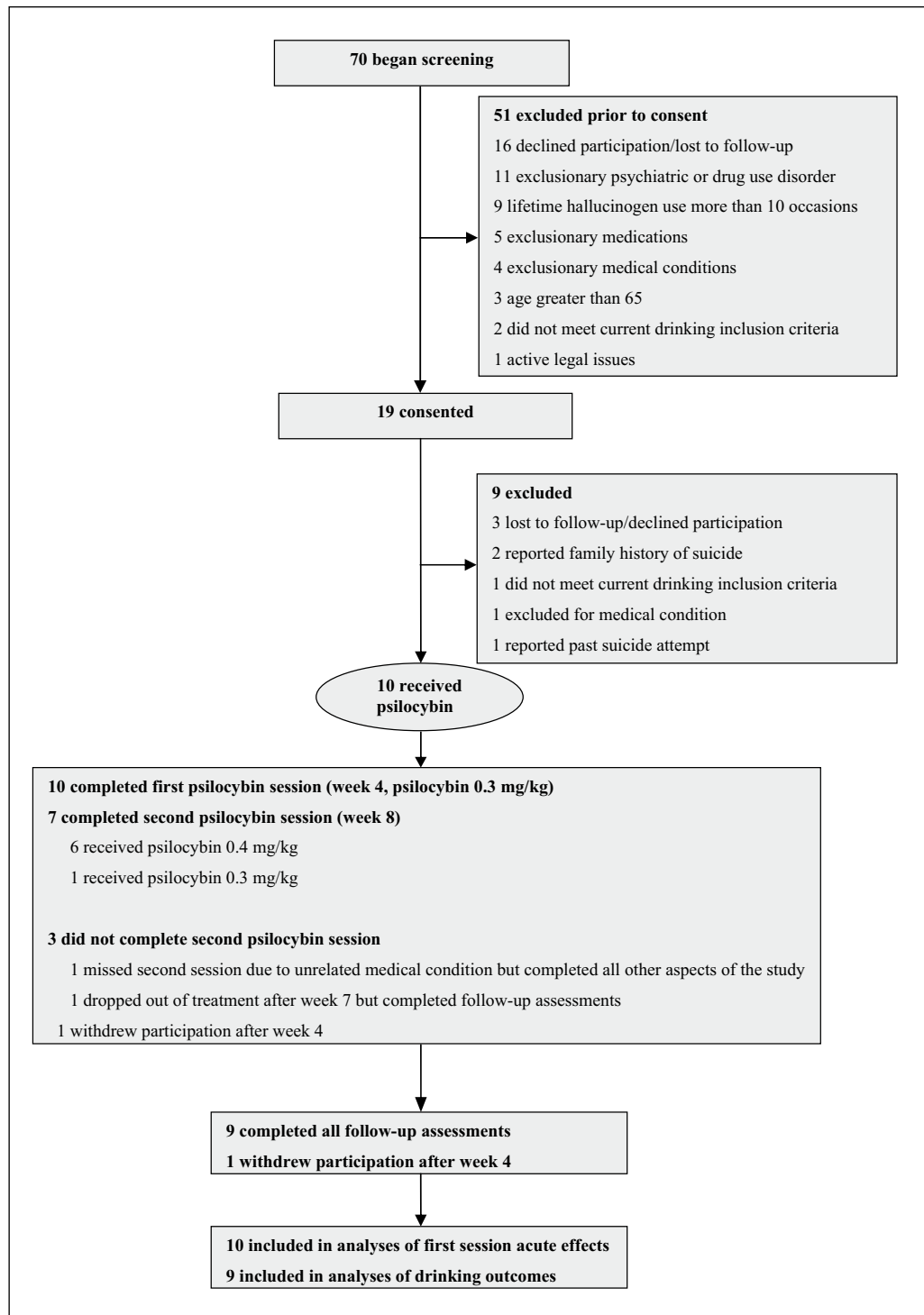


Figure 1. Participant flow.

percent heavy drinking days and percent drinking days over the course of the study. Improvement is not statistically significant during the first 4 weeks of participation, when participants received weekly counseling but had not yet received psilocybin. Following the first psilocybin session, percent heavy drinking days and percent drinking days are significantly lower than baseline at all follow-up points. Further, these measures are

significantly decreased relative to weeks 1–4 with the exception of heavy drinking days during weeks 9–12 ($p = 0.059$). Fifteen out of 16 contrasts were significant at the nominal 0.05 level, and all of these remained significant at a false discovery rate of 0.05. Effect sizes are large (greater than 0.8) with one exception, Cohen's d ranging from 0.75 to 1.38. Table 2 summarizes additional outcomes for study participants. Significant improvement

relative to baseline and/or week 4 is noted at multiple time points for drinking consequences, craving, self-efficacy, and motivation. Changes in POMS scores were not significant with one exception (increased Vigor at week 24 relative to baseline).

Relationships between acute effects and treatment response

Because the acute effects of psilocybin were quite variable, it was possible to explore the relationships between the intensity of acute effects and changes in drinking behavior. Table 3 shows correlations between three summary measures of the intensity of acute effects in the first psilocybin session and short-term clinical outcomes. Large correlations were observed between measures of acute effect intensity and change in drinking behavior, as well as changes in craving and self-efficacy in some cases. Supplemental Figure 1 displays scatterplots of the individual data points underlying these correlations.

Treatment-related adverse events

Five participants reported mild headaches which resolved within 24 hours following psilocybin administration, consistent with prior reports (Johnson et al., 2012). One participant had nausea with one episode of emesis during one psilocybin session. One participant with irritable bowel syndrome experienced diarrhea during one psilocybin session. One participant reported insomnia on the night following a psilocybin session. No participant required medication or other intervention for blood pressure, anxiety, or other psychiatric symptoms. There was no report of illicit hallucinogen use by any participant during study participation.

Discussion

Overall, the response of our alcohol-dependent participants to psilocybin was qualitatively similar to that which has been reported in other samples (Hasler et al., 2004; Griffiths et al., 2006, 2011; Grob et al., 2011). Medication-related AEs were transient and mild. However, subjective response was highly variable among participants in this study, and numerically weaker on average for some of the measures than that reported in normal volunteers at comparable doses (Griffiths et al., 2011). This is consistent with observations beginning in the 1950s that alcoholics tended to require larger doses of LSD to have a strong effect (Chwelos et al., 1959). Our findings suggest that some alcohol-dependent patients are relatively insensitive to the effects of psilocybin, although larger samples will be necessary to confirm this. The lack of significant differences between the 0.3 mg/kg and 0.4 mg/kg doses is most likely accounted for by the small sample size ($n = 6$) and/or idiosyncratic responses in a small number of participants.

Participants exhibited significant improvement in drinking, with large pre–post effect sizes, as well as significant changes in psychological measures relevant to drinking. Importantly, much of the improvement occurred following the administration of psilocybin, at which time participants had already received 4 weeks of psychosocial treatment and 4–6 hours of assessment. Also, strong correlations were observed between measures of intensity of the acute drug effects and clinical outcomes. Although

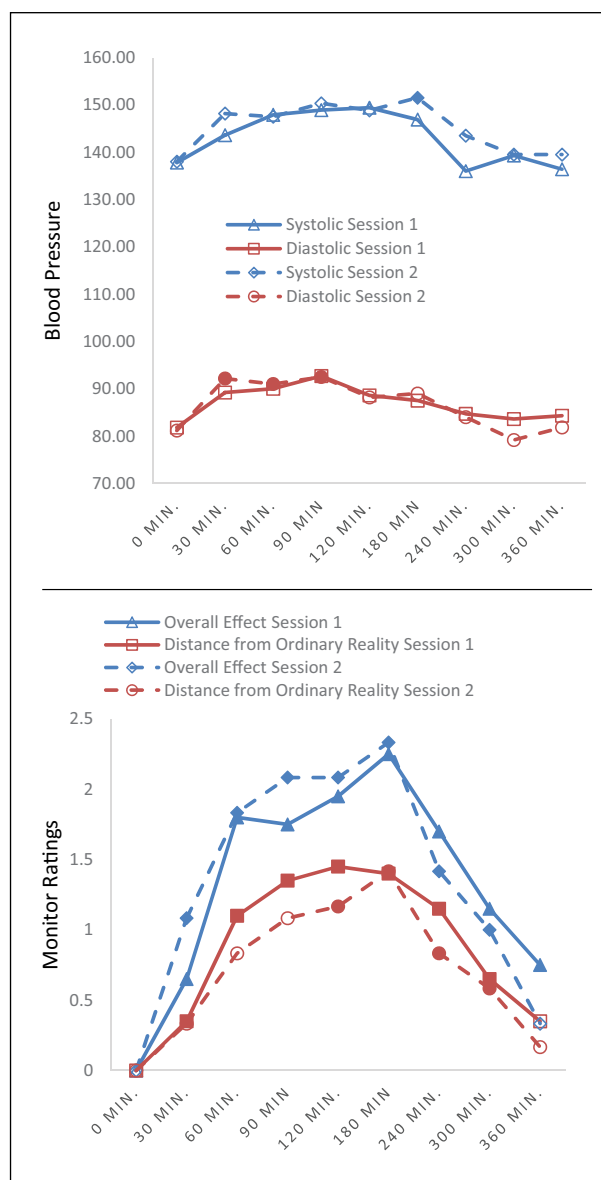


Figure 2. Within-session objective effects. Blood pressure (mm Hg) monitor ratings (0–4 Likert Scale).

Means are shown for 10 participants receiving psilocybin 0.3 mg/kg in the first session (solid lines), and the six participants who received psilocybin 0.4 mg/kg in the second session ($n = 6$, dashed line) during the 6 hours following drug administration. Solid markers indicate significant difference from baseline value.

change in drinking was correlated with the mystical quality of the experience, it was similarly associated with ratings of other acute effects. More work will necessary to determine whether there are particular characteristics of the acute psilocybin experience that are predictive of therapeutic benefit in alcohol use disorder.

While clearly demonstrating feasibility, this study has major, self-evident limitations including small sample size, lack of a control group or blinding, and lack of biological verification of alcohol use. Due to these limitations, it is not possible to separate unequivocally the effects of attention, psychosocial treatment, and time; expectancy effects related to knowledge of receiving psilocybin; and the specific effects of psilocybin. However, the

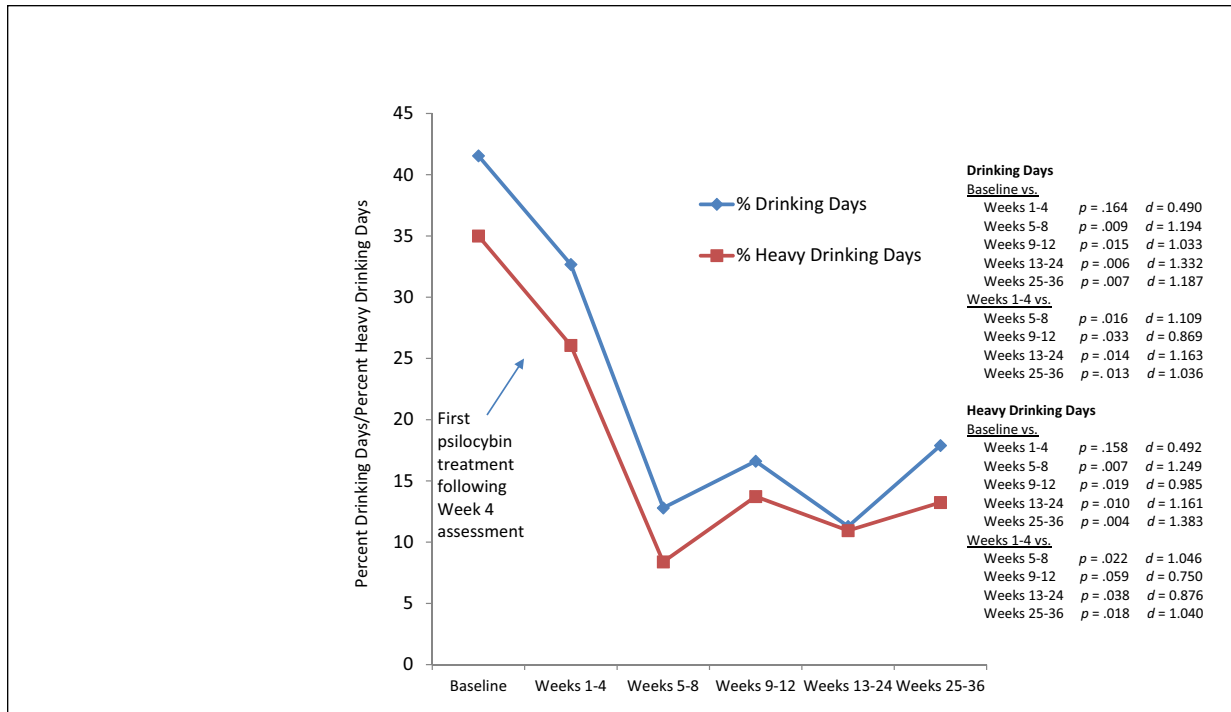


Figure 3. Drinking outcomes and effect sizes.

Means shown are for all available data ($n = 10$ at baseline, $n = 9$ at all other time points). p -values are from paired t -tests ($df = 8$). Cohen's d is shown for the contrast between baseline or weeks 1–4 and each follow-up time point.

Table 1. Acute effects of psilocybin 0.3 mg/kg and 0.4 mg/kg.

	0.3 mg/kg Session 1 ($n = 10$)				0.4 mg/kg Session 2 ($n = 6$)				r ($n = 6$)	Sig.
	Mean	(SD)	Min.	Max.	Mean	(SD)	Min.	Max.		
ASC OBN	960.4	(518.8)	91	1798	785.0	(977.3)	79	2107	0.649	0.163
ASC DED	499.6	(515.8)	38	1515	340.1	(445.2)	26	1021	0.808	0.052
ASC VRS	923.5	(396.8)	61	1516	610.2	(543.5)	188	1462	0.670	0.145
ASC AUA	302.5	(380.9)	26	1166	182.0	(288.5)	18	766	0.960	0.002
ASC VIR	394.2	(268.1)	49	819	244.4	(333.0)	36.5	883	0.828	0.042
G-ASC	2383.5	(1347.7)	235	4628	1735.3	(1761.1)	337.5	4590	0.827	0.042
MEQ total	0.473	(0.217)	0.016	0.768	0.387	(0.347)	0.011	0.924	0.843	0.035
HRS intensity	2.43	(1.03)	0	3.5	2.00	(1.14)	0.25	3.25	0.902	0.014
ARCI PCAG	8.00	(3.06)	3	12	5.50	(4.04)	1	12	0.287	0.581
ARCI BG	5.40	(1.58)	3	8	5.83	(2.99)	2	11	0.167	0.752
ARCI A	4.78*	(2.37)	0	8	4.50	(2.88)	2	9	0.198	0.707
ARCI MBG	5.33*	(3.61)	4	12	6.33	(4.55)	2	13	0.388	0.448
ARCI LSD	8.10	(3.21)	1	13	8.17	(2.99)	4	12	0.405	0.425

Shown are scores for all 10 participants in session 1, scores for the six participants who received psilocybin 0.4 mg/kg in the second session, and correlations between scores for the two sessions for these six participants.

* $n = 9$ due to incomplete questionnaire from one participant.

ASC: 5-Dimensional Altered States of Consciousness Scale; OBN: Oceanic Boundlessness subscale; DED: Dread of Ego Dissolution subscale; VRS: Visionary Restructuralization subscale; AUA: Auditory Alterations subscale; VIR: Vigilance Reduction subscale; G-ASC: summary score (sum of OBN, DED, and VRS); MEQ: Mystical Experience Questionnaire; HRS Intensity: Intensity subscale of the Hallucinogen Rating Scale; ARCI: Addiction Research Center Inventory; PCAG: Phenobarbital, Chlorpromazine, Alcohol Group subscale (sedation); BG: Benzadrine group subscale (stimulant); A: Amphetamine subscale (stimulant); MBG: Morphine-Benzadrine group subscale (euphoria); LSD: LSD subscale (dysphoria). Instruments are described in Methods section.

Table 2. Secondary outcomes.

	Baseline	Week 4	Week 5	Week 8	Week 9	Week 12	Week 24	Week 36
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
SIP								
Physical	4.60 (2.27)					4.89 (3.14)	2.78 (2.95)	2.78 (3.35)
Interpersonal	4.80 (2.57)					4.44 (3.17)	2.56 (3.05)**	2.56 (2.88)**
Intrapersonal	7.30 (1.70)					6.00 (3.12)	3.89 (3.76)*	3.67 (3.74)*
Impulse control	2.90 (1.29)					3.89 (2.47)	2.56 (2.24)	2.56 (3.05)
Responsibility	4.50 (2.37)					4.22 (3.46)	3.67 (3.81)	2.67 (2.87)
PACS	16.00 (5.59)	14.10 (7.17)	11.89 (8.64)	11.56 (5.85)*	10.00 (6.61)**§	12.11 (8.28)*	13.00 (9.59)	8.11 (9.16)***,§
AASE								
Temptation	38.30 (12.80)	38.10 (18.17)	28.11 (18.86)	32.78 (21.09)	24.56 (16.80)*,§	32.56 (21.67)	26.63 (18.70)*	27.22 (21.86)§
Confidence	40.10 (12.58)	40.30 (16.66)	55.56 (10.88)*,§§	49.00 (11.90)	53.67 (12.76)§	50.00 (13.21)	50.44 (13.09)	54.00 (19.87)§
SOCRATES								
Recognition	31.80 (3.22)	31.10 (5.26)	31.11 (5.33)	31.78 (5.89)	31.89 (5.33)	30.38 (8.02)	28.67 (7.89)	26.78 (9.56)
Ambivalence	15.70 (3.65)	13.90 (5.93)	14.22 (5.31)	14.56 (5.81)	13.11 (6.13)	13.00 (6.48)	12.00* (5.20)	11.56* (4.90)
Taking Steps	32.30 (3.20)	34.00 (5.03)	36.33 (2.65)*	36.33 (2.65)**	37.33 (3.46)**§	35.78 (3.80)*	36.00 (4.12)*	33.78 (5.36)
POMS								
Tension	7.20 (5.27)	6.22 (3.42)	4.67 (3.54)	5.78 (4.44)	5.89 (4.88)	8.00 6.06	5.78 (5.97)	5.33 (6.04)
Depression	6.50 (5.60)	3.40 (4.45)	4.89 (6.41)	4.44 (3.50)	3.22 (4.38)	6.78 7.45	6.11 (6.11)	5.00 (4.58)
Anger	4.40 (4.09)	2.40 (3.13)	4.67 (4.61)	3.89 (4.62)	2.22 (2.64)	4.50 (6.61)	3.56 (5.48)	4.56 (6.46)
Vigor	5.60 (4.01)	6.50 (3.34)	8.56 (4.61)	8.11 (5.46)	9.00 (5.85)	7.75 4.10	9.56 (4.90)*	7.50 (2.78)
Fatigue	8.70 (5.79)	6.60 (5.78)	6.22 (6.44)	5.44 (4.75)	5.56 (4.28)	7.67 6.28	6.67 (5.96)	6.89 (4.08)
Confusion	6.10 (2.69)	3.90 (1.79)*	4.67 (2.96)	5.33 (3.71)	5.56 (3.43)	5.13 3.36	5.56 (2.19)	4.44 (2.51)

SIP: Short Inventory of Problems; PACS: Penn. Alcohol Craving Scale; AASE: Alcohol Abstinence Self-Efficacy; SOCRATES: Stages of Change Readiness and Treatment Eagerness Scale; POMS: Profile of Mood States.

* Different from baseline, $p < 0.05$; ** Different from baseline, $p < 0.01$; *** Different from baseline, $p < 0.001$; § Different from week 4, $p < 0.05$; §§ Different from week 4, $p < 0.01$.

$n = 10$ at baseline and 4 weeks, and $n = 9$ at weeks 5–36 with the following exceptions due to missing questionnaire items: $n = 9$ for PACS baseline; $n = 8$ for SOCRATES Recognition week 12; AASE Confidence week 12; AASE Temptation week 24; POMS Anger week 12, POMS Confusion week 12, and POMS Vigor week 36.

Table 3. Correlations between acute effects and change in drinking, craving, and self-efficacy ($n = 9$).

	PDD (wk. 8 – wk. 4)	PHDD (wk. 8 – wk. 4)	PACS (wk. 5 – wk. 4)	AASE (wk. 5 – wk. 4)
HRS Intensity (wk. 4)	$r = -.844$ $p = .004$	$r = -.763$ $p = .017$	$r = -.823$ $p = .006$	$r = .753$ $p = .019$
MEQ total (wk. 4)	$r = -.885$ $p = .002$	$r = -.852$ $p = .004$	$r = -.810$ $p = .008$	$r = .762$ $p = .017$
G-ASC (wk. 4)	$r = -.838$ $p = .005$	$r = -.893$ $p = .001$	$r = -.654$ $p = .056$	$r = -.555$ $p = .121$

PDD: Percent Drinking Days; PHDD: Percent Heavy Drinking Days; PACS: Penn Alcohol Craving Scale; *AASE = Alcohol Abstinence Self-Efficacy Confidence score; HRS: Hallucinogen Rating Scale Intensity score; MEQ: Mystical Experience Questionnaire; G-ASC: Altered States of Consciousness Scale summary score.

time course of the observed changes and the striking relationship between intensity of response and clinical improvement provide support for the concept that psilocybin may produce lasting benefits in alcohol use disorder when administered under controlled conditions to carefully screened patients, in the context of appropriate psychosocial interventions. Adequately powered randomized trials will be necessary to test this hypothesis rigorously. Neuroimaging studies in alcohol use disorder trial participants would help characterize the persisting effects of psilocybin on brain activity (e.g. resting state functional connectivity, cue response, stress response, response to emotional stimuli, and inhibitory control). Studying the genetics of response to psilocybin may shed light on the variability of response, ultimately aiding in dose selection or identifying patients particularly likely to benefit.

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