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Classic hallucinogens in the treatment of addictions

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ABSTRACT

Addictive disorders are very common and have devastating individual and social consequences. Currently available treatment is moderately effective at best. After many years of neglect, there is renewed interest in potential clinical uses for classic hallucinogens in the treatment of addictions and other behavioral health conditions. In this paper we provide a comprehensive review of both historical and recent clinical research on the use of classic hallucinogens in the treatment of addiction, selectively review other relevant research concerning hallucinogens, and suggest directions for future research. Clinical trial data are very limited except for the use of LSD in the treatment of alcoholism, where a meta-analysis of controlled trials has demonstrated a consistent and clinically significant beneficial effect of high-dose LSD. Recent pilot studies of psilocybin-assisted treatment of nicotine and alcohol dependence had strikingly positive outcomes, but controlled trials will be necessary to evaluate the efficacy of these treatments. Although plausible biological mechanisms have been proposed, currently the strongest evidence is for the role of mystical or other meaningful experiences as mediators of therapeutic effects. Classic hallucinogens have an excellent record of safety in the context of clinical research. Given our limited understanding of the clinically relevant effects of classic hallucinogens, there is a wealth of opportunities for research that could contribute important new knowledge and potentially lead to valuable new treatments for addiction.

1. Introduction

The purpose of this paper is to provide a review and discussion of the scientific literature pertaining to the use of classic hallucinogens in the treatment of addiction. After highlighting the urgent need for new treatments for addiction, we provide background on the history of research on hallucinogens, a brief review of the biological and psychological effects of classic hallucinogens, and a description of the specific classic hallucinogens that have been studied in relation to addiction treatment. We then provide a comprehensive review of both historical and recent clinical research on the use of classic hallucinogens in the treatment of addiction, selectively review existing research on possible therapeutic mechanisms of action concerning hallucinogens, and suggest directions for future research on the use of classic hallucinogens in the treatment of addiction.

2. Background

2.1. The public health impact of addictions

Addictive disorders are very common, with lifetime prevalence rates in the US population estimated at 25% for nicotine use disorder (Hughes et al., 2006), 12% for alcohol use disorder (Hasin et al., 2007), and 10.3% for illicit drug use disorder (Compton et al., 2007). Addiction to alcohol, tobacco, and other drugs is the leading preventable cause of death and disability in the United States and globally (Rehm et al., 2006). Tobacco smoking alone causes 5 million deaths annually, including nearly a half million in the United States (US Department of Health and Human Services, 2014; World Health Organization, 2011). Alcohol use disorders are among the most disabling of all diseases worldwide, and account for 12.1% of disability-adjusted life-years in men, and 4.6% in women in the US (Rehm et al., 2009). The economic costs of substance use disorders are enormous, over half a trillion dollars per year in the US alone, including factors such as health care costs, lost productivity, crime, incarceration, and law enforcement (Volkow and Li, 2005).

2.2. Limitations of current treatments for addictions

A number of pharmacological and behavioral treatments have been developed that target specific aspects of addiction including motivation, coping skills, social support, reward, physical dependence and allostasis, the stress response, and relapse due to exposure to conditioned cues or to priming doses of the drug. However, the effects of most currently available treatments remain disappointingly small (Berglund, 2005). Despite the observation that 69% of United States smokers want to quit smoking completely (Centers, for Disease Control and Prevention, 2011),with approved medications less than 35% of participants remain smoke-free 6 months after quitting (Cahill et al., 2014). For alcohol,

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the most effective FDA-approved pharmacotherapies have small to moderate effect sizes, with approximately one person achieving abstinence or avoiding relapse for every 9 people treated (Rosner et al., 2010a; Rosner et al., 2010b).

2.3. Historical background

Classic hallucinogens have been used by humans for over 5000 years (El-Seedi et al., 2005), but scientific interest in hallucinogens dates to the late 1800s, when mescaline was isolated and its effects were described by Arthur Heffter (Heffter, 1896; Heffter, 1898). Following Albert Hoffman's accidental discovery of the psychoactive effects of LSD in 1943 (Hofmann, 1979) and isolation and synthesis of psilocybin in 1958 (Hofmann et al., 1958a; Hofmann et al., 1958b), the 1950s through the early 1970s saw an explosion or research on classic hallucinogens. Clinicians and clinical scientists explored the use of classic hallucinogens to facilitate rapid therapeutic effects in alcohol and drug addiction, as well as anxiety, depression, obsessive–compulsive disorder, and other conditions. LSD, psilocybin, and other hallucinogens were legally available for clinical use as an experimental treatment until the mid to late 1960s. Over a thousand papers document the treatment of over 40,000 people with classic hallucinogens during this period (Grinspoon and Balakar, 1997). Psycholytic and psychedelic therapy models of the 1950s through early 1970s both used hallucinogen-assisted treatment to achieve lasting personality change, behavior change, and symptom relief, although they emphasized different processes in bringing about therapeutic effects(Grinspoon and Balakar, 1997; Grof, 2008). The psycholytic method used low to moderate doses of hallucinogens, administered on multiple occasions, to facilitate therapy that was based on traditional psychoanalytic principles (Buckman, 1967; Leuner, 1967). The psychedelic method, rather than emphasizing resolution of childhood conflicts or traumatic experiences, used higher doses of hallucinogens, administered on one or a few occasions, with the goal of inducing a "psychedelic," "mystical," or "peak" experience, which, it was held, often induced lasting change in habitual patterns of thought, emotional response, and behavior (Hoffer, 1967; Sherwood et al., 1962). The primary focus of research on the use of hallucinogenic substances in the treatment of addiction was the use of the prototypical classic hallucinogen LSD in the treatment of alcoholism. Treatment of alcoholism with LSD using the psychedelic model was an accepted clinical treatment in Saskatchewan, and was subject of numerous studies (summarized below). In reaction to the cultural upheaval and concern about increasing misuse of psychedelics in the mid and late 1960s, clinical research on hallucinogens came to halt in the early 1970s, after enactment of the Controlled Substances Act placed all such compounds into the highly restrictive Schedule I class.

Although there were no further addiction treatment trials with classic hallucinogens for over 30 years, the past decade has witnessed renewed interest in this area. Early-stage clinical trials of psilocybin for nicotine dependence (Johnson et al., 2014) and alcohol dependence (Bogenschutz et al., 2015) have recently been completed, and further trials are currently under way. Observational studies have suggested that sacramental use of plant materials containing classic hallucinogens (peyote, containing mescaline, or ayahuasca, containing DMT) suggests that these practices are associated with decreased disordered use of substances and few if any detrimental effects (Albaugh and Anderson, 1974b; Barbosa et al., 2012; Doering-Silveira et al., 2005; Fabregas et al., 2010; Garrity, 2000; Halpern et al., 2005; Halpern et al., 2008; Kunitz and Levy, 1994; Lu et al., 2009; Roy, 1973). Ayahuasca and ibogaine are being used to treat addictions in many retreat centers and treatment programs in Latin America and the Caribbean, but efficacy studies have not been done. The relative safety of classic hallucinogens (particularly psilocybin and LSD) in clinical research settings has been thoroughly documented. Promising research on anti-addictive effects of the non-classic hallucinogens also suggest that therapeutic use of classic hallucinogens in the treatment of addiction deserves another look.

2.4. Neuropsychopharmacology of classic hallucinogens

2.4.1. Definition of classic hallucinogens

The research on classic hallucinogens is voluminous, and has been reviewed comprehensively by leading scientists in the field (Halberstadt, 2015; Nichols, 2004). Here we will briefly summarize some of the key features and actions of classic hallucinogens that are relevant to their potential application in the treatment of addiction. Despite the implications of the term "hallucinogen," these compounds rarely occasion frank hallucinations. Nomenclature is difficult because their clinical effects are unusual. The following is one reasonable definition of hallucinogens based on these effects: "A drug which, without causing physical addiction, craving, major physiological disturbances, delirium, disorientation, or amnesia, more or less reliably produces thought, mood, and perceptual changes otherwise rarely experienced except in dreams, contemplative and religious exaltation, flashes of vivid involuntary memory, and acute psychosis" (Grinspoon and Balakar, 1997). Classic hallucinogens share the additional characteristics that they are thought to exert their primary effects primarily through agonist or partial agonist activity at serotonin 2A (5HT2A) receptors, and that they substitute for the prototypical classic hallucinogen 2,5-dimethoxy-4-methylamphetamine (DOM) in drug discrimination experiments (Halberstadt, 2015). There are two main structural classes of classic hallucinogens: indoleamines and phenylalkylamines. The indoleamines include indolealkylamines such as dimethyltryptamine (DMT), psilocin (4-hydroxy-DMT), psilocybin (4-phosphoryloxy-DMT), and N-N-dipropyltryptamine (DPT), and the structurally more complex ergolines, of which lysergic acid diethylamide (LSD) is the most well-known. The phenylalkylamines include mescaline and a large number of synthetic hallucinogens including substituted amphetamines such as DOM and 2,5-dimethoxy-4-iodoamphetamine (DOI).

2.4.2. Basic biological mechanisms of classic hallucinogens

Classic hallucinogens bind to many serotonin receptor subtypes and other receptor types, and binding profiles vary considerably among the classic hallucinogens (Ray, 2010). However, the effects of all classic hallucinogens appear to depend primarily on their actions at 5HT2A receptors (Glennon et al., 1984; Halberstadt, 2015; Nichols, 2004; Vollenweider and Kometer, 2010). The 5HT2A antagonist ketanserin blocks most of the subjective effects of psilocybin in humans, supporting the primacy of this receptor in mediating its clinically relevant effects (Glennon et al., 1984; Vollenweider et al., 1998). 5HT2A receptor activation is coupled to several intracellular signaling pathways (reviewed in Halberstadt, 2015). G_q-mediated signaling activates the inositol triphosphate–diacylglycerol pathway leading to activation of protein kinase C. Behavioral effects of DOI are attenuated in G_q knockout mice (Garcia et al., 2007). Signaling through $G_{i/o}$, leading to activation of Src and expression of the immediate early genes egr-1 and egr-2, may be necessary to produce hallucinogenic effects. This pathway is activated by LSD but not by lisuride, a non-hallucinogenic ergoline and 5HT2A agonist structurally similar to LSD (Gonzalez-Maeso et al., 2007). The metabotropic glutamate mGlu2 receptor, which forms complexes with 5HT2A receptors, is necessary for the pharmacological and behavioral effects of hallucinogenic 5-HT2A agonists (Gonzalez-Maeso et al., 2008; Moreno et al., 2011).5HT2A agonists activate sub-populations of pyramidal cells in cerebral cortex by enhancing glutamatergic neurotransmission within intracortical networks, particularly those involving cortical layer V (Aghajanian and Marek, 1999; Beique et al., 2007; Puig et al., 2003; Zhang and Marek, 2008).

2.4.3. Acute effects of classic hallucinogens

The effects of all of the classic hallucinogens are similar, differing principally in duration and intensity, which in turn depend on the

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particular substance, the dose, and the route of administration (Nichols, 2004). Significant physiological toxicity is not seen in the doses of LSD, psilocybin, mescaline, DPT, or DMT that are typically used. Somatic effects may include chills, tremor, unsteadiness, nausea with or without vomiting, anorexia, xerostomia, paresthesias, and blurred vision. Pulse and blood pressure are often mildly to moderately elevated. Sensory effects include alteration in perception of shape, size, and color, and the illusion of movement. Vivid imagery is often perceived with eyes closed, ranging from elementary geometric or fractal patterns to vivid representational images of all kinds. Other sense modalities may be altered as well, and synesthesia can occur. The sense of time may be distorted, most commonly in the sense that time seems to pass slowly or not at all. The psychological content and emotional tone of the experience are unpredictable, but are thought to be influenced strongly by the mental state, preparation, and intention of the person taking the drug and the environment in which the effects are experienced, as well as the dose and the particular drug that is taken. Effects on emotion are extremely variable, and can change rapidly and frequently during a single episode of use. Feelings of bliss, joy, peace, anxiety, depersonalization, derealization, and paranoia can occur. Strong cathartic emotional experiences are common, often related to past or current life experience. The content of the experience may be dominated by personal experiences and concerns (e.g., conflicts, relationships, grief and loss), symbolic representations of a dream-like or narrative quality, or religious or spiritual matters. Particularly in high doses, mystical-type experiences are a frequent occurrence.

2.4.4. Relevant human neuroimaging

Recent neuroimaging studies in humans are providing insight into the acute effects of classic hallucinogens on brain activity. An fMRI study from Carhart-Harris and colleagues using psilocybin 2 mg IV found that psilocybin caused acute decreases in regional cerebral blood flow and BOLD signal, with strongest effects in anterior cingulate cortex/medial prefrontal cortex, posterior cingulate cortex, and thalamus (Carhart-Harris et al., 2012a). Psilocybin also decreased functional coupling between medial prefrontal cortex and posterior cingulate cortex. During the acute effects of psilocybin there was increased functional connectivity between two important brain networks: the default mode network, normally activated during internally oriented thinking, and the task-positive network, normally activated when attention is oriented toward external events or activities(Carhart-Harris et al., 2012b). Further work has shown a more general tendency for psilocybin to enhance resting state functional connectivity between networks (Roseman et al., 2014), and a wider range of connectivity states during psilocybin intoxication than in normal waking consciousness (Tagliazucchi et al., 2014).

In addition to studies of the brain at rest, evidence suggests that psilocybin acts to increase positive affect. For example, Kometer et al. (Kometer et al., 2012) showed that administration of psilocybin was associated with enhanced processing of positive cues (i.e., faces, words, and self-reported affect) and decreased processing of negative cues. Kraehenmann et al. (Kraehenmann et al., 2014) recently reported that psilocybin administration resulted in reduced amygdala response to negative pictures, and that the reduced amygdala response was significantly correlated with increases in self-reported positive mood. These findings are relevant to addiction treatment because negative affect is an important predictor of relapse in addiction (Connors et al., 1996).

Although these findings provide important information about the acute effects of classic hallucinogens on brain activity, it is important to remember that all of these studies were conducted during the acute effects of psilocybin. Persisting effects would be more directly relevant to therapeutic applications. There have not yet been any published studies of persisting effects of classic hallucinogen administration on brain function in humans.

2.4.5. Classic hallucinogens that have been used in the treatment of addiction

Among the many known classic hallucinogens, only a very few have been studied in any detail in relation to their effects in humans. Table 1 provides information about the specific classic hallucinogens that have been used in clinical trials of addiction or in therapeutic or religious contexts. Although these drugs vary widely in their structures, receptor binding profiles, potency, and duration of action, they are all relatively non-toxic, non-addictive, and similar in their subjective effects. Only LSD, psilocybin and, to a lesser extent, DPT and mescaline have been used in clinical trials for addiction. Mescaline was administered interchangeably or in combination with LSD in some of the early reports on psychedelic treatment of alcoholism (Sherwood et al., 1962; Smith, 1958; Smith, 1959), but there are no trials specifically examining the effects of mescaline. DMT (as an ingredient of ayahuasca, see below) has been used extensively for hundreds or thousands of years in religious contexts, and have been used with therapeutic intent within both religious and secular paradigms. However, its effects have not been studied in clinical trials.

3. Clinical trials of classic hallucinogens in the treatment of addiction

3.1. Alcoholism

3.1.1. LSD

In the 1950s through early 1970s over 30 publications reported on the effects of LSD in the treatment of alcoholism (for reviews see Abuzzahab and Anderson, 1971; Halpern, 1996; Mangini, 1998; Dyck, 2006; Grinspoon and Balakar, 1997). Early reports of clinical outcomes and uncontrolled trials had variable but encouraging results, particularly when the psychedelic model was used (Abuzzahab and Anderson, 1971). At least a dozen trials with some form of control group were ultimately conducted (Krebs and Johansen, 2012; Miller and Wilbourne, 2002), but these studies were under-powered, and results were mixed. Research on LSD treatments stopped abruptly in the early 1970s, and the consensus had long been that the data from these studies were too limited to warrant any conclusions as to efficacy.

However, a recent meta-analysis (Krebs and Johansen, 2012) of the 6 randomized trials of LSD for alcohol dependence that reported drinking outcomes (Bowen et al., 1970; Hollister et al., 1969; Ludwig et al., 1969; Pahnke et al., 1970; Smart et al., 1966; Tomsovic and Edwards, 1970) demonstrated consistent treatment effects favoring LSD. These studies included 325 participants who received active treatment with LSD and 211 who received control treatment. Participants were male inpatient alcoholics, and all of the studies employed a single high-dose LSD session. LSD doses ranged from about 210 to 800 mcg, and control conditions included placebo, low dose (50 mcg) LSD, ephedrine, and amphetamine. There was great variability in preparation and debriefing of subjects and in the conditions during the LSD sessions. In the meta-analysis, treatment effects were significant at the first post-treatment follow-up, and remained significant at 6 months. Fifty-nine % of the LSD-treated participants were significantly improved at the first post-treatment follow-up vs. 38% of the control participants (odds ratio 1.96, $p = .0003$). The effect was homogeneous across the 6 studies. Although these findings are not conclusive evidence of efficacy, they suggest that renewed clinical investigation of LSD and other classic hallucinogens for the treatment of alcoholism is warranted.

3.1.2. DPT

Limited research was also conducted on the use of dipropyltryptamine (DPT) in the treatment of alcoholism (Grof et al., 1973; Rhead et al., 1977). DPT is a classic hallucinogen (Fantegrossi et al., 2008), structurally very similar to DMT, which has clinical effects lasting from 1–6 h, depending on the dose, when given by intramuscular injection (Rhead et al., 1977). In a single-group pilot study involving

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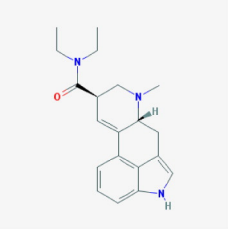
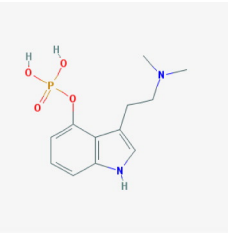
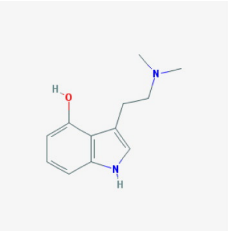
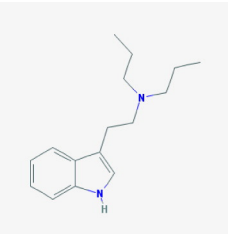
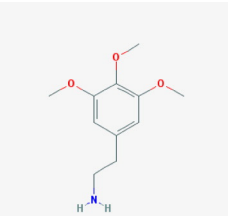
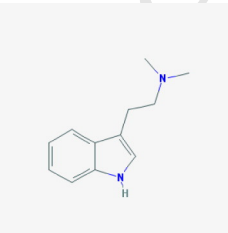
t1.1 **Table 1**
t1.2 Classic hallucinogens used in the treatment of addictions.

	Chemical structure[a]	Human serotonin receptor binding (K_i, in nM)[b]	Clinical dose range	Clinically relevant attributes	Clinical trials in addiction treatment	Other clinically relevant data
t1.4 t1.5 LSD (lysergic acid diethylamide)		5HT1A (.64–4.92) 5HT1D (14) 5HT2A (.760–21.4) 5HT2B (.977–8.91) 5HT2C (1.10–45.7) 5HT6 (2.29)	100–800 μgorally	Very high potency and low physiological toxicity Effects last 8–10 h.	Alcoholism: Opioid addiction	Trials for other indications: pain, existential anxiety and depression
t1.6 Psilocybin		Not relevant, as psilocybin is rapidly converted to psilocin in vivo.	20–40 mg orally	Psilocybin is prodrug of psilocin. Effects last 4–6 h. Main drug used in recent clinical work with classic hallucinogens	Alcoholism Nicotine addiction	Trials for other indications: existential anxiety and depression Thousands of years of use in traditional religious contexts
t1.7 Psilocin		5HT1A (49–567) 5HT1B (220) 5HT1D (36.4) 5HT1E (52.2) 5HT2A (107) 5HT2B (4.6) 5HT5 (83.7) 5HT6 (57) 5HT7 (3.5)		Subjective effects appear to be identical to those of psilocybin, potency slightly higher in proportion to lower molecular weight. Less stable molecule than psilocybin	None	
t1.8 t1.9 Dipropyl-tryptamine(DPT)		5HT1A (100)	15–165 mg IM	Effects last 1–6 h, depending on dose when given IM.	Alcoholism	
t1.10 Mescaline		5HT2A (150) (rat cortex)	200–500 mg orally	Low potency, therefore lower therapeutic index than other classic hallucinogens, although the therapeutic index is nonetheless very favorable for safe clinical use.	Alcoholism	Over 5000 years of use in traditional religious/ shamanic contexts. Effects similar to those of LSD. Used interchangeably with LSD in early psychedelic treatment
t1.11 DMT (ayahuasca)		5HT1A (120) 5HT1D (270) 5HT2A (462) 5HT6 (68)	Approx. 0.5 mg/kg to 1.76 mg/kg orally in ayahuasca; 0.1–0.4 mg/kg IV; or 25 mg smoked.	Ayahuasca contains the MAOIs harmine, harmaline, tetrahydroharmine: these render DMT orally active, and may have clinically relevant effects of their own. Effects of ayahuasca last about 4 h. DMT alone is inactive orally. Smoked or injected DMT has effects lasting about 15 min.	None	Centuries of use in traditional religious contexts Current clinical (where allowed) and underground (where illegal) use for addictions and other conditions

t1.12 [a] PubChem Compound Database: http://www.ncbi.nlm.nih.gov/pccompound, accessed Feb 18, 2015.
t1.13 [b] NIMH Psychoactive Drug Screening Program (Bryan Roth, PI) Ki database: http://pdsp.med.unc.edu/pdsp.php, accessed Feb 18, 2015. .

51 participants, Grof et al. reported highly significant improvement in clinical outcomes including abstinence among the 47 participants (92%) who received between 1 and 6 DPT (mean 1.9) sessions and completed follow-up at 6 months (Grof et al., 1973). A subsequent randomized trial conducted by the same group contrasted the effects of DPT treatment to those of "conventional treatment" (psychotherapy similar to that received by the DPT group, but without the DPT sessions) and "routine hospital treatment" (Rhead et al., 1977). Although post-treatment psychological outcomes suggested more favorable response in the DPT-treated group, there were no significant differences between the DPT-treated participants and the other groups in clinical outcomes assessed at 6 month follow-up, and the conventional treatment group

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members assessed at 12 months reported better drinking outcomes and social functioning than the other two groups. This study suffered from a number of methodological limitations including very high rates of drop-out both during treatment and in the follow-up period (only 37% of participants assessed at 12 months), as well as differential drop-out among the groups.

3.1.3. Psilocybin

The effects of psilocybin were characterized soon after its isolation (Isbell, 1959; Leary et al., 1963), and it was used in both psychedelic and psycholytic models of treatment, although much less than LSD (Metzner, 2005). However, other than very limited data published on a cohort of alcoholic patients treated with both psilocybin and LSD (Rydzyński and Gruszczyński, 1978; Rydzyński et al., 1968), we are not aware of any published studies of psilocybin used to treat alcoholism prior to one recently completed by one of the authors and colleagues (Bogenschutz et al., 2015). In a single-group proof-of-concept study, ten volunteers with DSM-IV alcohol dependence received orally administered psilocybin 0.3 mg/kg or 0.4 mg/kg in 1 or 2 supervised sessions scheduled 4 weeks apart. Psilocybin was administered in the context of a 12-week manualized therapy program which included 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, although some of the participants had a relatively mild response to the doses used. Drinking did not decrease significantly in the first 4 weeks of treatment (when participants had not yet received psilocybin), but decreased significantly following psilocybin administration. Gains were largely maintained during 36 weeks of follow-up. The intensity of self-reported effects during the first psilocybin session at week 4 was strongly correlated with improvement in drinking during weeks 5–8 ($r = 0.76$ to $r = 0.89$), and with decreases in craving and increases in abstinence self-efficacy during week 5. Based on these promising initial results, a larger double-blind trial to investigate efficacy and mechanisms is now under way.

3.2. Treatment of illicit drug use

Although alcoholism has been the main focus of addiction treatment using LSD, at least two studies have been conducted using LSD as component of treatment for opioid addicts. Ludwig and Levine conducted a study at the U.S. Public Health Service Hospital in Lexington, Kentucky in which 70 "post-narcotic drug addicts" were randomly assigned to receive 1 of 5 treatments (Ludwig and Levine, 1965). All participants received a single 2–3 h therapeutic session consisting of 1) psychotherapy using an "insight-interpretive" approach, 2) hypnotherapy (hypnosis followed by psychotherapy, 3) LSD (0.2 mcg/kg) with no psychotherapeutic intervention, 4) LSD with psychotherapy, or 5) LSD with hypnotherapy. The only outcome measure was a questionnaire designed to measure various dimensions of psychopathology, administered prior to the session, 2 weeks after the session, and 2 months after the session. All groups showed significant improvement on this measure at 2-month follow-up, with greater improvement reported in the hypnodelic group. Drug use behavior after discharge from the hospital was not investigated. The dose of LSD used in this study (140 mcg for a 70 kg person) was considerably lower than the doses used in the controlled alcohol trials summarized above.

Savage and McCabe conducted a controlled trial of LSD for the treatment of heroin addiction (Savage and McCabe, 1973). Seventy-eight incarcerated male heroin addicts eligible for parole were randomly assigned to usual care in an outpatient, abstinence-based program, including daily urine drug monitoring and weekly group therapy, or 4–6 weeks of residential treatment including a psychedelic therapy, followed by usual outpatient care. The psychedelic therapy included a single high dose (300–500 mcg) LSD session in the context of approximately 24 h of preparatory therapy and a 1-week integration period after the session. Participants in the psychedelic therapy condition had higher rates of abstinence during the 12-month follow-up period (25% vs. 5% continuous abstinence). While the design of this study does not separate the effects of the LSD from other aspects of the residential treatment period, the outcomes in the LSD-treated group are impressive for drug-free treatment of severe opioid addiction.

Although there have been no further trials of classic hallucinogens in the treatment of illicit drug addiction, such studies are now in the planning stages. A recent publication suggested such a study would be valuable and proposed a design to test the efficacy of psilocybin for prescription opioid dependence (Burdick and Adinoff, 2013). In addition, a study was recently approved to begin evaluation of the effects of psilocybin-assisted treatment in the treatment of cocaine dependence (NCT02037126). Q7

3.3. Nicotine (psilocybin)

A recent pilot study conducted by one of the authors and colleagues showed that a manualized 15-week program of cognitive-behavior therapy incorporating 2 or 3 psilocybin sessions (~0.29 mg/kg or ~0.43 mg/kg, administered on the target quit date and at 2 and 8 weeks post-target quit date) resulted in excellent clinical outcomes: 12 of the 15 participants (80%) were biologically confirmed as smoke-free at a 6 month follow-up (Johnson et al., 2014). Responses to psilocybin were similar to populations previously studied consisting of mostly non-smokers (Griffiths et al., 2006; Griffiths et al., 2011), with 31% of sessions meeting criteria for a "complete" mystical experience, and 40% of participants experiencing at least one psychologically challenging experience. Aside from these acute psychologically challenging experiences which were well managed, no clinically significant adverse events occurred during the study. Moreover, consistent with previous findings showing an important role of the nature of subjective experience occasioned by psilocybin, smoking cessation outcomes were significantly correlated with measures of mystical experience during sessions, and retrospective ratings of personal meaning and spiritual significance of psilocybin sessions (Garcia-Romeu et al., In press).

4. Supportive non-experimental data from religious and clinical contexts

Although ayahuasca and peyote have not been subjected to clinical trials, they are of interest because they contain classic hallucinogen compounds, and they have been and continue to be used extensively outside of clinical research, including current use with the intent of curtailing addiction. We briefly summarize the most relevant non-experimental research on these substances below.

4.1. Ayahuasca

Ayahuasca is a hallucinogenic tea containing the classic hallucinogen DMT and beta carbolines (monoamine oxidase inhibitors that render DMT orally active (McKenna et al., 1984; Callaway et al., 1996)). Ayahuasca has been used by indigenous peoples of the Amazon basin for centuries, and is used sacramentally by a number of organized religions, of which the União do Vegetal and Santo Daime are the best known (McKenna, 2007).

Cross-sectional studies have consistently shown decreased rates of alcohol misuse among members of both Brazilian and US religious sects using ayahuasca (Doering-Silveira et al., 2005; Halpern et al., 2008). In an assessment of mental health among ritual users of ayahuasca, Fabregas found that ayahuasca users had lower scores on the Addiction Severity Index (ASI) alcohol use and psychiatric subscales compared to a control group (Fabregas et al., 2010). Halpern et al. interviewed 34 American Santo Daime members regarding effects of church participation (Halpern et al., 2008). Participants reported a wide variety of psychological benefits. Of 24 members with a history

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of substance use disorder, 22 were in full remission, and all 5 who had a history of alcohol dependence reported that church involvement played a pivotal role in their recovery. Although proscription of alcohol and other drug use within these religions likely contributes to such effects, the consistency of results and individuals' accounts regarding the sacramental substance suggests the possibility of a pharmacological effect as well.

Ayahuasca is currently being used in treatment centers and in shamanic or "neo-shamanic" contexts for the treatment of various conditions including addiction and PTSD, as well as for purposes of personal or spiritual growth (Labate and Cavnar, 2011; Liester and Prickett, 2012). Although many individuals have reported that ayahuasca has facilitated their recovery from addiction, to our knowledge only one observational study has been published (Thomas et al., 2013), and controlled trials have not been conducted. A recent study showed that ayahuasca specifically blocked acquisition and reinstatement of behavioral sensitization to alcohol in mice (Oliveira-Lima et al., 2015).

4.2. Peyote

The peyote cactus (*Lophophora williamsii*), the San Pedro Cactus (*Trichocereus pachanoi*) and a number of other cacti contain psychoactive quantities of the classic hallucinogen mescaline and other related alkaloids (Gabermann, 1978; Ogunbodede et al., 2010). Peyote buttons have been harvested by Native peoples in North America for at least 5500 years (El-Seedi et al., 2005). Today peyote is used sacramentally by groups including the Native American Church (NAC) (Stewart, 1987) and the Huichol of northern Mexico (Meyerhoff, 1974). It has often been stated that taking peyote in the context of NAC ceremonies helps alcoholics achieve and maintain sobriety (Albaugh and Anderson, 1974b; Garrity, 2000; Kunitz and Levy, 1994; Lu et al., 2009). Proposed psychological mechanism includes emotional catharsis (Albaugh and Anderson, 1974a) and improved self-understanding and motivation for sobriety (Garrity, 2000). However, there are no published quantitative studies of alcohol use among NAC members.

5. Possible mechanisms of action

Since there are very few studies directly investigating the role of specific effects of classic hallucinogens in subsequent change in addictive behavior, this section is necessarily speculative. Still, we feel it is important to identify plausible mechanisms of action at the current early stage of investigation in order to generate hypotheses for future research. There are several known actions of classic hallucinogens that are related to mechanisms of addiction, and could possibly mediate anti-addictive effects.

5.1. The possible role of 5HT2A receptor modulation

In rat models, administration of classic hallucinogens induces down-regulation of 5HT2A receptors, particularly those in the anterior cingulate and frontomedial cortex, leading to the rapid development of behavioral tolerance (Buckholtz et al., 1990; Gresch et al., 2005). The rapid development of tolerance to most classic hallucinogens in humans (Nichols, 2004) suggests that 5HT2A receptors may be down-regulated, although the latter has not been demonstrated in humans. Such down-regulation would be behaviorally relevant. Increased 5HT2A receptor binding has been reported in people with depression (Shelton et al., 2009), neuroticism (Frokjaer et al., 2008), borderline personality disorder (Soloff et al., 2007), impulsive aggression (Rosell et al., 2010), and completed suicide (Anisman et al., 2008). Furthermore, fronto-limbic 5HT2A receptor density is positively correlated with increased anxiety and exaggerated stress response (Frokjaer et al., 2008). Given that anxiety and stress are important triggers for relapse to substance use (Sinha and Li, 2007), it is possible that 5HT2A receptor downregulation by classical hallucinogens could alter and diminish stress-induced substance relapse. Furthermore, increased activity in 5HT2A-mediated pathways relative to 5HT2C pathways is associated with increased response disinhibition and cue response and in rat models of cocaine addiction (Cunningham and Anastasio, 2014). The 5HT2A antagonists ritanserin and amperozide suppress alcohol consumption in animal models (Johnson, 2008). However, in humans alcoholism is not consistently associated with change in 5HT2A receptor levels (Thompson et al., 2012; Underwood et al., 2008), and the 5HT2A antagonist ritanserin did not improve drinking outcomes in people with alcohol dependence in two large-scale clinical trials (Johnson et al., 1996; Wiesbeck et al., 1999).

5.2. Neurotrophic factors and induction of neuroplasticity

Classic hallucinogens have effects on expression of brain-derived neurotrophic factor (BDNF) and glial cell line-derived neurotrophic factor (GDNF), neurotrophic factors which are relevant to addiction and other psychiatric disorders. BDNF and GDNF play critical roles in neurogenesis, synaptic plasticity, learning, and memory (Ghitza et al., 2010). DOI increases expression of BDNF mRNA in rat parietal cortex and other neocortical regions through its action at the 5HT2A receptor, but decreases BDNF expression in the dentate gyrus of the hippocampus (Vaidya et al., 1997). DOI can also increase expression of mRNA of GDNF through its action at 5HT2A receptors (Tsuchioka et al., 2008). BDNF and GDNF can facilitate or inhibit addictive behaviors in rats depending on the drug type and anatomical site of action, and the specific behavioral model being used (Ghitza et al., 2010). In the case of alcohol, the experimental data demonstrate a consistent pattern in that self-administration of alcohol and conditioned place preference are inversely related to level of BDNF or GDNF expression (Ghitza et al., 2010). Regarding cocaine, the picture is much more complicated. In the ventral tegmental area (VTA), BDNF increases drug reward, while GDNF decreases reward. Both BDNF and GDNF in the VTA potentiate relapse after withdrawal from cocaine. BDNF activity in the nucleus accumbens also facilitates cocaine seeking, but BDNF signaling in the medial prefrontal cortex diminishes cocaine seeking. There is some evidence that classic hallucinogens can induce neuroplastic changes, suggesting a possible biological basis for persisting behavioral change. Through its action at 5HT2A receptors DOI induces remodeling of pyramidal cell dendrites (Jones et al., 2009). The effects of classic hallucinogens on adult neurogenesis have not been established, although a recent publication began to explore these effects (Catlow et al., 2013). Clearly, much more work is needed to understand the region-specific effects of classic hallucinogens on neurotrophic factor expression and neuroplasticity, and the impact of these changes on addiction-related behaviors.

5.3. The role of subjective experience

Clinical work with classic hallucinogens has emphasized the central role of the patient's conscious experience during the drug's acute effects (Grof, 2008; Hoffer, 1967; Masters and Houston, 2000; Pahnke et al., 1970; Sherwood et al., 1962). Most of the clinical studies conducted in North America using LSD in the treatment of addiction or existential anxiety in terminal cancer during the 1950s–1970s employed the psychedelic model described in Section 2.3. The idea that a mystical-type experience can lead to lasting behavior change is consonant with the concept of "spiritual awakening" in the context of Alcoholics Anonymous (Forcehimes, 2004). Indeed, based on his own LSD experiences Bill Wilson, the founder of Alcoholics Anonymous, became an enthusiastic proponent of the use of LSD to help alcoholics experience spiritual insight (Kurtz, 2008). However, past studies of addiction treatment with classic hallucinogens have not assessed participants' experiences quantitatively or investigated the mediational role of dimensions of the experience. As noted above, recent pilot work with psilocybin for cigarette addiction demonstrated that strong mystical-type experiences were associated with greater improvement (Garcia-Romeu et al., In press). On

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the other hand, in the recent pilot study of psilocybin for alcohol dependence, both mystical experience and broader measures of the intensity of subjective effects were associated with improvement in drinking (Bogenschutz et al., 2015).

5.4. Persisting psychological changes

A number of persisting psychological changes have been proposed as possible mediators of effects of classic hallucinogens in the treatment of addiction (Bogenschutz and Pommy, 2012). The published pilot studies of psilocybin for alcohol or nicotine dependence have reported decreases in craving and increases in self-efficacy (Bogenschutz et al., 2015; Johnson et al., 2014). Long-term follow-up of normal volunteers who received psilocybin demonstrated increase in the personality dimension of openness, predicted by the intensity of mystical experience (Maclean et al., 2011). Positive behavior change and improvement in well-being and life satisfaction have also been reported (Griffiths et al., 2011). Controlled trials have not yet been conducted that would allow rigorous testing of such possible mediators of therapeutic effects.

6. Safety

The potential for classic hallucinogens in addiction treatment requires an understanding of risks and safety mechanisms to minimize potential harms. A broad exploration of risks and proposed safety issues has been previously described (Johnson et al., 2008). However, a brief description will be provided here.

6.1. Domains of risk

Although classic hallucinogens can be used in dangerous ways in non-clinical settings, they do not normally engender compulsive drug-seeking (addiction) as with most abused drugs (e.g., opioids, cocaine, methamphetamine, cannabis) (Fantegrossi et al., 2008; O'Brien, 2010). It appears that non-medical use of classic hallucinogens can precipitate prolonged psychiatric reactions (e.g., psychosis) in rare cases, although prolonged psychiatric reactions have very rarely been observed in medical settings (Cohen, 1960; McGlothlin and Arnold, 1971). Given the intensity of their subjective effects, it is remarkable that classic hallucinogens have very low physiological toxicity, with no evidence of resulting organ damage or neuropsychological deficits even at very high doses (Gable, 1993; Strassman, 1984). On rare occasions, nonmedical use of classic hallucinogens appears to result in clinically distressing persisting perceptual abnormalities (e.g., hallucinogen persisting perception disorder, HPPD). However such cases have not been observed in clinical research, and are perhaps related to factors absent in research settings (e.g., poor control of dose, polydrug use) (Johnson et al., 2008). For the large majority of participants, the most relevant safety concern is the potential for dangerous and erratic behavior given the intense subjective experiences possible with classic hallucinogens, including fear and anxiety.

6.2. Safeguards against risks

The risks of classic hallucinogen administration can be appropriately addressed with procedures, resulting in risk/benefit ratios in both basic human research and therapeutic studies that compare favorably with routine procedures in medical research and therapeutic practice (Johnson et al., 2008). Given clinical cases in which non-medical use of classic hallucinogens appeared to have precipitated prolonged psychiatric reactions (e.g., psychosis), participants should be screened and excluded for psychotic disorders (and related disorders such a bipolar disorder) or a predisposition to these disorders. A physician should be on call and immediately available during the drug administration sessions, and appropriate rescue medication (e.g., benzodiazepines, antihypertensives) should be available for administration, although such medications are rarely needed. Interpersonal reassurance is typically effective in dealing with challenging psychological reactions (Johnson et al., 2008). As the most likely risks are associated with behavior during acute drug administration, it is important that volunteers meet with research/clinical staff during preparatory meetings to develop rapport (minimizing paranoia regarding staff in sessions) and to prepare the volunteer for dealing with potentially powerful drug effects. During sessions, multiple individuals who have developed rapport should participate in monitoring the volunteer, so that the volunteer is never alone while experiencing acute drug effects, even if one leaves temporarily. Regardless of experimental or therapeutic intentions of studies, classic hallucinogen administration can occasion extremely salient and emotional experiences that may relate to one's past or current personal or family history, philosophical issues, and sometimes experiences described as spiritual in nature. It is important for volunteers to have follow-up contact with treatment staff in order to discuss and process such experiences. This contact serves as an opportunity to refer to the volunteer to additional care should that appear appropriate.

7. Conclusions/future directions

Taken as a whole, the evidence suggests that classic hallucinogens hold considerable promise in the treatment of addiction, particularly given the limited efficacy of extant treatments. The efficacy data are promising, but very limited except in the case of LSD treatment of alcoholism. Trials are only now beginning that will meet modern standards of design and statistical power. Classic hallucinogens have several features that one might want a priori in an anti-addiction drug. 1) They lack addictive effects themselves. 2) Extensive clinical research has shown them to be safe when appropriate precautions are taken. 3) They have molecular targets consistent with anti-addiction effects. 4) They occasion psychological effects that include intense self-reflection and sometimes mystical/spiritual/peak experience that are often associated with naturalistic addiction recovery. 5) They can induce persisting changes in behavior and personality, while for most medications it is expected that medication effects will only persist as long as the patient is taking the medication.

Although plausible biological mechanisms have been proposed, at this point the strongest evidence is for the role of mystical or other meaningful experiences as mediators of therapeutic effects. This is a unique mechanism among pharmacotherapies, and one that is fascinating from both biological and psychological perspectives. One process that bears some resemblance to this process is the pathogenesis of post-traumatic stress disorder (PTSD). In PTSD, an overwhelming psychological trauma can cause persisting *harmful* changes in brain structure and function, as well as sometimes permanent psychological change. It has therefore been proposed that mystical experiences occasioned by classic hallucinogens constitute inverse-PTSD-like effects (Garcia-Romeu et al., In press). "PTSD-like" refers to the lasting behavioral effects of discrete experiences. "Inverse" implies that persisting effects are beneficial rather than pathological. Although at this point we cannot say whether the neurobiology of these phenomena is related in specific ways, both situations could represent special forms of learning and memory in which the brain changes much more substantially than during a single ordinary experience.

Based on our limited understanding of the effects of classic hallucinogens in addiction, there are many avenues of research that could contribute important new knowledge and potentially lead to valuable new treatments. Further efficacy trials with psilocybin, and other classic hallucinogens (especially LSD) for alcohol, nicotine, cocaine, and opioids should be developed. Although the effects of psilocybin to date have been quite impressive, it cannot be assumed that all classic hallucinogens have the same clinical effects. Multiple agents should be studied. Research should also investigate whether efficacy depends on the presence and nature of concurrent psycho/social treatment accompanying classic hallucinogen treatment (e.g., cognitive-behavior therapy,

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Motivational Enhancement Therapy). More work needs to be done on mechanisms of action, e.g., psychological mediators and persisting psychological change, neuroimaging studies of persisting effects, other biomarkers, and the possible role of genetics in moderating response to psychedelics. Further thought should be given to optimizing the integration of the classic hallucinogen treatment with psychosocial treatments, and possibly with other medications. Previous and current methods have minimized the number of doses (sessions) provided. If one or two sessions are effective, additional "booster" sessions might or might not further improve outcomes. Finally, since all drugs have risks, continued attention to safety is critical, including optimizing screening, preparation, use of ancillary medications, and debriefing and follow-up following sessions.

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