Classic Psychedelics in Addiction Treatment: The Case for Psilocybin in Tobacco Smoking Cessation

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Contents

Abstract This manuscript reviews research suggesting that classic psychedelics (5-HT2A receptor agonists) are effective in treating addictions including tobacco use disorder. I review historical research from the 1950s to 1970s suggesting that classic psychedelics are associated with addiction recovery across pharmacologically distinct drugs of addiction. I then review anthropological reports about ceremonial use of classic psychedelics and epidemiological studies that are consistent with anti-addiction efficacy. I review modern research using psilocybin in the treatment of alcohol use disorder and tobacco use disorder. Both lines of research show high success rates in preliminary studies. General anti-addiction efficacy across a variety of classes of addictive drugs is consistent with the notion that the persisting positive behavior change prompted by psychedelic therapy is due to amplification of psychotherapeutic processes. Future research should examine classic psychedelic treatment of additional substance use disorders including for opioids, cocaine, methamphetamine, and cannabis, and other disorders broadly characterized as addictions (e.g., obesity, problem gambling, hypersexual disorder). Future research should also explore addiction treatments with other classic psychedelics including LSD, mescaline, DMT, 5-MeO-DMT, and yet-to-be-discovered

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compounds. Experimental research is also needed to test different protocols for the delivery of classic psychedelic therapy for addictions. Given the staggering society costs of substance use disorders, including the mortality caused by tobacco smoking, it is critical that public funding be made available for scientists to follow up on promising early findings of classic psychedelics in addiction treatment. The costs and risks of not conducting such research are too great.

Keywords Addiction · Hallucinogens · Psilocybin · Psychedelics · Smoking cessation · Substance use disorders · Tobacco use disorder

Annual smoking-related mortalities are estimated at 480,000 in the USA (US Department of Health and Human Services 2014) and nine million annually worldwide (Murray et al. 2020). These numbers dwarf similar statistics for all other drugs of abuse. In the USA, smoking is responsible for approximately five to seven times more deaths than alcohol, and approximately 26 times more deaths than all illicit drugs combined (Danaei et al. 2009; Mokdad et al. 2004). Most behavioral interventions and pharmacotherapies for smoking cessation have only modest long-term success rates (e.g., typically <35% at 6 months post-quit attempt; Cahill et al. 2014; Mottillo et al. 2009). These statistics are particularly devastating because 68% of US smokers want to quit (Babb et al. 2017). The staggering death toll of smoking and unmet clinical need means that novel approaches are desperately needed.

This manuscript reviews research suggesting that classic psychedelics might be effective in treating substance use disorders including tobacco use disorder. The classic psychedelics are defined as drugs with agonist activity at 5-HT2A receptor (5-HT2AR) as a primary mechanism, with prototypes including psilocybin (which is a prodrug for psilocin), lysergic acid diethylamide (LSD), mescaline, and dimethyltryptamine (DMT). Within this context of classic psychedelics as potential anti-addiction medicines, a special focus will be placed on work examining psilocybin as a smoking cessation medication for tobacco use disorder. First, I will describe historical clinical research evidence from the 1950s to 1970s suggesting that classic psychedelics are associated with addiction recovery across pharmacologically distinct drugs of addiction. I will then review nonclinical lines of evidence suggesting that classic psychedelics may possess anti-addiction efficacy, including anthropological reports about ceremonial use of classic psychedelics by indigenous societies and syncretic religions, and epidemiological studies. Next, I will describe modern research examining psilocybin in the treatment of alcohol use disorder. Then I will review extensively the evidence related to psilocybin and other classic psychedelics and tobacco smoking cessation. I will conclude by recommending future directions.

1 Historical Research

Although anthropological evidence suggests that 5-HT2AR agonists have been used by various indigenous peoples as sacraments and healing agents before recorded history (Akers et al. 2011), in the mid-twentieth century they came to occupy a place at the cutting edge of psychiatric research (Johnson et al. 2008). Although studies generally did not meet modern scientific standards (Bonson 2018), over 1,000 papers were published during the mid-twentieth century that described the treatment of over 40,000 patients with 5-HT2AR agonists (Grinspoon 1981). In addition to basic research, therapeutic applications of 5-HT2AR agonists were investigated, with promising findings in the treatment of both addiction and cancer-related existential distress (Johnson and Griffiths 2017).

During the twentieth-century zenith of 5-HT2AR agonist research from the 1950s through the 1970s, addiction was a main therapeutic target. The primary form of addiction treated was alcoholism, and the most frequently studied classic psychedelic to treat alcoholism was LSD, although mescaline (e.g., Smith 1958, 1959) and dipropyltryptamine (Rhead et al. 1977) were also examined. Investigators in Saskatchewan, Canada hypothesized that classic psychedelics might mimic delirium tremens, which sometimes prompted sobriety (Chwelos et al. 1959; Dyck 2006; Smith 1958). However, undergoing delirium tremens was dangerous and sometimes fatal, so the rationale was to prompt a similar experience with a drug like LSD which was relatively safe physiologically. Instead of observing reactions resembling delirium tremens, researchers often observed "mind-manifesting" experiences that could be leveraged for psychotherapy and prompt sobriety. Some of the early studies in the literature showed nonsignificant positive trends for LSD, leading to conclusions that efficacy was undetermined (e.g., Abuzzahab and Anderson 1971; Mangini 1998). More recently, a meta-analysis examined all of the studies that randomized patients to an LSD or control condition (six studies; $N = 536$), and found in aggregate a significant and large decrease in alcohol misuse at the first follow-up ($\geq$1 month post-treatment) for the LSD groups compared to control groups (Krebs and Johansen 2012).

Early research hinted that the classic psychedelics might have broad applicability in treating substance use disorders beyond alcoholism. Savage and McCabe (1973) tested LSD in the treatment of opioid dependence in a study of 78 heroin-using individuals under judicial correctional supervision. The study randomized individuals to undergo either a single administration of LSD (300–450 microgram) during a six-week residential stay or undergo a control condition with outpatient clinic visits, daily urine drug testing, and weekly group therapy. At all timepoints examined, the group that received LSD showed significantly greater biologically confirmed drug abstinence. At this longest follow-up of 12 months post-treatment, continuous abstinence rates were 25% and 5% in the LSD group and control groups, respectively. Although the results were limited by the fact that the LSD group received a six-week residential stay not experienced by the control group, the large difference in biologically confirmed abstinence indicated the approach was worthy of more intensive follow-up.

2 Resurgence of Modern-Day Research

Despite initial excitement, research on 5-HT2AR agonists became increasingly marginalized due to their growing use outside of clinical research settings, and their association with the counter-culture movement in the late 1960s and early 1970s. In the 1990s a small number of investigators in Europe and the USA re-initiated human studies with 5-HT2AR agonists (e.g., Spitzer et al. 1996; Strassman and Qualls 1994; Vollenweider et al. 1997). Non-human research in the intervening decades had identified agonist activity at 5-HT2AR as a key mechanism underlying the effects of classic psychedelics (e.g., Glennon et al. 1984), which include LSD as well as psilocybin (present in many mushroom species), mescaline (present in peyote and some other cacti), and dimethyltryptamine (DMT; present in a variety of plants). Studies by researchers since the 1990s have followed safety guidelines for administering 5-HT2AR agonists (Johnson et al. 2008). These guidelines involve careful screening and preparation before drug administration sessions, close monitoring during sessions, and follow-up care involving both clinically supportive discussion of session experiences and assessment for any adverse effects resulting from the session. Therapeutic effects of 5-HT2AR agonists have been reported for depression and anxiety related to cancer and other life-threatening illness (Gasser et al. 2014; Griffiths et al. 2016; Grob et al. 2011; Ross et al. 2016), major depressive disorder (Carhart-Harris et al. 2016, 2021; Davis et al. 2021; Palhano-Fontes et al. 2019), tobacco use disorder (Johnson et al. 2014, 2017a), and alcohol use disorder (Bogenschutz et al. 2015). Some studies have been randomized trials, while others have been initial non-randomized pilot studies designed to establish safety in new populations and test the waters for future randomized trials. Some of these studies have reported rapid efficacy persisting for at least 6 months after one or a few 5-HT2AR agonist administrations (for review, see Johnson et al. 2019).

3 Anthropological Evidence

Various anthropological reports have suggested that 5-HT2A agonist use in the context of ritualized sacramental practices of indigenous cultures is associated with high rates of recovery from addiction, achievement of long-term abstinence, and lower rates of addictive substance use. Such reports include those of peyote (5-HT2AR agonist mescaline) ceremonies within the Native American Church in the USA (Albaugh and Anderson 1974; Bergman 1971; Blum et al. 1977; Calabrese 1997; Menninger 1971; Pascarosa and Futterman 1976; Roy 1973) and ayahuasca (5-HT2AR agonist dimethyltryptamine) ceremonies within certain Amazonian societies and syncretic religions (Dobkin de Rios et al. 2002; Doering-Silveira et al. 2005; Fábregas et al. 2010; Halpern et al. 2008). It is not possible to definitively differentiate the causal role of the drug from the larger context of religious guidance

and community support provided in these settings. However, one large survey of over 8000 people in over 40 countries reported regression results suggesting that the association of ayahuasca use and lower use of addictive substances was apparent even after controlling for religious and social variables (Perkins et al. 2022).

4 Epidemiological Research

Using 6 years of data from the National Survey on Drug Use and Health, one analysis among people who had ever used illicit opioids ($N = 44{,}000$) found that a lifetime history of 5-HT2AR agonist use was associated with a significant 27% reduced risk of opioid dependence in the past year (Pisano et al. 2017). My laboratory recently conducted an online survey of individuals ($N = 343$) with prior AUD reporting cessation or reduction in alcohol use following 5-HT2AR agonist use in nonclinical settings (Garcia-Romeu et al. 2019). Participants reported 7 years of problematic alcohol use on average before the psychedelic experience to which they attributed reduced alcohol consumption. We also recently conducted an online survey of individuals reporting cessation or reduction in cannabis, opioid, or stimulant use following 5-HT2AR agonist use in nonclinical settings (Garcia-Romeu et al. 2020). Participants ($N = 444$) reported 4.5 years of problematic substance use on average before the psychedelic experience to which they attributed a reduction in drug consumption. In both Hopkins survey studies, greater 5-HT2AR agonist dose, insight, and personal meaning were associated with greater reductions in substance use. Like the anthropological studies, these surveys cannot definitively address the causal role of 5-HT2AR agonist use on addiction. However, combined with the clinical research described above, these survey data are suggestive of anti-addiction efficacy. It should be noted that the uncontrolled use of 5-HT2AR agonists is also associated with demonstrable harms (Carbonaro et al. 2016; Johnson et al. 2008). If these survey findings are suggesting anti-addictive effects can occur with uncontrolled use, carefully conducted clinical research (that includes screening, preparation, monitoring, and aftercare) is expected to further minimize the risks associated with uncontrolled use and to maximize the efficacy of 5-HT2AR agonists to increase abstinence.

5 Modern Research in Alcohol Use Disorder

Bogenschutz et al. (2015) conducted the first modern research using a 5-HT2AR agonist to treat alcohol use disorder. They administered one or two doses of psilocybin (0.3 and 0.4 mg/kg) and motivational enhancement therapy to ten treatment-seeking volunteers meeting DSM-IV criteria for alcohol dependence in an open-label trial. The percentage of drinking days and the percentage of heavy drinking days significantly decreased after the first psilocybin session. At 36 weeks

after treatment, the mean percentage of drinking days dropped from ~32.5% in the 4 weeks of treatment preceding the psilocybin session to ~12.5% in the 4 weeks following the psilocybin session, and ~17.5% during the final follow-up period of 21–32 weeks after the psilocybin session. Mean percentage of heavy drinking days (i.e., ≥5 drinks for men, ≥4 drinks for women) dropped from ~26% in the 4 weeks of treatment preceding the psilocybin session to ~8% in the 4 weeks following the psilocybin session, and ~13% at the final follow-up period 21–32 weeks after the psilocybin session. Consistent with earlier studies of LSD (Kurland et al. 1967; Pahnke et al. 1970), and contemporary pilot research of psilocybin treatment for tobacco use disorder (Garcia-Romeu et al. 2014), subjective effects of the drug experience (e.g., mystical-type effects, intensity) appeared to be potential key factors facilitating subsequent behavior changes (Bogenschutz et al. 2015; Nielson et al. 2018). Additional controlled research on the psilocybin-facilitated treatment of alcohol use disorder is currently underway (US National Library of Medicine 2021a).

6 Psychedelics in Tobacco Smoking Cessation

Given the older laboratory studies and anthropological studies suggesting anti-addiction efficacy of 5-HT2AR agonists across distinct classes of addictive drugs, my laboratory embarked on a line of research examining 5-HT2AR agonist psilocybin therapy for a previously unstudied target: Tobacco use disorder. We conducted an open-label pilot study in 15 nicotine-dependent, treatment-resistant cigarette smokers (Johnson et al. 2014). Participants consisted of ten men and five women. They were on average 51 years old, had been smoking for an average of 31 years, had made six prior serious cessation attempts, and smoked an average of 19 cigarettes per day. In addition to up to three psilocybin sessions, the intervention involved a 15-week program of manualized cognitive behavioral therapy (CBT) for smoking cessation. There were four preparation sessions for a collective total of approximately 8 h. These preparation sessions included CBT material in preparation for quitting smoking as well as preparation for the psilocybin sessions (see Johnson et al. 2008). The dose delivered in the first session was 20 mg/70 kg. We included two additional sessions at 2 and 8 weeks after the target quit date. The timing of these was determined by examining typical survival curves for smoking cessation, and selecting times during the portion of the survival curve with greatest risk of lapse. For the second and third psilocybin sessions, we administered a higher dose of 30 mg/70 kg unless the participant judged the first session dose to be sufficiently high. Only of the 15 participants opted to not increase the dose after the first session. Intermixed with the psilocybin administrations, participants came to the laboratory once per week, during which CBT material was covered.

As shown in Fig. 1, at 6 months post-target quit date, 12 out of 15 participants (80%) showed biologically verified 7-day point-prevalence abstinence (via breath CO and urine cotinine analysis) (Johnson et al. 2014). At 12-month follow-up, and at

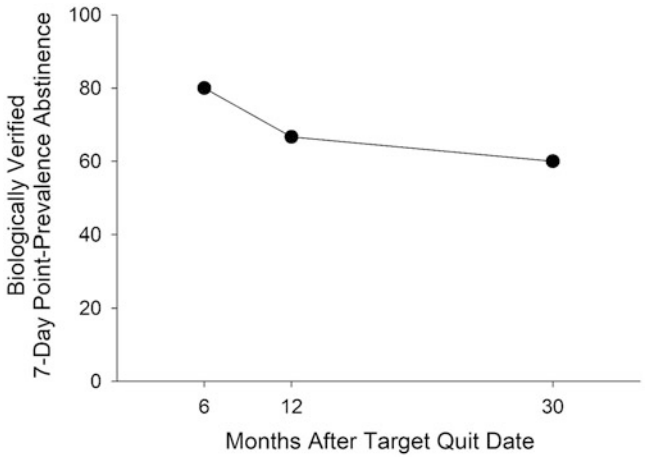

Fig. 1 Seven-day point-prevalence abstinence data as originally reported in Johnson et al. (2014, 2017a). Self-report data were biologically verified by both breath CO and urinary cotinine assays. The 30-month timepoint is the mean of long-term follow-up intervals that varied considerably across participants (range = 16–57 months)

the very long-term follow-up which was an average of 2.5 years after the target quit date, biologically confirmed point-prevalence abstinence rates were 67% and 60%, respectively (Johnson et al. 2017a). As shown in Fig. 2, continuous abstinence rates were 53% and 47% at the 12-month and 2.5-year follow-ups, respectively. Nine of the 15 participants (60%) met the threshold criteria to qualify as having had a "complete" mystical-type experience in at least one of their multiple sessions (Garcia-Romeu et al. 2014). A mystical experience is defined as an experience entailing the qualities of unity (e.g., with all things and humanity), sacredness, noesis, positive mood, transcendence of time and space, and ineffability (Johnson et al. 2019). This psychological construct is nominally divorced from any endorsement of the supernatural or of religion. Previous research in our research group and other research groups has shown that mystical experience as assessed on the session day is related to several positive long-term psychological outcomes including increases in the personality domain known as openness to experience in healthy volunteers (MacLean et al. 2011), decreases in depression and anxiety symptoms in cancer patients (Griffiths et al. 2016; Ross et al. 2016), decreases in alcohol use among those with alcohol use disorder (Bogenschutz et al. 2015), and decreases in depressive symptoms in those with major depressive disorder (Roseman et al. 2018). Those who were smoking abstinent at 6 months had significantly higher mystical-type experience scores on their session days. Moreover, a significant relationship was shown between greater mystical-type experience score on their session days, and greater cigarette craving reduction from study intake to the six-month follow-up.

At an average of 2.5 years after the target quit date, we conducted structured qualitative interviews with 12 of the 15 participants (Noorani et al. 2018). Key themes that emerge from participant interviews were that the psilocybin sessions had

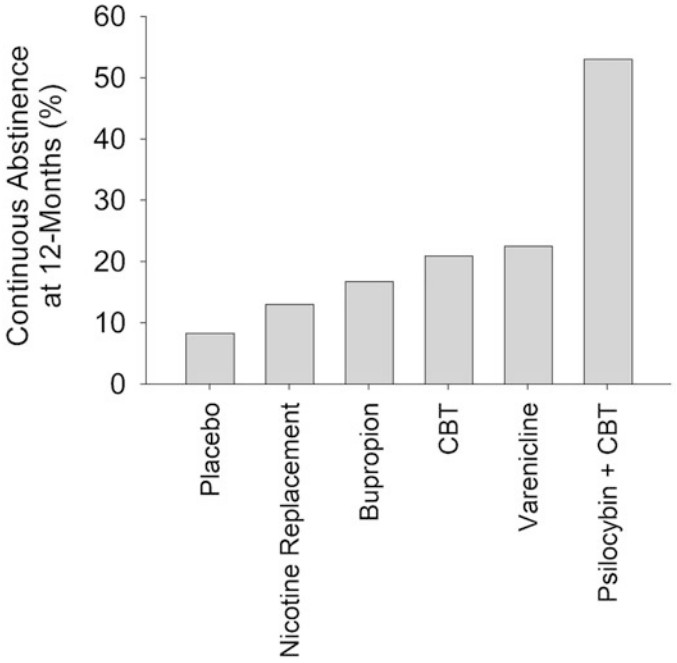

Fig. 2 Continuous abstinence rates for the psilocybin + CBT approach in the pilot study reported by Johnson et al. (2017a) compared to other smoking cessation results. The placebo, nicotine replacement, bupropion, and varenicline data are literature aggregate values provided by Jackson et al. (2019). CBT data are from primary care literature values provided by Wittchen et al. (2011). Although difference among studies preclude strict comparisons of values, the relative magnitude of continuous abstinence with psilocybin + CBT suggests that the pilot study was worthy of follow-up investigation

led to insights into self-identity and reasons for smoking, and participants were left with a lasting sense of interconnectedness, awe, and curiosity, which were helpful in remaining smoke-free. Participants also reported additional benefits of the sessions unrelated to smoking cessation, such as increased prosocial behavior. The promising data from our initial study paved the way for a currently running randomized comparative efficacy study, comparing the effects of a single psilocybin session to a standard course of transdermal nicotine patch treatment, with CBT as the psychosocial backdrop in both groups (US National Library of Medicine 2021b).

The Hopkins laboratory conducted a survey study examining individuals claiming to have quit or reduced smoking due to 5-HT2AR agonists (largely psilocybin and LSD) use in nonclinical settings ($N = 781$; with 358 individuals having had the psychedelic experience at least a year before survey completion). Participants who had the psychedelic experience at least a year before survey completion typically judged their withdrawal symptoms related to negative affect (e.g., depression, irritability, craving) to be much less severe after 5-HT2AR agonist

use compared to previous occasions in which they quit smoking (Johnson et al. 2017b). Although these data cannot test a causal role of 5-HT2AR agonist use on smoking behavior, they are consistent with laboratory research suggesting a causal effect. Moreover, these results may suggest that affective processing is a commonality in psychedelic therapy, considering the studies showing 5-HT2AR agonists to decrease depressive symptoms (Carhart-Harris et al. 2016, 2021; Davis et al. 2021; Gasser et al. 2014; Griffiths et al. 2016; Grob et al. 2011; Palhano-Fontes et al. 2019; Ross et al. 2016).

7 Future Directions

The reviewed data suggests that classic psychedelics hold promise as treatments for substance use disorders. Pilot research suggests promise in using psilocybin in the treatment of both tobacco use disorder and alcohol use disorder. Additional rigorous research should explore both indications, including double-blind and larger trials. The field also needs research examining dose effects in the treatment of disorders. If results continue to look promising, the conduct of Phase III trials will be appropriate, which may lead to the approval of psilocybin for these disorders by the Food and Drug Administration in the USA and other medical regulatory agencies internationally. In this respect the recent funding by the United States National Institute on Drug Abuse of a multi-site trials of psilocybin for tobacco smoking cessation may provide critical information for potential advancement along the medical pathway (Grant number U01DA052174).

Unlike most medications for substance use disorders, it may be that these therapies work against a wide variety of substance use disorders, regardless of the class of addictive drug being treated. This is suggested by early clinical evidence for alcohol use disorder (Bogenschutz et al. 2015; Krebs and Johansen 2012), opioid use disorder (Savage and McCabe 1973), and tobacco use disorder (Johnson et al. 2014). Supporting evidence also comes from anthropological and survey methods (Dobkin de Rios et al. 2002; Doering-Silveira et al. 2005; Fábregas et al. 2010; Garcia-Romeu et al. 2019, 2020; Halpern et al. 2008; Johnson et al. 2017b; Pisano et al. 2017). A general anti-addiction effect across classes of addictive drugs would be consistent with the notion that the persisting positive behavior change prompted by psychedelic therapy is due to amplification of psychotherapeutic processes such as the construction of meaning, corrective emotional experiences, and a change in self-narrative (Nayak and Johnson 2021). Such psychological mechanisms may be at play with the treatment of not only distinct substance use disorders, but also other disorders such as depression and cancer-related distress.

Given these potential general mechanisms, additional substance use disorders and other disorders which can be broadly characterized as addictions should be explored as treatment targets for classic psychedelics. As suggested by survey data (Garcia-Romeu et al. 2020), these include opioids, cocaine, methamphetamine, and cannabis. An ongoing trial is examining psilocybin in the treatment of cocaine use disorder

(US National Library of Medicine 2021c). Given ongoing concerns about the opioid crisis (Kolodny et al. 2015), we should test classic psychedelics in the treatment of opioid use disorder (e.g., clinicaltrials.gov: NCT04161066; NCT) and the treatment of chronic pain, an issue that partially drives the opioid crisis. In addition to substance use disorders, psychedelics should be examined as potential treatments for other disorders that could be considered forms of addiction. Examples include poor health behaviors such as obesity (Teixeira et al. 2021), problem gambling, and hypersexual disorder.

Another avenue for exploration is with other classic psychedelics compounds. While the large majority of therapeutic research in the last 20 years has been conducted with psilocybin, LSD was the classic psychedelic most frequently studied for addiction in the 1960s. Research should once again explore the efficacy and safety of LSD in substance use disorders. While LSD provides a much longer duration of action than psilocybin, which may possibly be beneficial in therapeutics, there should also be research with shorter acting classic psychedelics, including dimethyltryptamine (DMT) and 5-methoxy-dimethyltryptamine (5-MeO- DMT Ermakova et al. 2021) in the treatment of substance use disorders. If the longer duration is not always necessary for therapeutic effect, a shorter-duration treatment model would entail less cost and therefore increase dissemination. Beyond these, there are dozens of compounds that appear to be classic psychedelics awaiting both non-human and human research (e.g., Shulgin and Shulgin 1991, 1997).

Research should also examine how classic psychedelic therapy is delivered. One example is whether a particular psychotherapeutic backdrop (e.g., cognitive behavioral therapy, motivational enhancement therapy) or no formal therapy at all (but still including supportive preparation and follow-up sessions with treatment staff) is ideal for treating a particular disorder or type of patient with a disorder. The parameters of psychedelic therapy, including the use of eyeshades and encouragement toward introspection, are still yet to be experimentally tested. Indeed, a recent study experimentally manipulating the music played during sessions appears to be the only study to have randomized a "set and setting" variable in the context of the psychedelic treatment session (Strickland et al. 2021). Future research should manipulate a broader number of session variables (e.g., presence of music, extent of discussion, specific exercises such as examining a mirror or personal photos) to examine optimization of therapeutic response.

Given the staggering society costs of substance use disorders, including the mortality caused by tobacco smoking, it is critical that scientists conduct rigorous clinical trials to follow up on promising early findings to investigate with classic psychedelics in the treatment of substance use disorders and other addictions. To support this effort, it is time that public funding be provided to support such investigations. Twenty years of modern investigation indicates that such trials can be conducted with an acceptable level of safety when following appropriate research guidelines (Johnson et al. 2008). The costs and risks of not conducting research into classic psychedelics for addiction exceed those of conducting the science.

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References

Abuzzahab FS, Anderson BJ (1971) A review of LSD treatment in alcoholism. Int Pharmacopsychiatry 6(4):223–235. https://doi.org/10.1159/000468273

Akers BP, Francisco J, Piper A, Ruck CAP (2011) A prehistoric mural in Spain depicting neurotropic *Psilocybe* mushrooms? Econ Bot 65(2):121–128. https://doi.org/10.1007/s12231-011-9152-5

Albaugh BJ, Anderson PO (1974) Peyote in the treatment of alcoholism among American Indians. Am J Psychiatry 131(11):1247–1250. https://doi.org/10.1176/ajp.131.11.1247

Babb S, Malarcher A, Schauer G, Asman K, Jamal A (2017) Quitting smoking among adults – United States, 2000–2015. MMWR Morb Mortal Wkly Rep 65(52):1457–1464. https://doi.org/10.15585/mmwr.mm6552a1

Bergman RL (1971) Navajo peyote use: its apparent safety. Am J Psychiatry 128(6):695–699. https://doi.org/10.1176/ajp.128.6.695

Blum K, Futterman SFL, Pascarosa P (1977) Peyote, a potential ethnopharmacologic agent for alcoholism and other drug dependencies: possible biochemical rationale. Clin Toxicol 11(4):459–472. https://doi.org/10.3109/15563657708988210

Bogenschutz MP, Forcehimes AA, Pommy JA, Wilcox CE, Barbosa P, Strassman RJ (2015) Psilocybin-assisted treatment for alcohol dependence: a proof-of-concept study. J Psychopharmacol 29(3):289–299. https://doi.org/10.1177/0269881114565144

Bonson KR (2018) Regulation of human research with LSD in the United States (1949-1987). Psychopharmacology 235(2):591–604. https://doi.org/10.1007/s00213-017-4777-4

Cahill K, Stevens S, Lancaster T (2014) Pharmacological treatments for smoking cessation. J Am Med Assoc 311(2):193–194. https://doi.org/10.1001/jama.2013.283787

Calabrese JD (1997) Spiritual healing and human development in the native American church: toward a cultural psychiatry of peyote. Psychoanal Rev 84(2):237–255

Carbonaro TM, Bradstreet MP, Barrett FS, MacLean KA, Jesse R, Johnson MW et al (2016) Survey study of challenging experiences after ingesting psilocybin mushrooms: acute and enduring positive and negative consequences. J Psychopharmacol 30(12):1268–1278. https://doi.org/10.1177/0269881116662634

Carhart-Harris RL, Bolstridge M, Rucker J, Day CM, Erritzoe D, Kaelen M et al (2016) Psilocybin with psychological support for treatment-resistant depression: an open-label feasibility study. Lancet 3(7):619–627. https://doi.org/10.1016/S2215-0366(16)30065-7

Carhart-Harris R, Giribaldi B, Watts R, Baker-Jones M, Murphy-Beiner A, Murphy R et al (2021) Trial of psilocybin versus escitalopram for depression. N Engl J Med 384(15):1402–1411. https://doi.org/10.1056/NEJMoa2032994

Chwelos N, Blewett DB, Smith CM, Hoffer A (1959) Use of d-lysergic acid diethylamide in the treatment of alcoholism. Q J Stud Alcohol 20(3):577–590. https://doi.org/10.15288/qjsa.1959.20.577

Danaei G, Ding EL, Mozaffarian D, Taylor B, Rehm J, Murray CJL et al (2009) The preventable causes of death in the United States: comparative risk assessment of dietary, lifestyle, and metabolic risk factors. PLoS Med 6(4):e1000058. https://doi.org/10.1371/journal.pmed.1000058

Davis AK, Barrett FS, May DG, Cosimano MP, Sepeda ND, Johnson MW et al (2021) Effects of psilocybin-assisted therapy on major depressive disorder: a randomized clinical trial. JAMA Psychiat 78(5):481–489. https://doi.org/10.1001/jamapsychiatry.2020.3285

Dobkin de Rios M, Grob CS, Baker JR (2002) Hallucinogens and redemption. J Psychoactive Drugs 34(3):239–248. https://doi.org/10.1080/02791072.2002.10399960

Doering-Silveira E, Grob CS, Dobkin de Rios M, Lopez E, Alonso LK, Tacla C et al (2005) Report on psychoactive drug use among adolescents using ayahuasca within a religious context. J Psychoactive Drugs 37(2):141–144. https://doi.org/10.1080/02791072.2005.10399794

Dyck E (2006) 'Hitting highs at rock bottom': LSD treatment for alcoholism, 1950–1970. Soc Hist Med 19(2):313–329. https://doi.org/10.1093/shm/hkl039

Ermakova AO, Dunbar F, Rucker J, Johnson MW (2021) A narrative synthesis of research with 5-MeO-DMT. J Psychopharmacol. https://doi.org/10.1177/02698811211050543

Fábregas JM, González D, Fondevila S, Cutchet M, Fernández X, Barbosa PCR et al (2010) Assessment of addiction severity among ritual users of ayahuasca. Drug Alcohol Depend 111(3):257–261. https://doi.org/10.1016/j.drugalcdep.2010.03.024

Garcia-Romeu A, Griffiths R, Johnson M (2014) Psilocybin-occasioned mystical experiences in the treatment of tobacco addiction. Curr Drug Abuse Rev 7(3):157–164. https://doi.org/10.2174/1874473708666150107121331

Garcia-Romeu A, Davis AK, Erowid F, Erowid E, Griffiths RR, Johnson MW (2019) Cessation and reduction in alcohol consumption and misuse after psychedelic use. J Psychopharmacol 33(9):1088–1101. https://doi.org/10.1177/0269881119845793

Garcia-Romeu A, Davis AK, Erowid E, Erowid F, Griffiths RR, Johnson MW (2020) Persisting reductions in cannabis, opioid, and stimulant misuse after naturalistic psychedelic use: an online survey. Front Psych 10:955. https://doi.org/10.3389/fpsyt.2019.00955

Gasser P, Holstein D, Michel Y, Doblin R, Yazar-Klosinski B, Passie T et al (2014) Safety and efficacy of lysergic acid diethylamide-assisted psychotherapy for anxiety associated with life-threatening diseases. J Nerv Ment Dis 202(7):513–520. https://doi.org/10.1097/NMD.0000000000000113

Glennon RA, Titeler M, McKenney JD (1984) Evidence for 5-HT 2 involvement in the mechanism of action of hallucinogenic agents. Life Sci 35(25):2505–2511. https://doi.org/10.1016/0024-3205(84)90436-3

Griffiths RR, Johnson MW, Carducci MA, Umbricht A, Richards WA, Richards BD et al (2016) Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: a randomized double-blind trial. J Psychopharmacol 30(12):1181–1197. https://doi.org/10.1177/0269881116675513

Grinspoon L (1981) LSD reconsidered. Sciences 21(1):20–23. https://doi.org/10.1002/j.2326-1951.1981.tb01901.x

Grob CS, Danforth AL, Chopra GS, Hagerty M, McKay CR, Halberstadt AL et al (2011) Pilot study of psilocybin treatment for anxiety in patients with advanced-stage cancer. Arch Gen Psychiatry 68(1):71–78. https://doi.org/10.1001/archgenpsychiatry.2010.116

Halpern JH, Sherwood AR, Passie T, Blackwell KC, Ruttenber AJ (2008) Evidence of health and safety in American members of a religion who use a hallucinogenic sacrament. Med Sci Monit 14(8):SR15–SR22

Jackson SE, Kotz D, West R, Brown J (2019) Moderators of real-world effectiveness of smoking cessation aids: a population study. Addiction 114(9):1627–1638. https://doi.org/10.1111/add.14656

Johnson MW, Griffiths RR (2017) Potential therapeutic effects of psilocybin. Neurotherapeutics 14(3):734–740. https://doi.org/10.1007/s13311-017-0542-y

Johnson MW, Richards W, Griffiths RR (2008) Human hallucinogen research: guidelines for safety. J Psychopharmacol 22(6):603–620. https://doi.org/10.1177/0269881108093587

Johnson MW, Garcia-Romeu A, Cosimano MP, Griffiths RR (2014) Pilot study of the 5-HT2AR agonist psilocybin in the treatment of tobacco addiction. J Psychopharmacol 28(11):983–992. https://doi.org/10.1177/0269881114548296

Johnson MW, Garcia-Romeu A, Griffiths RR (2017a) Long-term follow-up of psilocybin-facilitated smoking cessation. Am J Drug Alcohol Abuse 43(1):55–60. https://doi.org/10.3109/00952990.2016.1170135

Johnson MW, Garcia-Romeu A, Johnson PS, Griffiths RR (2017b) An online survey of tobacco smoking cessation associated with naturalistic psychedelic use. J Psychopharmacol 31(7):841–850. https://doi.org/10.1177/0269881116684335

Johnson MW, Hendricks PS, Barrett FS, Griffiths RR (2019) Classic psychedelics: an integrative review of epidemiology, therapeutics, mystical experience, and brain network function. Pharmacol Ther 197:83–102. https://doi.org/10.1016/j.pharmthera.2018.11.010

Kolodny A, Courtwright DT, Hwang CS, Kreiner P, Eadie JL, Clark TW et al (2015) The prescription opioid and heroin crisis: a public health approach to an epidemic of addiction. Annu Rev Public Health 36(1):559–574. https://doi.org/10.1146/annurev-publhealth-031914-122957

Krebs TS, Johansen P (2012) Lysergic acid diethylamide (LSD) for alcoholism: meta-analysis of randomized controlled trials. J Psychopharmacol 26(7):994–1002. https://doi.org/10.1177/0269881112439253

Kurland AA, Unger S, Shaffer JW, Savage C (1967) Psychedelic therapy utilizing LSD in the treatment of the alcoholic patient: a preliminary report. Am J Psychiatry 123(10):1202–1209. https://doi.org/10.1176/ajp.123.10.1202

MacLean KA, Johnson MW, Griffiths RR (2011) Mystical experiences occasioned by the hallucinogen psilocybin lead to increases in the personality domain of openness. J Psychopharmacol 25(11):1453–1461. https://doi.org/10.1177/0269881111420188

Mangini M (1998) Treatment of alcoholism using psychedelic drugs: a review of the program of research. J Psychoactive Drugs 30(4):381–418. https://doi.org/10.1080/02791072.1998.10399714

Menninger J (1971) Discussion of Bergman RL (1971): Navajo peyote use: its apparent safety. Am J Psychiatr 128:695–699. https://doi.org/10.1176/ajp.128.6.695

Mokdad AH, Marks JS, Stroup DF, Gerberding JL (2004) Actual causes of death in the United States, 2000. JAMA 291(10):1238–1245. https://doi.org/10.1001/jama.291.10.1238

Mottillo S, Filion KB, Bélisle P, Joseph L, Gervais A, O'Loughlin J et al (2009) Behavioural interventions for smoking cessation: a meta-analysis of randomized controlled trials. Eur Heart J 30(6):718–730. https://doi.org/10.1093/eurheartj/ehn552

Murray CJL, Aravkin AY, Zheng P, Abbafati C, Abbas KM, Abbasi-Kangevari M et al (2020) Global burden of 87 risk factors in 204 countries and territories, 1990–2019: a systematic analysis for the global burden of disease study 2019. Lancet 396(10258):1223–1249. https://doi.org/10.1016/S0140-6736(20)30752-2

Nayak S, Johnson MW (2021) Psychedelics and psychotherapy. Pharmacopsychiatry 54(4):167–175. https://doi.org/10.1055/a-1312-7297

Nielson EM, May DG, Forcehimes AA, Bogenschutz MP (2018) The psychedelic debriefing in alcohol dependence treatment: illustrating key change phenomena through qualitative content analysis of clinical sessions. Front Pharmacol 9:132. https://doi.org/10.3389/fphar.2018.00132

Noorani T, Garcia-Romeu A, Swift TC, Griffiths RR, Johnson MW (2018) Psychedelic therapy for smoking cessation: qualitative analysis of participant accounts. J Psychopharmacol 32(7):756–769. https://doi.org/10.1177/0269881118780612

Pahnke WN, Kurland AA, Unger S, Savage C, Grof S (1970) The experimental use of psychedelic (LSD) psychotherapy. J Am Med Assoc 212(11):1856–1863. https://doi.org/10.1001/jama.1970.03170240060010

Palhano-Fontes F, Barreto D, Onias H, Andrade KC, Novaes MM, Pessoa JA et al (2019) Rapid antidepressant effects of the psychedelic ayahuasca in treatment-resistant depression: a randomized placebo-controlled trial. Psychol Med 49(4):655–663. https://doi.org/10.1017/S0033291718001356

Pascarosa P, Futterman S (1976) Ethnopsychedelic therapy for alcoholics: observations in the peyote ritual of the native American church. J Psychedelic Drugs 8(3):215–221. https://doi.org/10.1080/02791072.1976.10472016

Perkins D, Opaleye ES, Simonova H, Bouso JC, Tófoli LF, GalvÃo-Coelho NL et al (2022) Associations between ayahuasca consumption in naturalistic settings and current alcohol and drug use: results of a large international cross-sectional survey. Drug Alcohol Rev 41(1):265–274. https://doi.org/10.1111/dar.13348

Pisano VD, Putnam NP, Kramer HM, Franciotti KJ, Halpern JH, Holden SC (2017) The association of psychedelic use and opioid use disorders among illicit users in the United States. J Psychopharmacol 31(5):606–613. https://doi.org/10.1177/0269881117691453

Rhead JC, Soskin RA, Turek I, Richards WA, Yensen R, Kurland AA et al (1977) Psychedelic drug (DPT)-assisted psychotherapy with alcoholics: a controlled study. J Psychedelic Drugs 9(4):287–300. https://doi.org/10.1080/02791072.1977.10472060

Roseman L, Nutt DJ, Carhart-Harris RL (2018) Quality of acute psychedelic experience predicts therapeutic efficacy of psilocybin for treatment-resistant depression. Front Pharmacol 8:974. https://doi.org/10.3389/fphar.2017.00974

Ross S, Bossis A, Guss J, Agin-Liebes G, Malone T, Cohen B et al (2016) Rapid and sustained symptom reduction following psilocybin treatment for anxiety and depression in patients with life-threatening cancer: a randomized controlled trial. J Psychopharmacol 30(12):1165–1180. https://doi.org/10.1177/0269881116675512

Roy C (1973) Indian peyotists and alcohol. Am J Psychiatry 130(3):329–330. https://doi.org/10.1176/ajp.130.3.329-b

Savage C, McCabe OL (1973) Residential psychedelic (LSD) therapy for the narcotic addict: a controlled study. Arch Gen Psychiatry 28(6):808–814. https://doi.org/10.1001/archpsyc.1973.01750360040005

Shulgin AT, Shulgin A (1991) Pihkal: a chemical love story. Transform Press, Berkeley

Shulgin AT, Shulgin A (1997) Tihkal: the continuation. Transform Press, Berkeley

Smith CM (1958) A new adjunct to the treatment of alcoholism: the hallucinogenic drugs. Q J Stud Alcohol 19(3):406–417. https://doi.org/10.15288/qjsa.1958.19.406

Smith CM (1959) Some reflections on the possible therapeutic effects of the hallucinogens; with special reference to alcoholism. Q J Stud Alcohol 20(2):292–301. https://doi.org/10.15288/qjsa.1959.20.292

Spitzer M, Thimm M, Hermle L, Holzmann P, Kovar K, Heimann H et al (1996) Increased activation of indirect semantic associations under psilocybin. Biol Psychiatry (1969) 39(12):1055–1057. https://doi.org/10.1016/0006-3223(95)00418-1

Strassman RJ, Qualls CR (1994) Dose-response study of N,N-dimethyltryptamine in humans: I. neuroendocrine, autonomic, and cardiovascular effects. Arch Gen Psychiatry 51(2):85–97. https://doi.org/10.1001/archpsyc.1994.03950020009001

Strickland JC, Garcia-Romeu A, Johnson MW (2021) Set and setting: a randomized study of different musical genres in supporting psychedelic therapy. ACS Pharmacol Transl Sci 4(2):472–478. https://doi.org/10.1021/acsptsci.0c00187

Teixeira PJ, Johnson MW, Timmermann C, Watts R, Erritzoe D, Douglass H, Kettner H, Carhart-Harris RL (2021) Psychedelics and health behaviour change. J Psychopharmacol 36:12–19

US Department of Health and Human Services (2014) The health consequences of smoking – 50 years of progress: a report of the surgeon general. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, Atlanta

US National Library of Medicine (2021a) A double-blind trial of psilocybin-assisted treatment of alcohol dependence. https://clinicaltrials.gov/ct2/show/NCT02061293. Accessed 10 Oct 2021

US National Library of Medicine (2021b) Psilocybin-facilitated smoking cessation treatment: a pilot study. https://clinicaltrials.gov/ct2/show/NCT01943994. Accessed 10 Oct 2021

US National Library of Medicine (2021c) Psilocybin-facilitated treatment for cocaine use. https://clinicaltrials.gov/ct2/show/NCT02037126. Accessed 10 Oct 2021

Vollenweider FX, Leenders KL, Scharfetter C, Maguire P, Stadelmann O, Angst J (1997) Positron emission tomography and fluorodeoxyglucose studies of metabolic hyperfrontality and psychopathology in the psilocybin model of psychosis. Neuropsychopharmacology 16(5):357–372. https://doi.org/10.1016/S0893-133X(96)00246-1

Wittchen H, Hoch E, Klotsche J, Muehlig S (2011) Smoking cessation in primary care - a randomized controlled trial of bupropione, nicotine replacements, CBT and a minimal intervention. Int J Methods Psychiatr Res 20(1):28–39. https://doi.org/10.1002/mpr.328