

Clinical Applications of Hallucinogens: A Review

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Hallucinogens fall into several different classes, as broadly defined by pharmacological mechanism of action, and chemical structure. These include psychedelics, entactogens, dissociatives, and other atypical hallucinogens. Although these classes do not share a common primary mechanism of action, they do exhibit important similarities in their ability to occasion temporary but profound alterations of consciousness, involving acute changes in somatic, perceptual, cognitive, and affective processes. Such effects likely contribute to their recreational use. However, a growing body of evidence indicates that these drugs may have therapeutic applications beyond their potential for abuse. This review will present data on several classes of hallucinogens with a particular focus on psychedelics, entactogens, and dissociatives, for which clinical utility has been most extensively documented. Information on each class is presented in turn, tracing relevant historical insights, highlighting similarities and differences between the classes from the molecular to the behavioral level, and presenting the most up-to-date information on clinically oriented research with these substances, with important ramifications for their potential therapeutic value.

Public Health Significance

Although most hallucinogens are currently highly restricted, some of these substances may have therapeutic applications for a variety of difficult to treat conditions, such as substance use, anxiety, and mood disorders. This review presents data on several classes of hallucinogens with a particular focus on psychedelics, entactogens, and dissociatives, for which clinical utility has been most extensively documented. Findings presented here suggest several hallucinogens have a favorable safety profile when administered under carefully controlled conditions, and warrant reconsideration as tools for clinical treatment.

Keywords: club drugs, dissociative, drug policy, hallucinogen, psychedelic

Hallucinogens fall into several different classes, as broadly defined by pharmacological mechanism of action, and chemical structure (Nichols, 2004; Ray, 2010; Table 1). These include serotonin 2A receptor (5-HT_{2A}) agonists such as lysergic acid diethylamide (LSD), psilocybin, and *N,N*-dimethyltryptamine

(DMT), often referred to as classic hallucinogens or psychedelics; mixed serotonin and dopamine reuptake inhibitors and releasers such as 3,4-methylenedioxy-methamphetamine (MDMA), referred to as empathogens or entactogens (Nichols, 1986); *N*-methyl-D-aspartate (NMDA) antagonists such as ketamine and dextromethorphan (DXM), also known as dissociative anesthetics (Morris & Wallach, 2014); as well as atypical hallucinogens such as the kappa opioid receptor (KOR) agonist salvinorin A, the indole alkaloid ibogaine, which affects multiple neurotransmitter systems, and the anticholinergics such as atropine and datura, also known as deliriants. Finally, cannabis is sometimes attributed hallucinogenic properties (Keeler et al., 1971), and will therefore be discussed briefly in this review.

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Although these classes do not share a common primary mechanism of action, they do exhibit important similarities in their ability to occasion temporary but profound alterations of consciousness, including acute changes in somatic, perceptual, cognitive, and affective processes. Such effects likely contribute to their recreational use. However, a growing body of evidence indicates that these drugs may have other applications beyond their potential for abuse. A number of naturally occurring hallucinogens have a long history of use as religious sacraments dating back hundreds, and in some cases, thousands of years (El-Seedi et al., 2005;

Table 1
 Summary of Hallucinogens and Potential Clinical Applications

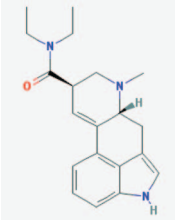
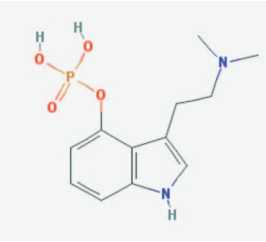
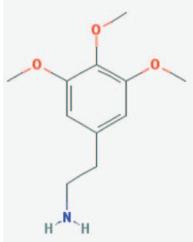
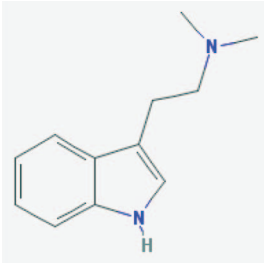
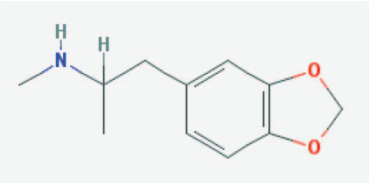
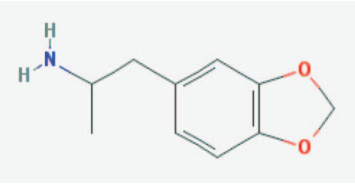
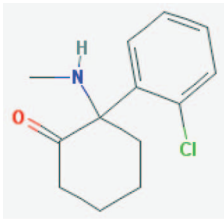
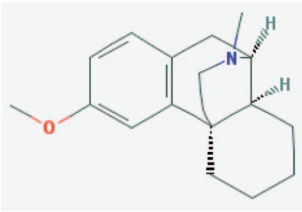
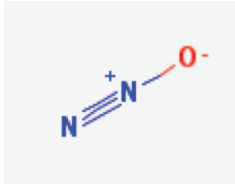
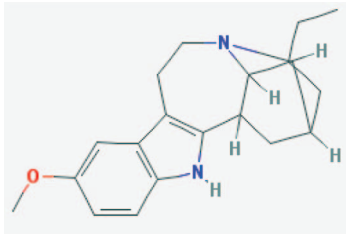
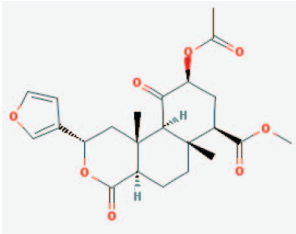
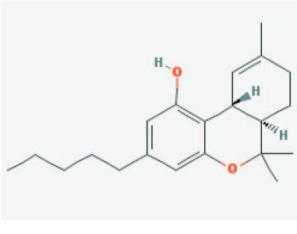
Subclass	Summary
Psychedelics	<p>A group of serotonergic agonists that are currently classified as Schedule I substances. Some, including psilocybin, peyote (mescaline) and the DMT containing admixture ayahuasca, have been used for hundreds to thousands of years for religious purposes by indigenous cultures (Guerra-Doce, 2015). Preliminary evidence indicates one or more of these may be useful in treating cluster headache (Sewell et al., 2006), substance use disorders (Bogenschutz et al., 2015; Johnson et al., 2014; Krebs & Johansen, 2012; Savage & McCabe, 1973), end-of-life anxiety and potentially depression (Carhart-Harris et al., 2016; Gasser, Holstein, et al., 2014; Grob et al., 2011), and obsessive compulsive disorder (Moreno et al., 2006). See below for examples.</p> <div style="display: flex; justify-content: space-around; text-align: center;"> <div> <p>LSD^a</p>  </div> <div> <p>Psilocybin</p>  </div> <div> <p>Mescaline</p>  </div> <div> <p>DMT^b (ayahuasca)</p>  </div> </div>
Entactogens	<p>A group of Schedule I monoamine releasers and reuptake inhibitors known for their ability to evoke a sense of emotional openness and connection (Nichols, 1986). MDMA in particular has shown potential therapeutic benefits in post-traumatic stress disorder (PTSD; Mithoefer et al., 2011, 2012), and is being evaluated as a treatment for social anxiety in adults with autism spectrum disorders (Danforth et al., 2015), and end-of-life anxiety. See below for examples.</p> <div style="display: flex; justify-content: space-around; text-align: center;"> <div> <p>MDMA^c</p>  </div> <div> <p>MDA^d</p>  </div> </div>
Dissociatives	<p>A group of glutamatergic NMDA^e antagonists that are either unscheduled (DXM and N₂O), or restricted but available for use as anesthetics (ketamine), and whose additional therapeutic uses are currently being explored in a variety of areas including depression (Abdallah et al., 2015a; Nagele et al., 2015; Nguyen et al., 2014), and substance use disorders (Krupitsky et al. 1992, 2007; Krupitsky & Grinenko, 1997, 1998). See below for examples.</p> <div style="display: flex; justify-content: space-around; text-align: center;"> <div> <p>Ketamine</p>  </div> <div> <p>DXM^f</p>  </div> <div> <p>Nitrous Oxide</p>  </div> </div>
Atypical	<p>A group of unrelated, pharmacologically distinct substances with some hallucinogenic properties, exhibiting diverse mechanisms of action, legal status, and therapeutic potentials. Ibogaine (Schedule I, US) acts as a serotonin 2A agonist, MOR^g agonist, KOR^h antagonist, and NMDA antagonist, displaying potentials as an anti-addiction agent, particularly for opioids (Alper et al., 1999; Schenberg et al., 2014). The unscheduled KOR agonist Salvinorin A exhibits preclinical evidence for potential in treating addiction (Butelman & Kreek, 2015; Freeman et al., 2014). The CB1ⁱ receptor agonist THC is the main psychoactive chemical in cannabis, and has recognized therapeutic utility for nausea and vomiting due to chemotherapy, chronic neuropathic or cancer pain, and spasticity due to multiple sclerosis (Whiting et al., 2015). Many other cannabinoids and terpenes are present in whole plant cannabis and are being explored for their own therapeutic purposes (e.g., Devinsky et al., 2014). Cannabis and cannabinoids are currently undergoing a major shift in legal status, and range from Schedule I to unscheduled. See below for examples.</p>

Table 1 (continued)

Subclass	Summary		
Atypical	Ibogaine	Salvinorin A	THC ^j
			

Note. Chemical structures retrieved from PubChem Compound Database: <http://www.ncbi.nlm.nih.gov/pccompound>, accessed Jan. 22, 2016. All legal status information refers to United Nations international drug control conventions unless otherwise noted.

^a LSD = lysergic acid diethylamide. ^b DMT = *N,N*-dimethyltryptamine. ^c MDMA = 3,4-methylenedioxy-methamphetamine. ^d MDA = 3,4-methylenedioxyamphetamine. ^e NMDA = *N*-methyl-D-aspartate. ^f DXM = dextromethorphan. ^g MOR = μ opioid receptor. ^h KOR = κ opioid receptor. ⁱ CB1 = cannabinoid 1. ^j THC = Δ^9 -tetrahydrocannabinol.

Guerra-Doce, 2015; Li, 1973). Furthermore, despite their current classification as controlled substances, recent analyses have found that psychedelics and cannabinoids in particular exhibit relatively lower risk of harm to the user and society than other currently available drugs such as alcohol and tobacco (Carhart-Harris & Nutt, 2013; Fantegrossi et al., 2004; Nutt et al., 2010; Van Amsterdam et al., 2010, 2011). In a burgeoning revival of clinical research, several hallucinogens have shown promise for a number of difficult to treat medical and psychological conditions, including chronic pain, cluster headache, posttraumatic stress disorder (PTSD), mood disorders, substance use disorders, and psychological distress associated with life-threatening illness, among others (Tupper et al., 2015).

Contemporary research has revisited the potential of hallucinogen-facilitated treatment paradigms, often involving use of these substances in conjunction with psychotherapy, to facilitate salient and cathartic emotional experiences, sometimes leading to lasting benefits. The present paper will offer an examination of several classes of hallucinogens with a particular focus on psychedelics, entactogens, and dissociatives, for which clinical utility has been most extensively documented. Information on each class is presented in turn, tracing relevant historical insights, highlighting similarities and differences between the classes from the molecular to the behavioral level, and presenting the most up-to-date information on clinically oriented research on these substances, with important ramifications for their potential utility to alleviate human suffering.

Psychedelics

From its inception, research with 5-HT_{2A}R agonist hallucinogens was marked with considerable controversy surrounding the nature of these drugs and their effects. Early researchers struggled to create a context within which to understand these unusual substances (Osmond, 1957; Ruck et al., 1979). Many were intrigued by the psychosis mimicking or *psychotomimetic* properties of these compounds. Isbell (1959) described LSD as “the most effective and safest agent for inducing an experimental, but reversible, psychosis in nonpsychotic subjects” (p. 468). Others

investigated these substances’ putative ability to generate insightful, therapeutic, and even spiritual¹ experiences, leading to alternative characterizations such as *phantastica* (i.e., producing hallucinations and/or visionary states; Lewin, 1931; Stoll, 1947), *psychedelic* (i.e., mind-manifesting, or soul-revealing; Osmond, 1957, p. 429), and *entheogenic* (i.e., evoking the divine within; Ruck et al., 1979). For the purpose of the present article, the term *psychedelic* will be used to denote 5-HT_{2A}R agonist hallucinogens (e.g., LSD, psilocybin, mescaline, DMT, and ayahuasca).

The first generation of clinical psychedelic research began in the mid-20th century and focused almost exclusively on LSD, mescaline, and psilocybin (e.g., Cohen, 1959; Evarts, 1957; Hollister & Hartman, 1962; Isbell, 1959; Isbell, 1959; Rinkel, 1957; Sandison et al., 1954; Stoll, 1947; Wolbach et al., 1962). At the time these compounds, LSD in particular, were seminal in the field of neurochemistry, where they helped advance our understanding of serotonin, and its role in the brain (Aghajanian & Marek, 1999; Brodie & Shore, 1957; Cozzi, 2013; Whitaker-Azmitia, 1999; Woolley & Shaw, 1954a, 1954b, 1957).

After extensive experimentation in humans, it became apparent that the pharmacology of psychedelics was not solely responsible for determining their subjective effects. The expectations and personal experiences of the individual taking them as well as the external environment were recognized as vitally important in influencing users’ experiences. These factors were respectively dubbed *set* and *setting*, and are now well-established elements of human hallucinogen research (Johnson et al., 2008; Fadiman, 2011; Leary et al., 1963). This insight also helps explain the widely varied reactions to these substances observed across different studies. For instance, one study of LSD for the treatment of alcoholism administered high doses (i.e., 800 μ g) of the drug to patients strapped to a hospital bed, and without prior preparation (Smart et al., 1966). Such studies stand in stark contrast to research administering psychedelics in aesthetically pleasing, interperson-

¹ By spiritual we mean here that the experience held some quality perceived by the experiencer to be related to a higher power, divinity, or a transcendent dimension of existence.

ally supportive environs, which have generally been associated with more beneficial outcomes (Chwelow et al., 1959; Griffiths et al., 2006; Pahnke, 1969).

Lysergic Acid Diethylamide (LSD)

Background. LSD was first synthesized in 1938 by Albert Hofmann, a medicinal chemist employed at Sandoz Laboratory in Switzerland. Its psychoactive properties, however, were not discovered until five years later (Hofmann, 1979, 2013). One of the remarkable early findings concerning LSD was its incredible potency, the dose for minimal psychoactive effects being only 20 μ g (Greiner et al., 1958), and its therapeutic ‘optimal’ dose lying between 100 and 200 μ g (Passie et al., 2008). For nearly 20 years LSD remained relatively obscure in the public sphere. Although legitimate scientific research flourished during this period, LSD as a cultural phenomenon was not yet known.

In the 1950s, magazine articles chronicling the LSD experiences of highly visible journalists and movie stars such as Cary Grant began to be published (Bergquist, 1959; Katz, 1953). During this time, the Central Intelligence Agency (CIA) was allegedly sponsoring covert research with LSD as a potential tool for espionage and mind control (Lee & Shlain, 1992; Mashour, 2007), and in the early 1960s Harvard psychologists Richard Alpert and Timothy Leary began their now infamous experimentations with LSD and psilocybin, culminating in their departure from the university in 1963. In 1965, with the media craze reaching a fever pitch, Sandoz Laboratory immediately halted the production and distribution of LSD (Hofmann, 2013). Furthermore, the United Nations (UN) Single Convention on Narcotic Drugs in 1961, and UN Convention on Psychotropic Substances in 1971 placed tight restrictions on psychedelics and other drugs in 183 countries (Nutt, 2014); whereas in the U.S., the Controlled Substances Act was signed into law by President Richard Nixon in 1970. In this context, scientific research with LSD, psilocybin, DMT, and mescaline ground to a halt virtually overnight.

Before this, a large body of human subjects research with LSD was accumulated, including over 1,000 published papers by 1961 (Dyck, 2005), presenting data on an estimated 40,000 participants (Grinspoon & Bakalar, 1997; Masters & Houston, 2000; Nutt et al., 2013). Much of the earliest work with LSD centered on its psychotomimetic properties, see Osmond (1957) for a seminal review of this early period. However, some argued that to best understand these new compounds it would be necessary to transcend the pathological. In the words of early psychedelic researcher Humphry Osmond,

If mimicking mental illness were the main characteristic of these agents, ‘psychotomimetics’ would indeed be a suitable generic term. It is true that they do so, but they do much more. Why are we always preoccupied with the pathological, the negative? Is health only the lack of sickness? (1957, p. 429)

The work of Osmond (1957); Grof et al. (1973), and others significantly contributed to the development of a psychotherapeutic paradigm of psychedelic research (Dyck, 2005). Many studies in the late 1950s and 1960s examined LSD’s efficacy in the treatment of a broad variety of conditions including alcoholism (Smart et al., 1964, 1966), opioid dependence (Savage et al., 1973), pain (Kast & Collins, 1964), neurosis (Cohen, 1959; Eisner

& Cohen, 1958), and cancer-related anxiety (Grof et al., 1973), among others. Researchers also examined LSD as an aid in facilitating creativity and problem solving in healthy volunteers (Harman et al., 1966; McGlothlin et al., 1967).

Use of LSD in the treatment of alcoholism was one of the most widely studied therapeutic applications of psychedelics. A recent meta-analysis of six double-blind, placebo controlled studies from this period (total $N = 536$) found that individuals receiving a single dose of LSD in the context of alcoholism treatment exhibited significantly reduced alcohol misuse at initial follow-up compared with patients receiving nonpsychedelic control treatments (Krebs & Johansen, 2012). Although much of the early research with LSD suffered from methodological shortcomings such as the absence of proper controls or blinding procedures, the sheer outpouring of research during this relatively short period serves as a useful metric for the considerable interest initially generated by LSD (Dyck, 2005; Mangini, 1998; Passie et al., 2008; Strassman, 1995).

Pharmacology. Lysergic acid diethylamide (LSD) is a semi-synthetic tryptamine derived from the naturally occurring ergot alkaloid ergotamine (Nichols, 2004). LSD acts primarily as a serotonergic agonist, but also shows action at dopaminergic and adrenergic receptor sites (Halberstadt, 2015; Nichols, 2004). Substantial research in both animals and humans has implicated 5-HT_{2A}R agonism as a primary mechanism for LSD and related psychedelics’ psychoactive effects (Glennon et al., 1983; Titeler et al., 1988; Vollenweider et al., 1998). In animal models this has been demonstrated with regard to particular behavioral effects such as the head-twitch response, as well as drug discrimination models (Fantegrossi et al., 2004; Carbonaro et al., 2015). However, differential actions at other serotonergic, dopaminergic, and downstream glutamatergic targets are known to modulate the effects of distinct psychedelics (Moreno et al., 2011; Nichols, 2016; Pieri et al., 1974; Ray, 2010; Vollenweider et al., 1999; Vollenweider & Kometer, 2010). Animal models have not found consistent self-administration of LSD, suggesting a low addictive potential for this drug class (Fantegrossi et al., 2008; Hoffmeister & Wuttke, 1975; Poling & Bryceland, 1979; Schuster & Thompson, 1969).

In humans, the subjective effects of LSD can last up to 12 hours, with rapid tolerance developed after repeated administration, and no evidence of withdrawal (Isbell, 1959; Schmid et al., 2015). Recent research has shown that LSD acutely increases plasma cortisol, prolactin, oxytocin, and epinephrine levels (Schmid et al., 2015). Subjective effects of LSD in humans last slightly longer than other psychedelics such as psilocybin and mescaline, though their effects are otherwise considered similar (Abramson et al., 1967; Wolbach et al., 1962). These effects can vary widely, but include altered mood, perception, cognition, the occurrence of elementary and complex hallucinations, as well as experiences described as insightful, transcendent, and/or mystical in nature (i.e., marked by a sense of all encompassing unity; Pahnke & Richards, 1966).

LSD has not been found to produce physiological toxicity, and there have been no documented human deaths from LSD overdose (Passie et al., 2008). However, drug effects can result in disorientation, anxiety, fear of insanity, and feelings that one is dying, which have been characterized colloquially as a “bad trip.” These effects typically resolve during the time course of acute drug

action (i.e., within 12 hours; Cohen, 1960; McGlothlin & Arnold, 1971; Strassman, 1984). However, in some rare cases ongoing psychotic symptoms and other psychological sequelae have been reported (Glass & Bowers, 1970; Smart & Bateman, 1967). Although uncommon, it has been hypothesized that such persisting negative effects of hallucinogens may be related to personal or familial predisposition to psychotic disorders (Strassman, 1984), thus underscoring the importance of careful screening in clinical research.

Another potential persisting effect of LSD is hallucinogen persisting perceptual disorder (HPPD) or “flashback,” which is the intermittent reemergence of perceptual distortions weeks, months or longer after the drug’s effects have worn off. What little data are available on HPPD suggest that it occurs with very low prevalence (Baggott et al., 2011; Halpern & Pope, 2003). Data from a 10-year follow-up survey of 247 individuals who received LSD in experimental or psychotherapeutic settings in the 1960s found that 12 individuals (4.9%) reported instances of perceptual disturbances after the drug sessions had concluded, with individuals who received LSD on 10 or more occasions more likely to report such effects (McGlothlin & Arnold, 1971).

A more recent review of 20 studies confirmed that although HPPD is indeed reported as an adverse effect in some early studies of LSD, prevalence estimates vary widely (ranging from <5% to 77% of participants), in part because researchers had little or no prior knowledge of such a syndrome, and formal criteria were not devised until years later (Halpern & Pope, 2003). Nevertheless, the authors confirmed that prevalence appears higher among recreational psychedelic users than those administered the drugs in controlled settings, possibly as a result of careful screening procedures used in research settings (Halpern & Pope, 2003).

Early researchers found evidence suggesting that LSD may cause chromosomal damage, creating considerable concern about its use as a therapeutic agent (e.g., Auerbach & Rugowski, 1967; Cohen et al., 1967; Egozcue et al., 1968). In the early 1960s, the drug thalidomide was linked to thousands of birth defects and children’s deaths resulting in a massive public outcry (Lenz et al., 1962). Against this historical backdrop, preliminary reports of LSD’s effects on chromosomes generated a highly charged response from the media and public (Fort & Metzner, 1968). However, risks related to these early findings on LSD and chromosomal damage were later thought to be overstated, as *in vitro* chromosomal damage could not be consistently replicated *in vivo* in humans (Cohen & Shiloh, 1977; Dishotsky et al., 1971).

Contemporary research. In 2014 a double-blind, randomized, active placebo-controlled study investigating LSD-assisted psychotherapy for anxiety associated with life-threatening illnesses was published, the first human trial of LSD in the 21st century (Gasser, Holstein, et al., 2014). This study compared 20 µg LSD (i.e., active placebo) to 200 µg LSD using a crossover design in 12 patients with anxiety secondary to a life-threatening illness. Results showed that the 200 µg treatment condition significantly reduced state measures of anxiety up to 12 months posttreatment (Gasser, Holstein, et al., 2014). Qualitative analysis of participant interviews at 12 months posttreatment found no evidence of lasting adverse effects, with participants largely reporting reduced anxiety (77.8%) and increased quality of life (66.7%) since their study participation (Gasser, Kirchner, & Passie, 2015).

Other recent pilot studies ($N = 10$) found that LSD may increase suggestibility and creative imagination in healthy volunteers (Carhart-Harris et al., 2015), and can evoke heightened emotional responses to music (Kaelen et al., 2015). These results could have important implications for the therapeutic use of LSD, as suggestibility has been associated with enhanced treatment outcomes for a number of conditions including pain (Patterson & Jensen, 2003) and depression (Kirsch & Low, 2013). Furthermore, this work can contribute to guiding more refined application of musical stimuli in LSD-facilitated treatments (e.g., McKinney et al., 1997). Research on the neural mechanisms of LSD is currently underway at Imperial College in London and the University of Zurich, demonstrating a renewed interest in the basic science and potential therapeutic effects of this drug (Geyer, 2015).

Psilocybin

Background. Psilocybin is found in more than 100 species of mushrooms (Stamets, 1996) and was first isolated in 1958 (Hofmann et al., 1958; Hofmann, 2013). The religious use of psilocybin containing mushrooms has been extensively studied with documented evidence of use throughout Mesoamerica as early as the arrival of Cortés in Mexico in 1519 (McKenna & Riba, 2015; Metzner, 2004; Ott, 1993; Schultes et al., 2001; Wasson, 1980), and mushroom-shaped artifacts dating as far back as 500 BCE (Guerra-Doce, 2015). In Nahuatl, the language of the Aztecs, psilocybin-containing mushrooms are referred to as Teonanácatl or “divine flesh” (Schultes, 1940).

Pharmacology. Pharmacologically, psilocybin (4-phosphoryloxy-N,N-dimethyltryptamine) is most accurately characterized as a prodrug, and is dephosphorylated by hepatic first pass metabolism into the 5-HT_{2A}, 1A and 2C receptor agonist psilocin (Presti & Nichols, 2004), with subjective effects lasting between 4 and 6 hours (Passie et al., 2002). Recent analysis has demonstrated a largely benign safety profile for psilocybin (van Amsterdam et al., 2011), with independent analyses finding that psilocybin exhibits the least risk of harm to self or others when assessed relative to other commonly abused drugs (Carhart-Harris & Nutt, 2013; Nutt et al., 2010; van Amsterdam et al., 2010). Nevertheless, users may acutely experience moderate to severe disorientation, anxiety, or fear responses under the influence (Griffiths et al., 2006, 2011), a risk shared with LSD and the other psychedelics.

Early research. The volume of clinical research with psilocybin during the 1950s and 1960s was nowhere near that of LSD. Many early researchers seemed more interested in studying the subjective effects of psilocybin simply as they compared with LSD (Hollister & Hartman, 1962; Isbell, 1959; Malitz et al., 1960). This period did however produce several landmark psilocybin studies including a 1963 study by Timothy Leary and colleagues remarking on the protective benefit of “set and setting” on the subjective effects of psilocybin (Leary et al., 1963), as well as Walter Pahnke’s (1963) oft-cited dissertation, commonly referred to as the Good Friday experiment.

The Good Friday experiment was an investigation of mysticism and psychedelics in which psychedelic-naïve divinity students were administered either psilocybin or an active placebo in a religious chapel on Good Friday. Among a group of religiously inclined people in a setting designed to amplify religious sentiments, psilocybin (30 mg dose) was significantly more effective

than an active placebo (i.e., nicotinic acid) at increasing measures of mystical experience and self-reported ratings of personal meaningfulness at 6-month follow-up (Pahnke, 1963).

Doblin (1991) provided a notable long-term follow up and methodological critique of the Good Friday experiment, which found that approximately 25 years later, among 16 of the original 20 participants who could be found, quantitative measures of mystical experience in the psilocybin group ($n = 7$) were still significantly greater than those of the control group ($n = 9$). Furthermore, interview data indicated that among those who had received psilocybin, the experiences retained a deep sense of meaningfulness, and were still considered “to have made a uniquely valuable contribution to their spiritual lives” (Doblin, 1991, p. 23) more than two decades later. However, Doblin (1991) also reported that in the original study two volunteers who received psilocybin had challenging experiences and attempted to leave the chapel where the experiment was being held, resulting in one of them being administered thiorazine as a tranquilizer, details which were not fully acknowledged in earlier reports.

Another noteworthy early study examined psilocybin-facilitated treatment for rehabilitation of incarcerated men (Leary et al., 1965; Leary, 1969). In this study, 32 male inmates at the Massachusetts Correctional Institute at Concord underwent a psilocybin-facilitated group therapy program focused on reducing subsequent recidivism. Volunteers received two to four administrations of psilocybin with doses ranging from 20 to 70 mg during a 6-week group therapy intervention, and were monitored after parole to determine effects on recidivism. Leary (1969) reported that 73% of the study sample managed to avoid parole violation and new crimes leading to arrest and reincarceration during the follow-up period. However, in a subsequent long-term follow-up to this study conducted by Doblin (1998) some 34 years after the original study, recidivism rates of 59% to 71% were reported among experimental participants approximately 2.5 years postrelease, roughly equivalent to that of the larger prison population, thus indicating no significant effects of the intervention. Doblin's (1998) results should be interpreted with caution, as data were limited to only 21 of the original 32 participants whose records could be located.

Leary maintained that these results were not attributable to treatment failure per se, but could be attributed to lack of structured support after parole, which make it very difficult for such programs to have lasting effects (Doblin, 1998; Leary et al., 1965; Leary, 1969). Nevertheless, as Doblin remarked, “Whether a new program of psilocybin-assisted group psychotherapy and post-release programs would significantly reduce recidivism rates is an empirical question that deserves to be addressed within the context of a new experiment” (1998, p. 425).

A recent longitudinal study of more than 25,000 individuals in the criminal justice system in the Southeastern U.S. reported some pertinent findings in this area (Hendricks et al., 2014). All participants had a history of drug use, and were under community corrections supervision. Results found that among the sample, hallucinogen use was significantly associated with reduced rates of supervision failure (i.e., parole or probation violations), whereas use of other drugs such as cocaine predicted increased supervision failure. These findings suggest additional potential for psychedelics in rehabilitation programs among correctional populations (Hendricks et al., 2014).

Contemporary research. Psilocybin has received renewed attention in the 21st century with multiple studies in various populations. Results from some of the first human laboratory research with psilocybin in decades found that in healthy normal volunteers, 30 mg/70 kg psilocybin facilitated mystical-type experiences with sustained meaning and persisting beneficial effects (Griffiths et al., 2006, 2008), consistent with earlier findings from Pahnke (1963) and Doblin (1991). Furthermore, pooled analyses revealed that psilocybin-occasioned mystical experiences were significantly correlated with persisting increases in the personality domain of openness (MacLean et al., 2011), representing the first discrete laboratory manipulation shown to elicit significant, lasting changes in personality, a construct which is considered generally stable throughout adulthood (Terracciano et al., 2005).

Participants also reported experiences of a challenging and sometimes frightening nature under the influence. However, these acute dysphoric responses were well managed with interpersonal support, and resolved by the end of the day-long session. Importantly, even in cases where individuals reported strong ratings of fear or anxiety, the majority of these sessions were still judged as personally meaningful, and no volunteer rated the experience as having decreased their sense of well being or life satisfaction (Griffiths et al., 2006, 2011).

A recent meta-analysis of eight double-blind, placebo-controlled experiments conducted in a single laboratory over the course of 10 years analyzed the acute and persisting effects of 227 psilocybin sessions (dose range from 0.115–0.315 mg/kg) across 110 healthy volunteers (Studerus et al., 2011). In line with recent work on long lasting personal meaningfulness, 60% of the volunteers in that analysis rated their psilocybin experience “very enriching” and 90% rated it enriching to at least a medium degree between 8 and 16 months after administration (Studerus et al., 2011). The most common adverse side effect of psilocybin was found to be mild and well-tolerated headache (e.g., Johnson et al., 2012), and lethargy immediately after psilocybin administration with normal function largely restored after 24 hours. Interestingly, psilocybin and LSD have been implicated as potential treatments for cluster headache, a highly debilitating pain syndrome; however, most data in this area remain anecdotal in nature, and controlled studies are necessary to assess efficacy (Schindler et al., 2015; Sewell et al., 2006).

Regarding Hallucinogen-Persisting Perception Disorder (HPPD) or related symptoms, Studerus et al. (2011) reported that at baseline nine of the 110 volunteers (10%) reported lifetime prevalence of nondistressing, spontaneously occurring altered states of consciousness (e.g., perceptual alterations), and after study participation, eight (9%) reported recurrences of such instances. That sample comprised 60% hallucinogen naïve individuals, and 40% volunteers with prior hallucinogen use, thus data indicate no significant increase in spontaneous perceptual disturbances after experimental drug sessions (Studerus et al., 2011). Additional studies administering from 5 to 30 mg/70 kg of psilocybin to healthy volunteers reported no bothersome or clinically significant perceptual phenomena at 14-months postsession (Griffiths et al., 2008, 2011).

A related meta-analysis examined psilocybin effects across 23 trials (dose range from 0.115–0.315 mg/kg) in a sample of 261 healthy volunteers, finding that drug dose, the personality trait absorption, a positron emission tomography (PET) scanning envi-

ronment, and age were significant factors predicting response to psilocybin (Studerus et al., 2012). Specifically, higher dose predicted greater overall drug effects, greater personality absorption predicted more mystical-type effects, and lower age and PET scanner environment predicted greater anxiety (Studerus et al., 2012). Participant gender was not found to have any significant effects on psilocybin response (Studerus et al., 2012), consistent with the limited human data examining sex differences in classic psychedelics' effects (e.g., Leary et al., 1963). Studerus and colleagues noted that similarity of psychedelic effects across males and females may be attributable to lack of sex differences in 5-HT_{2A}R binding in the cortex (Adams et al., 2004).

Clinical research. The 21st century has also seen a new wave of clinical research with psilocybin (see Table 2), including pilot studies of psilocybin for the treatment of anxiety secondary to a cancer diagnosis (Grob et al., 2011), for obsessive-compulsive disorder (Moreno et al., 2006), for treatment-resistant depression (Carhart-Harris et al., 2016), for smoking cessation (Johnson et al., 2014; Garcia-Romeu et al., 2014), and for alcoholism (Bogenschutz et al., 2015). Grob and colleagues administered 0.2 mg/kg psilocybin and a placebo in counterbalanced order to 12 individuals with cancer, and found significant reductions in anxiety at one month and 3 months post-psilocybin administration, and reductions in depression 6 months post-psilocybin administration (Grob et al., 2011). In keeping with these results Carhart-Harris et al. (2012) conducted functional MRI in 15 healthy volunteers during intravenous (i.v.) psilocybin administration² (2 mg in 10 mL saline infusion), finding decreased activity in the medial prefrontal cortex (mPFC), an area known to exhibit increased activation in individuals experiencing depression (Drevets et al., 2008). Additionally, Kraehenmann et al. (2015) found reduced amygdala activity in response to negative stimuli and increased positive mood during 0.16 mg/kg psilocybin effects in healthy volunteers, indicating possible neural mechanisms for psilocybin in treatment of mood disorders.

Another pilot study examining psilocybin in nine individuals with treatment-resistant obsessive-compulsive disorder (OCD) found significant improvement on measures of OCD symptoms at four, eight, and 24 hours post-psilocybin administration across a range of doses from 0.025 mg/kg (very low dose) to 0.3 mg/kg (Moreno et al., 2006). Furthermore, Carhart-Harris and colleagues (2016) recently published results from an open-label pilot study in which 12 participants with unipolar treatment-resistant major depression received a low (10 mg) and high (25 mg) dose of psilocybin in a supportive setting a week apart. On average, scores on the Quick Inventory of Depressive Symptoms (QIDS) showed significant reductions relative to baseline QIDS scores, from one week ($p = .002$; Hedges' $g = 3.1$) to 3 months ($p = .003$; Hedges' $g = 2$) after high-dose psilocybin administration (Carhart-Harris et al., 2016). Scores on the Beck Depression Inventory showed complete remission in 8 (67%) participants at one week, and 5 (42%) participants at 3 months after high-dose psilocybin administration, suggesting psilocybin may function as a rapid acting antidepressant with sustained therapeutic benefits (Carhart-Harris et al., 2016).

Pilot studies examining psilocybin as an aid in treating substance use disorders have also shown promise. In one open-label pilot study, Johnson and colleagues found that two to three doses of psilocybin (20 mg/70 kg and 30 mg/70 kg) in combination with

cognitive-behavioral therapy for smoking cessation resulted in an 80% success rate at 6 months, with 12 of 15 participants demonstrating biologically verified smoking abstinence (Johnson et al., 2014). Secondary analyses found a significant correlation between acute mystical-type effects of psilocybin and treatment outcomes at 6-month follow-up (Garcia-Romeu et al., 2014). Similarly, in another open-label pilot study ($N = 10$), Bogenschutz and colleagues reported that one to two administrations of psilocybin (0.3 mg/kg and 0.4 mg/kg) in the context of motivational enhancement therapy for alcoholism significantly increased abstinence up to 36 weeks later (Bogenschutz et al., 2015). Results from these studies are limited, as both were conducted open-label with small samples, and did not employ a control condition. However, further studies of psilocybin-facilitated treatment of substance use disorders are currently in progress, including randomized controlled trials investigating psilocybin as an aid in smoking cessation and alcoholism treatment, as well as a pilot study of psilocybin for cocaine dependence.

Mescaline

Background. Mescaline was isolated from *Lophophora williamsii*, a small cactus native to northern Mexico and the southwestern United States, in 1896 by German chemist Arthur Heffter. It was the first naturally occurring psychedelic alkaloid to be isolated in the laboratory (Heffter, 1896). The *Lophophora williamsii* cactus has a long history of religious use among the indigenous peoples of North and South America, and is often referred to using the Nahuatl term péyotl (aka peyote; Prue, 2013). Religious use of peyote has been estimated to extend back more than 5,700 years (Bruhn et al., 2002; El-Seedi et al., 2005). Despite its Schedule I classification, peyote use is constitutionally protected in the U.S. on the basis of religious freedom when used by the Native American Church (NAC; de Verges, 1974).

Why mescaline never attracted significant cultural attention while LSD would go on to galvanize an entire nation remains an interesting historical question. Despite its comparable obscurity, Aldous Huxley stimulated scientific and artistic curiosity about mescaline when he wrote of his experiences with the drug in *The Doors of Perception* (Huxley, 1954). Nevertheless, contemporary research with mescaline has remained limited relative to the other psychedelics, possibly due to its tendency to induce nausea (Deniker, 1957), or its longer duration of action and lesser potency compared to psilocybin and LSD (Wolbach et al., 1962).

Later in the 20th century, chemist and pharmacologist Alexander Shulgin's pioneering work included modification of the mescaline molecule to create many highly potent phenethylamine hallucinogens such as 4-Bromo-2,5-dimethoxyphenethylamine (2C-B) and 2,5-Dimethoxy-4-Methylamphetamine (DOM) among many others, some of which are growing increasingly popular as recreational drugs in recent years (Caudevilla-Gálligo et al., 2012; Faillace et al., 1970; Shulgin, 1973; Shulgin & Shulgin, 1995; Shulgin & Nichols, 1978).

Pharmacology. Mescaline (3,4,5-trimethoxy- β -phenethylamine) is a naturally occurring psychedelic found in a number of cacti

² This study administered psilocybin by intravenous infusion specifically to examine onset of psychedelic effects. All other studies in this section administered psilocybin capsules orally.

Table 2
Summary of Clinical Research With Psychedelics

Study	Drug (dose)/Design	Total N (No. females)/ Diagnosis	Key findings
Bogenschutz et al., 2015	Psilocybin (.3–.4 mg/kg) with MET ^a /open-label	10 (4)/Alcohol dependence	Significant reduction in self-reported drinking days and heavy drinking days for 32 weeks after psilocybin administration compared with baseline ($p < .05$).
Carhart-Harris et al., 2016	Psilocybin (10 mg and 25 mg) in a supportive setting, open-label	12 (6)/Treatment-resistant unipolar major depression	Significant reductions in baseline Quick Inventory of Depressive Symptoms (QIDS) scores from one week ($p = .002$; Hedges' $g = 3.1$) to 3 months ($p = .003$; Hedges' $g = 2$) after 25 mg psilocybin. Beck Depression Inventory (BDI) showed complete remission in 8 (67%) participants at one week, and 5 (42%) participants at 3 months after 25 mg psilocybin.
Gasser et al., 2014a	LSD (200 μ g) with psychotherapy/randomized double-blind active placebo (20 μ g LSD), cross-over	11 (4)/Anxiety associated with life-threatening illness	Significant reductions in State-Trait Anxiety Inventory (STAI) scores at 2 months post-drug administration, with sustained decrease in STAI scores to 12-month follow-up ($p < .05$).
Grob et al., 2011	Psilocybin (.2 mg/kg)/randomized double-blind active placebo (niacin)	12 (11)/Anxiety associated with advanced cancer	Significant reductions in STAI trait anxiety at 1 and 3 months post-treatment ($p < .05$). Significant reductions in Beck Depression Inventory scores at 6-months post-treatment ($p < .05$).
Johnson et al., 2014	Psilocybin (20 and 30 mg/70 kg) with CBT ^b /open-label	15 (5)/Tobacco dependence	Biologically verified smoking abstinence in 80% ($n = 12$) of volunteers at 6-month follow-up, as assessed by exhaled breath carbon monoxide and urine cotinine levels.
Krebs & Johansen, 2012	LSD (200–800 μ g) with counseling/meta-analysis of controlled trials	536 (2)/Alcohol dependence	Individuals receiving a single dose of LSD in the context of alcoholism treatment exhibited significantly reduced alcohol misuse at initial follow-up compared with patients receiving non-psychedelic control treatments (OR, 1.96; 95% CI, 1.36–2.84; $p = .0003$).
Moreno et al., 2006	Psilocybin (.025–.3 mg/kg)/double-blind dose escalation	9 (2)/Obsessive compulsive disorder	Marked reductions on Yale-Brown Obsessive Compulsive Scale (YBOCS) scores for all participants during one or more psilocybin sessions, ranging from 23–100% decrease in YBOCS score, with effects generally lasting more than 24 hours post-drug administration.
Osório et al., 2015	Ayahuasca (2.2 mL/kg) ^c /open-label	6 (4)/Recurrent major depressive disorder	Significant reductions in Hamilton Rating Scale for Depression (HAM-D) and Montgomery-Åsberg Depression Rating Scale (MADRS) scores between baseline and 1, 7, and 21 days after ayahuasca administration.

^a MET = Motivational Enhancement Therapy. ^b CBT = Cognitive behavioral therapy. ^c Ayahuasca contained: .8 mg/mL dimethyltryptamine, .21 mg/mL harmine, and no harmaline.

including peyote (*Lophophora williamsii*), and San Pedro cactus (*Echinopsis pachanoi*), and derived from the amino acid phenylalanine. The first generation of scientists to conduct human subjects mescaline research seemed most interested in mescaline simply as it compared to LSD, similar to early research with psilocybin, and these findings confirmed that the effects and risks of mescaline are largely comparable with those of LSD and psilocybin (Rinkel, 1957; Hollister & Hartman, 1962). Although some research has been forthcoming examining the effects of mescaline in humans as a model psychosis (Hermle et al., 1992, 1998), clinical research investigating mescaline as a potential therapeutic aid has been lacking. However, research examining the indigenous use of peyote holds some clinical relevance.

Early research. Early observational studies of peyote use by the Native American Church (NAC) concluded that religious use

of peyote seemed safe and may prove effective in the treatment of alcoholism (Albaugh & Anderson, 1974; Bergman, 1971; Garrity, 2000; Prue, 2013). These findings are limited because of their reliance on naturalistic observation rather than human laboratory administration. However, more recent data seem to corroborate these results. One study compared the mental health of long-term peyote using NAC members who reported minimal use of any other drugs ($n = 61$) with a median of 300 lifetime episodes of peyote use, to Native Americans with a history of alcohol abuse ($n = 36$), and nondrug using Native American controls ($n = 79$). Results found that long-term peyote users demonstrated no cognitive deficits compared to nondrug controls. Additionally peyote users showed significantly greater psychological well-being and general positive affect than nondrug using controls, whereas individuals in the chronic alcohol use group exhibited significant

cognitive and neuropsychological deficits compared to both control and peyote using participants (Halpern et al., 2005). These data, though limited in scope, suggest a potential role for mescaline, and possibly other phenethylamines, as therapeutic agents warranting further investigation.

DMT

Background. The subjective effects of N, N-Dimethyltryptamine (DMT) were discovered in 1956 (Szara, 1956). Early research on DMT focused on the basic physiological effects and psychotomimic effects of DMT as well as the synthesis of several new DMT analogs such as N, N-Diethyltryptamine (DET) and N, N-dipropyltryptamine (DPT; Böszörményi, Der, & Nagy, 1959). DMT has become increasingly visible in recent years due to its coverage in several popular online media outlets and in film (e.g., Barclay, 2012). Recent survey data from the Global Drug Survey suggests DMT may be growing in popularity as a recreational drug and is almost always vaporized and inhaled when not prepared as ayahuasca, a South American DMT containing brew which will be covered in the following subsection (Winstock, Kaar, & Borschmann, 2014).

Pharmacology. Although similar to LSD and psilocybin in many regards, including molecular composition and affinity for the 5-HT_{2A}R, DMT also possesses many unique characteristics. This first became evident in 1965 when DMT was detected in the urine and blood of healthy adults (Franzen & Gross, 1965). Since then, many studies have identified DMT in the body fluids both of schizophrenics and healthy, nondrug using individuals (Barker et al., 2012). DMT has also been identified in whole rat brain homogenate and more recently in rat pineal gland (Barker et al., 1980, 2013; Christian et al., 1977). Besides the serotonin 2A, 2C, and 1A receptors, DMT also displays affinity and agonist activity at the sigma-1 and trace amine associated receptors, among others (Bunzow et al., 2001; Fontanilla et al., 2009).

Indolethylamine-N-methyltransferase (INMT), the enzyme responsible for synthesizing DMT from tryptamine, is widely expressed in the body including in the lungs, thyroid, adrenal glands, placenta, skeletal muscle, heart, small intestine, stomach, pancreas, and lymph nodes (Thompson et al., 1999). Many suggestions have been put forth regarding DMTs physiological role in the body, though there is no widely accepted consensus (Burchett & Hicks, 2006; Callaway, 1988; Frecska et al., 2013; Jacob & Presti, 2005; Su et al., 2009). For instance, DMT has been implicated as a mediator of consciousness and perception, particularly visual perception, via interactions with trace amine associated receptors (Wallach, 2009).

Other researchers have proposed an immunomodulatory role of DMT, suggesting that

while DMT is a substance which produces powerful psychedelic experiences, it is better understood not as a hallucinogenic drug of abuse, but rather an agent of significant adaptive mechanisms that can also serve as a promising tool in the development of future medical therapies. (Frejska et al., 2013, p. 1295)

Along these lines, Szabo (2015) suggested a possible therapeutic role for psychedelics in modulating immune function and reducing inflammation, potentially through sigma-1 receptor mediated pathways. These claims are consistent with preclinical data showing

administration of the 5-HT_{2A}R agonist (R)-2,5-dimethoxy-4-iodoamphetamine (R-DOI) greatly suppresses tumor necrosis factor alpha (TNF- α) induced inflammation in vitro (Yu et al., 2008), and in vivo (Nau et al., 2013). Furthermore, these results have been found to generalize to a rodent model of allergic asthma, indicating considerable clinical potential (Nau et al., 2015).

Early research. Early human subjects research with DMT focused largely on basic psychopharmacology, and psychotomimetic effects of this substance (e.g., Gillin et al., 1976). Like other classic hallucinogens, research with DMT ceased with the passage of the Controlled Substances Act, and was never investigated as an aid in clinical treatment to the extent LSD was. However, research with dipropyltryptamine (DPT), a closely related synthetic analog of DMT, revealed some promise as an adjunct to psychotherapy both with alcoholics (Grof et al., 1973; Rhead et al., 1977; Soskin et al., 1973), and those with anxiety associated with a terminal cancer diagnosis (Richards et al., 1977, 1980; Richards, 1978). Contemporary survey data from a sample of 121 Australian recreational DMT users found that 31.1% of lifetime DMT users claimed psychotherapeutic benefits as a reason for DMT use, and 75.5% reported psychospiritual insight as their primary motivation for DMT use (Cacic et al., 2010), consistent with earlier research on DPT as an adjunct to psychotherapy.

Contemporary research. Human subjects research with DMT resumed in 1990 after a long hiatus, with several experiments performed to assess the basic pharmacological and subjective effects of DMT in experienced hallucinogen users (Strassman, 1996; Strassman & Qualls, 1994; Strassman et al., 1994a; Strassman et al., 1996). Major contributions of this work included the finding that i.v. administration of DMT to carefully screened volunteers was physiologically and psychologically well tolerated. Unlike other 5-HT_{2A}R agonists, closely spaced administrations of DMT did not result in psychological tolerance.

More recently, researchers have administered DMT and ketamine to experienced drug users in order to better characterize serotonergic and glutamatergic models of psychosis (Daumann et al., 2008, 2010; Gouzoulis-Mayfrank et al., 2005; Heekeren et al., 2007). Results showed that in healthy subjects, DMT was associated with incidence of positive symptoms of schizophrenia (e.g., thought disorder, inappropriate affect), whereas ketamine was associated with more negative symptoms (e.g., catatonia, body perception disturbances), suggesting differentially mediated effects of serotonin and glutamate in the manifestation of psychotic disorders (Gouzoulis-Mayfrank et al., 2005). Data additionally showed that DMT had no significant effect on prepulse inhibition (PPI) of the acoustic startle reflex in healthy subjects, and ketamine increased PPI, responses which are inconsistent with the diminished PPI startle reflex observed in schizophrenia (Heekeren et al., 2007).

Another study found differential alterations in neural correlates related to visual and auditory processing tasks during acute DMT and ketamine administration (Daumann et al., 2008, 2010). These results highlight some noteworthy differences between hallucinogen-induced model psychoses, and naturally occurring schizophrenia, and furthermore make the case for continued human subjects hallucinogen research as a means of enhancing our understanding of organically occurring psychotic disorders and symptoms. Nevertheless, although data on pure DMT as a clinical aid are still lacking, ayahuasca, an indigenous

DMT-containing formulation is receiving increasing attention as a potential tool in therapy.

Ayahuasca

Background. Western scientific knowledge of ayahuasca, a Quechua term for “vine of the soul” (McKenna, 2004) dates to the 19th century when it was first described by pioneering botanist Richard Spruce on a botanical expedition to the Amazon (Spruce, 1873). We now know that what we call ayahuasca is a loosely defined admixture that has been documented to contain “more than 90 different plant species from 38 plant families” (Ott, 1993, p. 221). Luna (1986a, 1986b) identified 72 indigenous groups reported to use ayahuasca and 42 different indigenous names for the beverage. Although the use of ayahuasca by indigenous populations dates back thousands of years (Naranjo, 1979), its broader use in a syncretic religious context is a product of the 20th century. The oldest syncretic ayahuasca church, Santo Daime, was founded in the 1930s. By 2005 Santo Daime had at least one church in 23 different countries (Labate et al., 2008; MacRae, 1992). Religious ayahuasca use was legalized in Brazil in 1987 (Grob et al., 1996). In 2006, O Centro Espirita Beneficente Uniao do Vegetal (UDV) another prominent ayahuasca church, was granted the legal right to conduct ayahuasca ceremonies in the United States as an expression of religious freedom, despite the Schedule I status of DMT, which is contained in ayahuasca (Bullis, 2008). In 2008, ayahuasca was formally declared a part of the national cultural heritage of Peru by the Peruvian government (Instituto Nacional de la Cultura, 2008).

Pharmacology. Despite their chemical and botanical diversity, the majority of ayahuasca brews are characterized by the combination of DMT, the only major alkaloid present in the leaves of *Psychotria viridis*, and the β -carboline alkaloids harmine, tetrahydroharmine, and harmaline present alongside additional trace alkaloids in the bark and stems of the vine *Banisteriopsis caapi* (McKenna et al., 1984a, 1984b). DMT is rapidly metabolized by monoamine oxidase (MAO) in the gut following oral administration, however the β -carboline alkaloids harmine, tetrahydroharmine, and harmaline are potent MAO inhibitors (MAOIs), preventing the first-pass oxidative deamination of DMT (Callaway et al., 1999; McKenna & Towers, 1984).

Concentrations of DMT and β -carboline alkaloids vary widely by batch, however laboratory analysis of one batch of Santo Daime Brazilian ayahuasca contained 0.53 mg/mL DMT, 0.9 mg/mL harmine, 0.06 mg/mL harmaline, and 0.72 mg/mL tetrahydroharmine. The above study considered a high dose of ayahuasca to be 0.85 mg/kg bodyweight of DMT, 1.4 mg/kg of harmine, 0.09 mg/kg of harmaline, and 1.16 mg/kg of tetrahydroharmine (Riba et al., 2003). The same study identified peak plasma concentrations of DMT at 1.5 hours, peak plasma levels of harmaline at 2 hours and peak plasma levels of tetrahydroharmine at 3 hours and undetectable plasma levels of harmine in blood plasma after a high dose. Peak subjective effects coincided with peak plasma DMT levels at both dose ranges. Cardiovascular effects were modest with a statistically significant increase in diastolic blood pressure (9 mm/Hg at 75 min) in the high dose condition only, and no significant effect on systolic blood pressure or heart rate at any dose (Riba et al., 2003).

Contemporary research. Although research with pure DMT has remained largely focused on pharmacology and psychotomimetic effects, the rapid growth of ayahuasca as a cultural phenomenon and religious sacrament has put increased pressure on researchers around the world to study its effects scientifically. A seminal study of ayahuasca use among 15 adult male members of the UDV was initiated in 1993, and subsequently known as the ‘Hoasca Project’ (Grob et al., 1996; McKenna, 2004; McKenna et al., 1998). Results indicated that structured ayahuasca consumption was medically safe (Callaway et al., 1996, 1999), and exhibited a potential protective psychological effect. Semistructured clinical interviews found higher rates of adverse psychiatric diagnoses and symptoms including violent behavior, substance abuse, depression, and anxiety disorders in UDV members as compared with nonayahuasca using controls *before* their initiation into the UDV, and near complete remission of all pathological behaviors after their long-term involvement with the UDV (Grob et al., 1996). Later research has confirmed and elaborated on the medical safety and pharmacology of ayahuasca use (Barbosa et al., 2012; Bouso et al., 2012; Dos Santos et al., 2007, 2011, 2012; Gable, 2007; Riba et al., 2001; Riba & Barbanoj, 2005).

Initial research on the long-term neuropsychological effects of ayahuasca (e.g., Grob et al., 1996) has continued in the 21st century with several teams conducting similar lines of research on a variety of ayahuasca using populations. As a whole, this literature has shown decreases in measures of psychopathology and increases in performance on cognitive tasks in a Brazilian cohort of adult ayahuasca users as compared with matched nonayahuasca using controls at baseline and 1 year follow up (Bouso et al., 2012); decreases in alcohol consumption and measures of addiction severity in both urban and rural ayahuasca users as compared with matched controls (Fábregas et al., 2010); decreased rates of psychopathology as well as alcohol and amphetamine use among Brazilian adolescent religious ayahuasca users compared with matched controls (Da Silveira et al., 2005; Doering-Silveira, Grob, et al., 2005; Doering-Silveira, Lopez, et al., 2005); and decreased substance use and psychopathology among a group of American religious ayahuasca users (Halpern et al., 2008).

One recent study of note compared 22 regular ayahuasca with 22 matched controls, finding that ayahuasca users exhibited significantly greater self-transcendence (ST), a personality trait related to spirituality, and significantly less cortical thickness in the posterior cingulate than nonusers (Bouso et al., 2015). Furthermore, an inverse correlation between ST and cortical thickness in the posterior cingulate cortex was found, suggesting a compelling link between psychedelic use, brain structure, and spiritual attitudes. Additionally, Alonso and colleagues reported that ayahuasca’s acute effects may in part be associated with alterations of functional coupling and information flow between brain regions particularly, potentially through enhancement of bottom-up information transfer (Alonso et al., 2015). This work represents some of the most clinically relevant findings among a rapidly growing literature on 5-HT_{2A}R agonists and other hallucinogens’ effects on the brain and neurological function (e.g., Carhart-Harris et al., 2012, 2014; Palhano-Fontes et al., 2015; Petri et al., 2014; Roseman et al., 2014; Tagliazucchi et al., 2014), a full review of which lies outside the scope of the current paper.

Addiction. Interest in ayahuasca as a potential aid in the treatment of substance abuse has been encouraged by observa-

tional findings including decreased rates of alcohol use among current users of ayahuasca, as well as reduction of substance abuse upon initiation of religious ayahuasca use have been reported in multiple studies (Bousso & Riba, 2014; Da Silveira et al., 2005; Doering-Silveira, Grob, et al., 2005; Doering-Silveira, Lopez, et al., 2005; Fábregas et al., 2010; Grob et al., 1996; Halpern et al., 2008; Labate et al., 2010). Multiple rehabilitation centers structured around religious ayahuasca use for the treatment of substance abuse have opened in Brazil, Peru, Argentina, Uruguay, and Chile (Mabit, 2002, 2007; Prickett & Liester, 2014). Although intriguing, none of these centers have been examined by any independent researchers. An internal report from one such center in Peru documents their activities from the year 1992 to 1998, during which Time 380 patients were admitted, stating that 62% claimed to have benefitted in some capacity from their treatment model (Mabit, 2002). Data from two recent pilot studies of ayahuasca-assisted treatment in drug dependent individuals further suggest ayahuasca's potential for enhancing psychological well-being and decreasing problematic substance use among these populations (Fernández et al., 2014; Thomas et al., 2013). However, larger, more carefully controlled studies are necessary before results can be deemed conclusive.

Depression. Interest in ayahuasca for the treatment of major depressive disorder (MDD) has also been forthcoming, and stems largely from its influence on serotonergic neurotransmission, where both DMT and β -carboline alkaloids have demonstrated activity (de Lima et al., 2011; Palhano-Fontes et al., 2014). One of the seminal findings in this area was the discovery that long-term ayahuasca use was correlated with an increased density of serotonin transporters in platelets (Callaway et al., 1994; McKenna, 2004), deficits of which have been implicated in aggression, substance abuse, and MDD (Gorwood et al., 2000; Hallikainen et al., 1999; Tiihonen et al., 1997).

Additionally, ayahuasca has demonstrated effects in other biological systems implicated in depression. These include effects on hypothalamic-pituitary-adrenal (HPA) axis function (Dos Santos et al., 2011, 2012), which regulates the production and transmission of hormones throughout the brain and body, mediating the body's stress response through hormones such as cortisol and adrenaline, which also affect the latency and duration of REM sleep (Buckley & Schatzberg, 2005). Ayahuasca has been found to inhibit REM sleep and increase slow-wave activity without reducing subjective sleep quality (Barbanoj et al., 2008). These effects are largely consistent with those exhibited by approved serotonergic antidepressants such as mirtazapine, which down-regulate HPA axis hyperactivity in depressed patients and inhibit REM sleep (Mayers & Baldwin, 2005; Schüle, 2007; Tsuno et al., 2005). Furthermore, β -carbolines found in ayahuasca (e.g., harmine) have also demonstrated antidepressant properties in rodent models of depression (Aricioglu & Altunbas, 2003; Farzin & Mansouri, 2006; Fortunato et al., 2009, 2010).

Pilot findings have demonstrated acute reductions in hopelessness and panic-like symptoms among a small sample of religious ayahuasca users ($N = 9$) during active ayahuasca administration compared with placebo control conditions (Dos Santos et al., 2007), as well as statistically significant reductions in depression scores for up to 21 days after administration of a single dose of ayahuasca in an open-label pilot of six patients with a current depressive episode (Osório et al., 2015). Furthermore, ayahuasca

has recently been reported to significantly increase mindfulness related capacities, reducing participants' judgment and reactivity toward inner experiences, 24 hours after ayahuasca use in a sample of 25 healthy volunteers (Soler et al., 2016). Such effects may indicate a potential psychological mechanism mediating therapeutic effects of ayahuasca, as successful mindfulness-based treatments for depression have been shown to decrease brooding, in part by enhancing nonjudgmental awareness (Shahar et al., 2010).

Although the majority of this research suggests ayahuasca use is safe, has a low abuse potential, does not exhibit many of the problems typically associated with drug abuse, and may even be useful in the treatment of psychiatric conditions (Barbosa et al., 2012; Osório et al., 2015), methodological shortcomings, and the possibility of self-selection bias should also be noted. Future research should make an effort to study individuals who used ayahuasca in religious contexts for a period of time before abandoning the practice to compare to active users. Thus far, only a small number of studies have been published studying individuals before and after participating in their first ayahuasca ceremony, much of which has focused on qualitative data and motivation for using ayahuasca for the first time (Barbosa et al., 2005, 2009; Harris & Gurel, 2012; Trichter, Klimo, & Krippner, 2009).

Entactogens

The term entactogen, from the Greek meaning "to touch within," was coined by Nichols (1986) to describe the psychoactive effects of the synthetic drugs 3,4-methylenedioxy-methamphetamine (MDMA), 3,4-methylenedioxy-amphetamine (MDA), and 3,4-methylenedioxy-*N*-ethyl-amphetamine (MDEA; Nichols, 1986). Entactogens combine the catecholaminergic effects of methamphetamine, from which they are derived, with the serotonergic effects of psychedelics, exhibiting a unique profile of prosocial and interpersonal effects. Evidence for the distinction of entactogens from both methamphetamine and psychedelics comes from studies of molecular structure-activity relationships and animal models of self-administration (Nichols, 1994; Nichols & Oberlender, 1989), indicating the robustness of the drug family. The main focus of the following section is MDMA, by far the most widely studied and recreationally used entactogen (Freudenmann et al., 2006; McDowell & Kleber, 1994).

3, 4-methylenedioxymethamphetamine (MDMA)

Background. 3,4-methylenedioxymethamphetamine (MDMA) is a methamphetamine derivative first synthesized in 1912 for use as an intermediary in the production of other chemicals (Karch, 2011). Although in the first half of the 20th century produced some preliminary human and animal data on MDMA, it did not rise from scientific and cultural obscurity until the second half of the 20th century. In 1976, Dr. Leo Zeff became the first psychotherapist in the United States to incorporate MDMA into his independent practice psychotherapy, conducting hundreds of sessions and proselytizing for its therapeutic use among fellow therapists. On the East coast of the U.S. especially, MDMA became an increasingly popular tool for therapists who believed it encouraged the psychotherapeutic alliance, increased empathy and openness, and allowed for the expression of highly charged and traumatic emotional material (Greer & Tolbert, 1986; Pentney, 2001; Stolaroff, 1997).

One MDMA psychotherapist estimated that as many as 4,000 therapists were introduced to MDMA during this period (Holland, 2001).

During the late 1970s and early 1980s MDMA began to gain popularity for recreational use. By 1981 MDMA acquired the street name 'Ecstasy,' and in 1985 was classified as a Schedule I controlled substance during an emergency session of the DEA (Riedlinger, 1985). The first peer-reviewed papers on MDMA psychotherapy were not published until after its emergency scheduling (Greer & Tolbert, 1986, 1990, 1998). It is estimated that during the period from 1990 to 1995 global MDMA use increased by 4,000% (Holland, 2001). In the first five months of the year 2000 more than four million doses of the drug were confiscated by United States authorities alone (Holland, 2001). This explosion of recreational use was accompanied by an entirely new youth culture, the rave and electronic dance music culture (Arria et al., 2002).

Pharmacology. Pharmacologically, MDMA possesses properties of both methamphetamine and mescaline. Like methamphetamine, MDMA is a potent releaser of catecholamine neurotransmitters (i.e., epinephrine, norepinephrine, and dopamine) via action at presynaptic reuptake sites. MDMA is also a potent releaser of presynaptic serotonin (De la Torre et al., 2004; Nichols, 1994; Nichols & Oberlander, 1989, 1990). Like mescaline and other classic hallucinogens, the subjective effects of MDMA are also attenuated by the 5-HT_{2A}R antagonist ketanserin (Liechti et al., 2000).

MDMA is usually taken orally, however limited i.v. use has been observed among some experienced users with an eventual return to oral use in most cases (Topp et al., 1999). Peak plasma levels occur within 1 to 2 hours, with subjective effects lasting between 2 and 4 hours (De la Torre et al., 2004). The full range of subjective and cardiovascular effects are evident at doses at or above 1.0 mg/kg (Dumont & Verkes, 2006). Of potential relevance to its therapeutic utility, MDMA has been shown to have dramatic effects on plasma levels of oxytocin, cortisol, and prolactin (Dumont & Verkes, 2006; Dumont et al., 2009; Harris et al., 2002; Parrott et al., 2013; Wolff et al., 2006, 2012).

Safety. The safety of MDMA continues to be an area of intense controversy, the breadth of which is outside the scope of this review. However, for a thorough review of this topic see Parrott (2013, 2014); Doblin et al. (2014); Nutt (2009); and Henry and Rella (2001). It is important to make a distinction between the medical risks of controlled MDMA use and recreational use which is often associated with prolonged dancing and physical exertion, lack of proper hydration, and additional confounds such as poly drug use and the fact that black market 'Ecstasy' is sometimes adulterated with other potentially dangerous drugs such as amphetamine, ephedrine, ketamine, methamphetamine, MDA, MDEA, and caffeine, and may not contain any MDMA at all (Cole et al., 2002; Sherlock et al., 1999).

In laboratory studies of human volunteers, MDMA exposure is associated with increased heart rate, increased systolic and diastolic blood pressure, accelerated breathing, jaw clenching, thirst, and increases in core body temperature (Dumont & Verkes, 2006; Freedman et al., 2005; Kirkpatrick, Baggott, et al., 2014; Liechti et al., 2001). In combination with strenuous activity and warm, poorly ventilated indoor areas which are often encountered in recreational settings, MDMA use can result in hyperthermia which

in extreme cases can lead to hospitalization, organ failure and even death (Chadwick et al., 1991). Recent research using animal models has demonstrated a pronounced effect of ambient temperature on MDMA induced hyperthermia. For a review on the thermal effects of MDMA see Parrott (2012).

Recreational 'Ecstasy' use has also been associated with cognitive deficits, including memory deficits (Laws & Kokkalis, 2007; Nulsen et al., 2010; Rogers et al., 2009). Interpretation of this literature is sometimes complicated by poly drug use and the unknown content and dosage of black market 'Ecstasy.' In an attempt to address this issue, one study compared 12 moderate 'Ecstasy' users (22–50 lifetime uses), and 11 heavy users (60–450 uses) who self-reported minimum exposure to any other drugs including alcohol, and 16 individuals reporting no lifetime 'Ecstasy' use. Findings showed no significant differences between moderate users and nondrug controls on a battery of cognitive tasks. Significant differences were found between heavy users and nondrug controls, with heavy users exhibiting decreased mental processing speed and greater impulsivity (Halpern et al., 2004). However, as Lyvers and Hasking (2004) noted, Halpern et al.'s (2004) results may have been overstated, as the study used a large number of measures (39 total) in a relatively small sample ($N = 39$), performing 117 between-groups comparisons without adjusting for Type I error, and furthermore cannot demonstrate causation as such between group differences may have been preexisting, potentially contributing to heavy users' more extensive recreational drug use.

Two similar studies in larger samples examined cognitive function in current and ex-'Ecstasy' users, poly drug users, and drug-naïve controls (Hoshi et al., 2007; Roiser et al., 2007). The first ($N = 109$) found no significant differences in cognitive processing between current 'Ecstasy' users and drug-naïve controls; however among both current- and ex-'Ecstasy' users greater impulsivity was correlated with greater cognitive impairment, a relationship which was not apparent among controls, suggesting impulsivity as a mediator of vulnerability to cognitive deficits in chronic 'Ecstasy' users (Roiser et al., 2007). Another comparable study ($N = 109$) reported that although current 'Ecstasy' users and poly drug users showed subtle impairment in verbal learning and memory, as well as response inhibition in a Go/No-go task, the majority of assessments did not show significant differences from drug-naïve controls, indicating that recreational drug use, and particularly recent drug use were more likely associated with the observed cognitive deficits rather than 'Ecstasy' use per se (Hoshi et al., 2007).

The debate on MDMA neurotoxicity goes back more than 20 years (Baggott & Mendelson, 2001; Baumann et al., 2007; McKenna & Peroutka, 1990; Parrott, 2002, 2013, 2014). Extensive animal data has shown reduced levels of serotonin (5-HT), the 5-HT metabolite 5-hydroxyindoleacetic acid (5-HIAA) and the 5-HT transporter (SERT) after exposure to MDMA, as well as damage and or loss of serotonergic axon fibers after exposure to MDMA (O'hearn et al., 1988; Ricaurte, Yuan, & McCann, 2000; Scallet et al., 1988). Although compelling, many unresolved questions cloud interpretation of this literature, including determination of comparable doses of MDMA in nonhuman animals, the validity of using extremely high doses and exposing the test animal to multiple doses in a short amount of time, and questions such as the lack of a clear and unambiguous definition of neurotoxicity (Bau-

mann et al., 2007; Easton & Marsden, 2006). In a review of the rodent literature Baumann and colleagues point out that 1 to 2 mg/kg doses of MDMA elicit comparable neurochemical effects in rats and humans, and thus doses do not necessarily need to be adjusted between these species (Baumann et al., 2007). Furthermore, although relatively high doses of MDMA (e.g., 10–20 mg/kg) in rodent models show evidence of serotonin depletion, other markers of neurotoxicity such as cell death are not reliably evoked (Baumann et al., 2007). Nevertheless, the presence of persisting anxiety-like behavior in rats administered moderate doses (5–7.5 mg/kg) of MDMA do pose a potential risk in addition to concerns about neurotoxicity (Baumann et al., 2007).

Recently, some researchers have proposed that rather than MDMA neurotoxicity, the observed effects represent a neuroadaptive response to a foreign stimulus (e.g., Kindlundh-Högberg et al., 2008). Taken together, evidence indicates that chronic recreational ‘Ecstasy’ users may experience some lasting functional impairment (Parrott, 2013), though such effects are not known to generalize to individuals undergoing limited exposure to MDMA of established dosage and purity in controlled settings for MDMA-assisted treatment paradigms (Doblin et al., 2014).

Contemporary research. In recent years laboratory data on subjective effects of MDMA, and in particular social–cognitive effects of potential clinical relevance, have begun to accumulate (Bedi et al., 2009; Danforth et al., 2015; Kamilar-Britt & Bedi, 2015; Kirkpatrick, Baggott, et al., 2014; Kirkpatrick, Lee, et al., 2014b; Kirkpatrick et al., 2015; Wardle & de Wit, 2014; Wardle, Kirkpatrick, & de Wit, 2014). Such findings include acute reduction in the recognition of fearful faces and identification of negative emotions in an ‘eyes only’ emotion recognition task (Bedi et al., 2010; Hysek et al., 2012), and slowed perception of angry expressions and an increased psychophysiological response to happy expressions after MDMA administration (Wardle & de Wit, 2014). Utilizing measures of facial emotion recognition in a functional MRI paradigm, researchers observed a decreased amygdala response to angry faces and increased ventral striatum activity in response to happy faces suggesting an enhanced response to rewarding social cues (Bedi et al., 2009). MDMA has also been demonstrated to acutely increase social–cognitive factors such as generosity, communicativeness, and self-compassion (Baggott et al., 2015; Kamboj et al., 2015; Kirkpatrick & de Wit, 2015).

Unlike the classic psychedelics, MDMA has shown significant sex differences in human subjects (Liechti et al., 2001). In a pooled analysis of three double-blind placebo controlled trials Liechti et al. (2001) compared the effects of MDMA (dose range 75–150 mg) in 54 male and 20 female volunteers, finding that subjective effects of MDMA were more intense in women, with female volunteers exhibiting greater perceptual changes, thought disturbances, and fear of loss of body control, as well as more adverse effects and sequelae postdrug administration. MDMA has also been found to increase measures of emotional empathy and prosocial behavior in men, while impairing identification of negative emotions in women (Hysek et al., 2014). Such differential effects may have significant ramifications for use of MDMA and other entactogens as therapeutic agents, and warrant further investigation.

Multiple studies of social behavior in rodents after MDMA exposure have reported significant prosocial effects (Kamilar-Britt & Bedi, 2015), including decreased aggressive behavior and in-

creased social interaction (Morley & McGregor, 2000). Some of these effects have been shown to be attenuated by pretreatment with an oxytocin receptor antagonist (Thompson et al., 2007). Recent neurobiological models for MDMA in the treatment of anxiety disorders have drawn on this body of work proposing three mechanisms by which MDMA may be an effective pharmacotherapy in the treatment of anxiety disorders. The authors suggest that increased oxytocin levels may account for the strengthening of the psychotherapeutic alliance first described by the earliest MDMA psychotherapists. Furthermore, increased ventromedial prefrontal activation and decreased amygdala activation were hypothesized to improve emotional response to emotionally difficult material. Finally, acute increases in cortisol levels under the influence of MDMA may facilitate the extinction of learned fear associations within a therapeutic context (Johansen & Krebs, 2009).

Clinical research. The clinical research available on MDMA-assisted psychotherapy consists of data collected by MDMA therapists in the U.S. before the scheduling of MDMA in 1985 (Greer & Tolbert, 1986), data from a Swiss team collected between 1988 and 1993 (Gasser, 1994), and a more recent wave of preliminary clinical trials in the 21st century. The early data consists largely of retrospective, qualitative analyses of MDMA-assisted psychotherapy sessions, which were proposed to “reduce or somehow eliminate the neurophysiological fear response to a perceived threat to one’s emotional integrity” (Greer & Tolbert, 1998, p. 377), thereby facilitating therapeutic outcomes. Follow-up data collected from 29 subjects who underwent MDMA-assisted psychotherapy found the most commonly reported benefits to be positive changes in attitudes or feelings, expanded mental perspective, increased insight into personal problems, and positive changes in their relationships. Common negative effects of MDMA-assisted psychotherapy included undesirable emotional symptoms such as anxiety during and following the session and undesirable physical symptoms such as jaw clenching. Consistent with psychedelic research from two decades prior, the importance of set, setting, and careful preparation were also cited as crucial factors in effective MDMA-assisted psychotherapy (Greer & Tolbert, 1986).

Additionally, a team of Swiss researchers collected quantitative long-term follow-up data on 121 patients who had undergone at least one session of MDMA-assisted psychotherapy, with 84.3% of completers reporting increased quality of life and 90.9% reporting good or slight improvement in their condition after MDMA-assisted psychotherapy (Gasser, 1994). The mean number of MDMA-assisted sessions was 6.8. It should be noted that 71% of participants who were mailed the questionnaire completed and returned it, making positive selection bias a possibility. Additionally, both the American and the Swiss teams reported decreased drug use after MDMA-assisted psychotherapy, particularly with regards to alcohol and cannabis (Gasser, 1994; Greer & Tolbert, 1986).

More recent clinical MDMA research has largely focused on treatment-resistant posttraumatic stress disorder (PTSD) with three double-blind, placebo-controlled pilot trials of MDMA-assisted psychotherapy for PTSD and one long-term follow-up study published since 2008, and several more underway. Of these, one study conducted by Bouso et al. (2008) was cut short before its completion. Of the two remaining studies, each used the Clinician Administered PTSD Scale (CAPS) as the primary outcome measure (see Table 3).

Table 3
 Summary of Clinical Research With Entactogens

Study	Drug (dose)/Design	Total <i>N</i> (No. females)/ Diagnosis	Key findings
Bouso et al., 2008	MDMA ^a (50–75 mg) with psychotherapy/not completed	6 (6)/chronic PTSD ^b after sexual assault	Low doses (50–75 mg) of MDMA were physiologically and psychologically well-tolerated in the study sample. However the study was not completed and therefore statistical analyses could not be conducted.
Mithoefer et al., 2011, 2012	MDMA (125–187.5 mg) with psychotherapy/randomized double-blind placebo-controlled cross-over	20 (17)/chronic treatment-resistant PTSD	Significant decreases in Clinician-Administered PTSD Scale (CAPS) scores from baseline to 2 months post-treatment, with sustained decreases in CAPS scores in 16 volunteers who completed a long-term follow-up 17–74 months post-treatment.
Oehen et al., 2013	MDMA (125–187.5 mg) with psychotherapy/randomized double-blind active placebo (25–37.5 mg MDMA)	12 (10)/chronic treatment-resistant PTSD	Decreases in CAPS scores that did not reach statistical significance ($p = .066$) at 2 months post-treatment. Clinically and statistically significant self-reported improvement on Posttraumatic Diagnostic Scale ($p = .014$) at 2 months post-treatment. CAPS scores improved further at 12-month follow-up. Three MDMA sessions were more effective than two ($p = .016$).

^a MDMA = 3,4-Methylenedioxymethamphetamine. ^b PTSD = Posttraumatic stress disorder.

The first study administered placebo or MDMA (125 mg with optional supplemental dose of 62.5 mg approximately 2 hours later) during two 8–10 hour sessions approximately four weeks apart, under double-blind conditions in conjunction with psychotherapy (11 sessions) to individuals with chronic PTSD ($N = 20$). Results found significant reductions in CAPS scores in the MDMA group as compared to placebo 4 days after each session and 2 months following the second session. Four days after the second Session 10 of 12 (83.3%) participants in the MDMA condition showed clinically significant reductions in CAPS score, as opposed to 2 of 8 (25%) participants in the placebo condition (Mithoefer et al., 2011). Furthermore, 7 of the 8 participants who received placebo opted to participate in an open-label crossover, in which they received MDMA-assisted psychotherapy for PTSD after completing their initial 2-month follow-up. All of these individuals showed a clinically significant reduction in CAPS score after their MDMA-assisted treatment.

The long-term follow-up to this study invited all original participants who received MDMA-assisted psychotherapy ($N = 19$) to complete a long-term follow-up questionnaire, and a reassessment of current CAPS score, taking place between 17 and 74 months after the final MDMA session (Mithoefer et al., 2013). For the 16 individuals who agreed to repeat the follow-up CAPS, results showed that long-term posttreatment CAPS scores showed no significant differences from CAPS score administered 4 days after the second MDMA session of the original study. Furthermore, a persisting effects questionnaire inquiring into long-term benefits of their participation found that 89% of subjects endorsed both a general well-being and increased self-awareness and understanding as a benefit of their participation while 79% endorsed less

excessive vigilance and less avoidance of people or places as a persisting benefit.

Additionally, a more recent study published in this area ($N = 12$) found less dramatic results, with reductions in CAPS scores that failed to reach statistical significance ($p = .066$; Oehen et al., 2013), though a secondary outcome measure, the Posttraumatic Diagnostic Scale did show significant posttreatment reductions ($p = .014$; Oehen et al., 2013). Among these three clinical trials of MDMA for PTSD, no serious drug-related adverse events were reported. Further trials in this area are ongoing, as well as novel research investigating the use of MDMA-assisted therapy for autistic adults with social anxiety (Danforth et al., 2015), and individuals suffering from anxiety at the end-of life, whose results are forthcoming. Despite the risks associated with chronic recreational and black-market use, clinical research with MDMA in controlled settings represents an important direction in treating a number of clinical syndromes such as PTSD, which currently lack highly efficacious treatment models.

Dissociative Anesthetics

Dissociative anesthetics comprise a large drug family including phencyclidine (PCP), ketamine, dextromethorphan (DXM) and nitrous oxide, among others (Morris & Wallach, 2014). Although not true of all dissociative anesthetics, each compound listed above acts as an antagonist at the N-methyl-D-aspartate (NMDA) glutamate receptor as a key mechanism of action, which may contribute to the well-documented rapid antidepressant effects of ketamine (Abdallah, Sanacora, et al., 2015), as well as the potential antidepressant action of both

nitrous oxide (Nagele et al., 2015), and DXM (Lauterbach, 2011; Nguyen et al., 2014; Nguyen & Matsumoto, 2015). The anesthetic properties of this drug class have earned several of these drugs important roles in medicine, most notably ketamine and nitrous oxide. However, their marked perception altering and dissociative effects have also made them popular with recreational users (Addy, 2007; Corazza et al., 2013). Recent research with ketamine and DXM have set them apart as drugs with novel clinical potential that will be discussed in greater depth in the following sections (see Table 4).

Ketamine

Background. Ketamine is an N-methyl-D-aspartate receptor (NMDAR) antagonist with dissociative, anesthetic, analgesic, and hallucinogenic properties first synthesized in 1962 from phencyclidine (PCP; Wolff & Winstock, 2006). It first saw medical use in the mid 1960s when it was used extensively as a battlefield anesthetic in the Vietnam War, and remains the most widely used veterinary anesthetic today (Morgan & Curran, 2012). The first recorded evidence of recreational ketamine abuse dates to 1971,

Table 4
Summary of Selected Clinical Research With Dissociatives

Study	Drug (dose)/Design	Total N (No. females)/ Diagnosis	Key findings
Berman et al., 2000	Ketamine (.5 mg/kg, i.v.)/randomized double-blind placebo-controlled	9 (5)/MDD ^a (<i>n</i> = 8); BPD ^b (<i>n</i> = 1)	Significant decrease in depression from 4 to 72 hours post-ketamine infusion, with mean Hamilton Depression Rating Scale (HDRS) scores decreased by $14 \pm SD$ 10 points vs. 0 ± 12 points, respectively during active and sham treatment (<i>p</i> = .02).
Cummings et al., 2015	DXM (20–60 mg daily) + quinidine (10–20 mg daily)/randomized double-blind placebo-controlled	220 (126)/AD ^c with agitation	Significantly reduced Neuropsychiatric Inventory Agitation/Aggression scores for dextromethorphan-quinidine vs. placebo (<i>p</i> < .001).
Diazgranados et al., 2010b	Ketamine (.5 mg/kg, i.v.)/randomized double-blind placebo-controlled	18 (12)/treatment-resistant BPD, current depressive episode	Significant decrease in Montgomery-Åsberg Depression Rating Scale (MADRS) scores from 40 minutes to 3 days post-ketamine infusion (<i>p</i> < .001); 71% of volunteers responded to ketamine vs. 6% responded to placebo.
Feder et al., 2014	Ketamine (.5 mg/kg, i.v.)/randomized double-blind active placebo (midazolam)	41 (19)/chronic PTSD ^d	Significant and rapid reduction in PTSD symptom severity on the Impact of Event Scale in ketamine vs. midazolam at 24 hours post-treatment (<i>p</i> = .02).
Krupitsky & Grinenko, 1997	Ketamine (2.5 mg/kg, i.m) with psychotherapy/open-label vs. control (TAU) ^e	211 (0)/chronic alcohol dependence	Significantly greater abstinence in ketamine group (65.8%) vs. treatment as usual control group (24%) at 12-month follow-up (<i>p</i> < .01).
Krupitsky et al., 2002	Ketamine (2.0 mg/kg, i.m) with psychotherapy/randomized double-blind active placebo (.2 mg/kg ketamine, i.m.)	70 (15)/opioid dependence	Significantly greater biochemically verified opioid abstinence in ketamine group vs. active-placebo control group at 12-month and 24-month follow-up (<i>p</i> < .05).
Murrough et al., 2013	Ketamine (.5 mg/kg, i.v.)/randomized double-blind active placebo (midazolam)	73 (37)/treatment-resistant MDD	Significantly greater decrease in MADRS scores in the ketamine group than control group 24 hours post-treatment (<i>p</i> ≤ .002); 64% of volunteers responded to ketamine vs. 28% to placebo at 24 hours post-treatment.
Nagele et al., 2015	N ₂ O ^f (50% + 50% oxygen inhalation for 60min)/randomized double-blind placebo-controlled cross-over	20 (12)/treatment-resistant MDD	Significantly greater decrease in HDRS scores at 2 hours and 24 hours after N ₂ O vs. placebo (<i>p</i> < .001). 20% of volunteers responded to N ₂ O vs. 5% responded to placebo at 24 hours post-treatment.
Rodriguez et al., 2013	Ketamine (.5 mg/kg, i.v.)/randomized double-blind placebo-controlled cross-over	15 (7)/OCD ^g	Significantly greater decrease in Yale-Brown Obsessive Compulsive Scale scores in ketamine than placebo group (<i>p</i> < .01); 50% of volunteers responded to ketamine vs. 0% responded to placebo at 7 days post-treatment.
Zarate et al., 2006	Ketamine (.5 mg/kg, i.v.)/randomized double-blind placebo-controlled	18 (12)/treatment-resistant MDD	Significant decrease in HDRS scores from 110 minutes to 7 days post-ketamine infusion vs. placebo (<i>p</i> < .05); 71% of volunteers responded to ketamine vs. 0% placebo at 24 hours post-treatment.

^a MDD = Major depressive disorder. ^b BPD = Bipolar disorder. ^c AD = Alzheimer's disease. ^d PTSD = Posttraumatic stress disorder. ^e TAU = Treatment as usual. ^f N₂O = Nitrous oxide. ^g OCD = Obsessive-compulsive disorder.

with anecdotal evidence reaching back into the late 1960s. Ketamine abuse, however, did not reach appreciable levels until its adoption as a 'club drug' in the 1990s (Morgan & Curran, 2012). As a result, ketamine was classified as a schedule III drug in the U.S. in 1999, and is still used in medicine as an anesthetic in humans.

Pharmacology. Ketamine can be administered via a variety of routes including oral, intravenous (i.v.), and intramuscular (i.m.), though the majority of recreational users report intranasal use (Morgan & Curran, 2012). Depending on the route administered, the subjective effects of ketamine last between 10 min and four hours. As a general rule, recreational doses fall between 10% and 25% of an anesthetic dose in nonchronic, tolerant users, or roughly 350–500 mg taken orally, 50–150 mg i.m., or 200 mg intranasally (Jansen, 2000). Anesthetic doses of ketamine typically fall in the 1–4.5 mg/kg, i.v. dose range (Miller et al., 2011), whereas sub-anesthetic doses used for antidepressant purposes are generally around 0.5 mg/kg, i.v. (Abdallah, Averill, & Krystal, 2015).

Chronic ketamine abuse is known to cause serious toxicity to both the gastrointestinal and urinary track with ulcerative cystitis, hepatic dysfunction, and abdominal cramps among the most common medical problems associated with chronic use (Bokor & Anderson, 2014). Withdrawal symptoms among chronic users are less extensively studied, however craving, sweating, shaking, and palpitations have been documented among a small sample of chronic users (Morgan & Curran, 2012). Recreational ketamine use has also been linked to persisting cognitive deficits (Morgan et al., 2004; Morgan et al., 2010), however to date controlled administration of ketamine in medical and research settings has not been linked to lasting complications such as ketamine abuse or cognitive impairment (e.g., Krupitsky et al., 2002).

At low doses (~150 mg intranasal), ketamine induces visual distortions along with mild dissociative and stimulant effects, whereas at higher doses the dissociative effects intensify and predominate with many users claiming complete mental dissociation from the physical body (Muetzelfeldt et al., 2008; Wolff & Winstock, 2006). A qualitative interview study of 90 infrequent, frequent, and ex-ketamine users revealed the most appealing aspects of ketamine use to be melting into the surroundings, visual hallucinations, out-of-body experiences, and "gigglingness" (Muetzelfeldt et al., 2008). The profound dissociative effects of ketamine have led to comparisons both to lucid dreaming and near death experiences (Jansen, 2000; Krupitsky & Grinenko, 1997). The dissociative and perceptual effects, importance of set and setting, and possibility of personal meaningfulness of ketamine have led some to classify it as a psychedelic drug (Bowdle et al., 1998; Jansen, 2000; Krupitsky & Grinenko, 1997). Ketamine's psychedelic-like effects were systematically characterized by Bowdle and colleagues (1998), who found a strong correlation between ketamine plasma concentration and subjective drug effects, and a psychometric profile on the Hallucinogen Rating Scale comparable to that of DMT. A within-subjects comparison of DMT and ketamine administration examined the glutamate and serotonin models of schizophrenia, finding administration of ketamine to be associated with negative symptoms of schizophrenia including catatonic behavior and psychomotor retardation, whereas the 5-HT_{2A} agonist DMT was associated with more positive symptoms of schizophrenia such as thought disorder and inappropriate affect, suggesting distinct roles for the glutamate

and serotonin systems in the manifestation of psychotic symptoms and psychedelic effects (Gouzoulis-Mayfrank et al., 2005).

Ketamine for addiction. The marked subjective effects of ketamine first began to be noted within the scientific literature at approximately the same time as the scheduling of the serotonergic psychedelics, around 1970 (Krupitsky & Grinenko, 1997). Reports of ketamine's psychedelic-like effects, together with the increased restrictions on serotonergic psychedelics, led to ketamine's incorporation into psychotherapy in 1973 (Khorrarnzadeh & Lofty, 1973). The most relevant of this initial work explored ketamine psychotherapy for the treatment of addiction. In the 1980s and 90s, more than 1,000 alcoholic patients were treated with ketamine psychedelic therapy (KPT) without any complications such as psychosis or ketamine abuse (Krupitsky et al., 1992; Krupitsky & Grinenko, 1997, 1998). The KPT method developed during this period employed intramuscular injections of ketamine in a supervised environment, and anticipated many contemporary recommendations for human hallucinogen research (e.g., Johnson et al., 2008), including extensive preparation for the psychedelic sessions as well as postsession integration. Follow-up data on a subset of participants showed increased rates of alcohol abstinence in a KPT group ($n = 111$) compared with a control group ($n = 100$) at one year posttreatment (65.8% vs. 24%), as well as continued abstinence in 40.7% of the KPT group at two years posttreatment ($n = 81$) and 33.3% at three years posttreatment ($n = 42$). Two- and three-year follow-up data were not collected from the control group because of funding limitations. Secondary findings included internalization of the locus of control as well as positive changes in life values associated with KPT (Krupitsky & Grinenko, 1997, 1998).

This approach was later applied in the treatment of heroin dependence. The first study utilized a single session of KPT (2 mg/kg im; $n = 35$) compared with a very low (nonhallucinogenic) dose of ketamine (0.2 mg/kg im; $n = 35$). High-dose ketamine was found to produce greater levels of biologically verified heroin abstinence in all but two of 16 follow-up visits including the final follow-up at 24 months after treatment. Both doses of ketamine also reduced craving for heroin from baseline measures as evaluated by a visual analog scale, however the high dose was significantly more effective in reducing cravings than the low dose (Krupitsky et al., 2002). A second study ($N = 59$) examined the possible benefits of multiple sessions of KPT as opposed to a single session (Krupitsky et al., 2007). Participants randomized to the multiple session treatment had three sessions of drug-assisted KPT in total, and showed significantly greater abstinence at one year follow-up (50%) than those randomized to the single-session group (22.2%; $p < .05$).

More recent work probing the psychological dimensions of ketamine's antiaddictive properties in eight nontreatment seeking cocaine-dependent volunteers have demonstrated that a single i.v. ketamine infusion (0.41 mg/kg) was effective in increasing motivation to quit cocaine 24 hours postinfusion as well as reducing cue-induced cravings for cocaine as compared to an active placebo (lorazepam 2 mg), with a second ketamine infusion (0.71 mg/kg) resulting in further decreases in cue-induced craving. Additionally, four of the eight (50%) individually achieved biologically verified abstinence from cocaine two weeks after their ketamine infusions even though no outpatient treatment was provided (Dakwar et al., 2013).

A secondary analysis found that ketamine produced dose-related increases in a measure of mystical experience which were significantly correlated with changes in motivation to quit (Dakwar et al., 2014), similar to findings from psilocybin-facilitated addiction treatment pilot studies (Bogenschutz et al., 2015; Garcia-Romeu et al., 2014). Furthermore, mystical experience predicted motivation to quit with greater accuracy than a clinician administered scale of dissociative symptoms, suggesting a mediating role of mystical-type effects in ketamine's addiction treatment outcomes (Dakwar et al., 2014).

Current methods of evaluating the subjective and mystical-type effects of hallucinogens, as well as their relative contribution to clinical treatment outcomes are still in need of further refinement. Quantitative assessments such as the Hallucinogen Rating Scale (Strassman et al., 1994b), APZ (altered states of consciousness) Questionnaire (Dittrich, 1998), Hood Mysticism Scale (Hood, 1975), and more recently the Mystical Experience Questionnaire (Barrett et al., 2015; MacLean et al., 2012) have been used to characterize hallucinogen effects. However, these scales often focus on particular qualities or features of the drug experience such as intensity, affective response, feelings of unity, or a sense of oceanic boundlessness, to the detriment of other effects that are not specifically queried. Thus, while such scales have been helpful in quantifying some aspects of hallucinogens' subjective effects, the variability of responses to hallucinogens make this an ideal area for qualitative approaches, which allow participants to describe experiences in their own words (Addy et al., 2015; Gasser et al., 2015). By expanding on current methodologies of studying subjective drug effects, we may gain a more nuanced and well-formulated understanding of the role of mystical and other types of drug experiences in hallucinogen-facilitated treatments.

Ketamine as antidepressant. Ketamine has additionally shown promise as a rapid-acting antidepressant, with multiple studies showing robust effects in treatment-resistant populations (Abdallah, Sanacora, et al., 2015; Berman et al., 2000; Diazgranados, Ibrahim, Brutsche, Newberg et al., 2010; Murrough et al., 2013; Valentine et al., 2011; Zarate et al., 2006, 2012). Research has found that i.v. administration of a single subanesthetic infusion of ketamine (0.5 mg/kg over 40 min) can attenuate depressive symptoms within 4 hours of administration (Berman et al., 2000).

Ketamine's antidepressant effects generally last from 3 to 7 days, and have been observed to persist as long as two weeks in some cases (e.g., Diazgranados, Ibrahim, Brutsche, Newberg, et al., 2010). However, ketamine is largely eliminated from the body within 3 hours of administration (Mion & Villeveille, 2013), suggesting a significant role for downstream mechanisms triggered by ketamine in mediating its antidepressant effects. Ketamine has shown a clinical response rate of 40% to 60% at 24 hours postinfusion in treatment-resistant populations experiencing both unipolar (MDD) and bipolar depression (Abdallah, Sanacora, et al., 2015), and has additionally exhibited notable antisuicidal properties (Diazgranados, Ibrahim, Brutsche, Ameli, et al., 2010; Larkin et al., 2011; Price et al., 2009, 2014).

Converging evidence from animal models and human research suggests that the observed rapid antidepressant effects of ketamine are attributable in part to a cascade of activity beginning with a surge of glutamate, leading to activation of α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, and downstream activity resulting in neuroplastic changes including synap-

togenesis, or the formation of new neural pathways (Abdallah, Averill, & Krystal, 2015; Li et al., 2010; Zhou et al., 2014). Ketamine's antidepressant effects have additionally been linked to increases in brain-derived neurotrophic factor (BDNF; Haile et al., 2014), and enhanced cortical excitability (Cornwell et al., 2012), suggesting further potential mechanisms of action. Preclinical models have demonstrated sex differences in ketamine effects, with female rats showing greater sensitivity to ketamine's antidepressant properties than male rats, and the hormones estrogen and progesterone mediating ketamine's antidepressant effects in female rats (Carrier & Kabbaj, 2013). Although these sex differences in the effects of ketamine and other dissociatives have yet to be thoroughly examined in human subjects, they represent an important area requiring additional attention in future research.

Ketamine's hallucinogenic properties have been implicated as a mediator of antidepressant effects in some, but not all research. For instance, in a double-blind, crossover, placebo-controlled clinical trial ($N = 27$), Sos and colleagues (2013) found a significant correlation between acute psychotomimetic effects (e.g., perceptual disturbances, euphoria) during ketamine infusion, and decreased depression scores at 7 days postinfusion ($r = -0.40$, $p = .04$). Similarly, Luckenbaugh et al. (2014) found that acute dissociative effects of ketamine were significantly associated with decreased depression scores at 230 min, $r = -0.35$, $p = .007$, and 7 days postinfusion, $r = -0.41$, $p = .01$, in a sample of treatment-resistant inpatients with MDD or bipolar depression ($N = 108$). These results suggest that the acute subjective effects of ketamine may be linked to later efficacious treatment outcomes, consistent with preliminary results from related hallucinogen-facilitated addiction treatment paradigms (Bogenschutz et al., 2015; Dakwar et al., 2014; Garcia-Romeu et al., 2014). Despite a possible association with favorable outcomes, these subjective effects are generally referred to as psychotomimetic in the literature, and otherwise considered as undesirable, adverse side effects.

In addition to ketamine's potential as an aid in addiction treatment and antidepressant, recent studies have shown some promise for ketamine as a treatment for obsessive-compulsive disorder (Bloch et al., 2012; Rodriguez et al., 2013) and posttraumatic stress disorder (Feder et al., 2014; Zeng et al., 2013), representing novel avenues for research with NMDAR antagonist pharmacotherapies. Evidence regarding ketamine's efficacy for treating obsessive-compulsive disorder is limited, however Rodriguez and colleagues (2013) found significant antiobsessive effects of a single subanesthetic ketamine infusion in a small sample of individuals ($N = 15$) experiencing near constant, intrusive obsessions, with effects lasting as long as 7 days in some participants.

Furthermore, Feder et al. (2014) studied the effects of 0.5 mg/kg infusion of ketamine over 40 min versus the active comparator midazolam (a benzodiazepine), in a randomized double-blind crossover clinical trial ($N = 41$). Ketamine showed a significant and rapid decrease in PTSD symptoms compared to midazolam at 24 hours postinfusion, with some patients showing clinically significant decreases in PTSD symptoms for as long as 2 weeks. Taken together, these findings suggest that ketamine, and potentially other NMDAR antagonists, deserve consideration for further clinical development and proliferation for a number of conditions. Some issues that will need to be addressed include the relatively short

duration of ketamine's efficacy for treatment of mood disorders, the role of so called psychotomimetic subjective effects in observed therapeutic effects, as well as its potential for toxicity in repeated administration models seeking to extend beneficial effects, and its abuse liability. Nevertheless, this remains a very promising area for future research.

Dextromethorphan (DXM)

Background. Dextromethorphan (DXM) is an analogue of the opioid analgesic levorphanol (Bem & Peck, 1992). DXM is a noncompetitive antagonist of the N-methyl-D-aspartate (NMDA) receptor (Zhou & Musacchio, 1991), which also acts upon the serotonin transporter (SERT), sigma-1 receptors (Werling et al., 2007), and $\alpha 3\beta 4$ nicotinic acetylcholine receptors (Hernandez et al., 2000). At low doses in the range of 10 to 30 mg (usually administered orally), DXM is an effective cough suppressant that has been available as an FDA approved over-the-counter medication since 1958 (Carter et al., 2013; Morris & Wallach, 2014). DXM is widely used, and has a high margin of safety, and low abuse liability at recommended antitussive doses (Bem & Peck, 1992; Gutstein & Akil, 2001). Supratherapeutic doses of DXM have been abused recreationally since the 1970s (Addy, 2007).

Contemporary research. Human laboratory research has shown that at supratherapeutic doses (e.g., 200–800 mg/70 kg), DXM exhibited psychedelic-like effects in a sample of 12 healthy volunteers with history of recreational hallucinogen use (Reissig et al., 2012). Participants self-reported beneficial persisting effects at 1 month after multiple high-dose administrations of DXM, including increased spirituality, and positive changes in attitudes, mood, and behavior (Reissig et al., 2012). High doses of DXM in the range of 400 to 800 mg/70 kg (i.e., ≥ 10 –30 times the therapeutic dose of DXM) were also shown to elicit acute cognitive impairment in attention, memory, and metacognition comparable to a large dose (0.5 mg/70 kg) of the benzodiazepine triazolam under double-blind conditions, with doses in the 100–300 mg/70 kg range (i.e., 3–10 times the therapeutic dose of DXM) showing relatively milder impairment, indicating a broad therapeutic window for DXM (Carter et al., 2013).

Though clinical research with high-dose DXM has been limited, using modified dosing regimens, DXM has shown safety and preliminary feasibility as an aid in pain management (Siu & Drachtman, 2007; Weinbroum et al., 2000), and in attenuating opioid withdrawal (Koyuncuoğlu & Saydam, 1990; Koyuncuoğlu, 1991). Additionally, because DXM is rapidly metabolized by cytochrome P450 2D6 (CYP2D6), low-doses (~10 mg) of the CYP2D6 inhibitor quinidine have been added to novel drug formulations with DXM to alter the drug's pharmacokinetic and pharmacodynamic profile, allowing for more prolonged exposure to DXM in the central nervous system (Doody et al., 2015). This DXM/quinidine combination has shown promise as a treatment for agitation in Alzheimer's patients (Cummings et al., 2015), and pseudobulbar affect in dementia patients (Doody et al., 2015).

It has been hypothesized that DXM may possess rapid-acting antidepressant properties (Lauterbach, 2011, 2012), based on its pharmacological similarities to the NMDA antagonist ketamine, which has demonstrated robust rapid-acting antidepressant properties. Furthermore, recent preclinical data have demonstrated that DXM exhibits antidepressant effects in animal models mediated

by its activity at Sigma-1 and glutamatergic α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors (Nguyen et al., 2014; Nguyen & Matsumoto, 2015). Specifically, Nguyen and colleagues (2014) found that in mice, DXM occasioned significant, dose-dependent increases in locomotor activity, as well as decreases in immobility time in the forced swim test, a commonly used rodent model of depression. In a follow-up study, Nguyen and Matsumoto (2015) additionally found that DXM produced significant, dose-dependent decreases in immobility in mice subjected to the tail suspension test, suggesting an antidepressant effect. A clinical trial of DXM/quinidine for treatment resistant depression is currently underway (clinicaltrials.gov identifier NCT01882829).

Atypical Hallucinogens

For our purposes, the atypical hallucinogens are defined as substances capable of engendering psychedelic-like effects through diverse pharmacological mechanisms in addition to the previously described monoaminergic and glutamatergic mechanisms. The atypical hallucinogens include the indole alkaloid ibogaine, which affects multiple neurotransmitter systems, the kappa opioid receptor (KOR) agonist salvinorin A, and the anticholinergics such as atropine and datura, also known as deliriants, which will not be discussed here. Finally, cannabis is sometimes attributed psychedelic-like properties (Keeler et al., 1971), and has exhibited therapeutic potential for a number of indications, which will be briefly presented.

Ibogaine

Background. Ibogaine is one of several indole alkaloids found in the root and root cortex of the African shrub *Tabernaemontana iboga*, native to West Central Africa including Gabon, the Democratic Republic of the Congo, and Angola (Rätsch, 2005). Its ceremonial use has been most extensively documented among the Bwiti religion, dating back to the early 20th century (Fernandez, 1982). Recent scientific and cultural attention has focused on ibogaine's purported utility as an opioid detoxification agent (Brown, 2013; Popik, Layer, & Skolnick, 1995), a use first suggested by anecdotal reports (Lotsof, 1985, 1995).

In 1991 the National Institute of Drug Abuse (NIDA) initiated its ibogaine research program, including FDA approval for a phase I dose escalation human study in which humans were administered low doses of ibogaine. However all federally funded human trials were discontinued in 1995 due to concerns of neurotoxicity and fatalities (Alper, 2001). Medical ibogaine treatment centers first opened their doors in 1994 in Panama and 1996 in St. Kitts where they continue to function. Underground ibogaine treatment centers and drug scenes eventually appeared both in Europe and in the United States (Alper, 2001). A recent qualitative analysis submits that in the United States alone an estimated 3,414 individuals have taken ibogaine since February 2006, more than four times more than similar estimates reaching back to 2001. Of those 3,414, 68% reported taking it for a substance abuse related disorder and 55% specifically for opioid withdrawal (Alper et al., 2008).

Pharmacology. The neuropharmacology of ibogaine is complex and remains incompletely understood (Koenig & Hilber, 2015; Mash et al., 1998, 2001). Antagonism of the $\alpha 3\beta 4$ nicotinic

acetylcholine receptor has been proposed as a potential mechanism of action for ibogaine's withdrawal attenuating effects (Pace et al., 2004; Taraschenko et al., 2005), as has agonism at the mu opioid receptor for which affinity has been demonstrated in vitro (Glick et al., 2001; Sweetnam et al., 1995). Furthermore, preclinical data suggest that Ibogaine's antiaddiction effects may be mediated by normalization of accumbal dopamine increases associated with the rewarding effects of morphine, nicotine, and amphetamine (Glick et al., 1993; Maisonneuve et al., 1997). Ibogaine's properties as a serotonergic agonist are not thought to be relevant to its withdrawal attenuating effects (Glick et al., 2001; Wei et al., 1998), however more research is needed in this area.

The most controversial aspect of clinical ibogaine use is concerns of both neurotoxicity and cardiac toxicity. At dosages of 100 mg/kg several studies have demonstrated degeneration of cerebellar Purkinje cells in rats after a single administration of ibogaine (O'Hearn & Molliver, 1993, 1997; O'Hearn et al., 1993). However, at a lower dose of 40 mg/kg, a dose known to be sufficient for reducing both morphine and cocaine self-administration and morphine withdrawal in rats, one study was unable to find any cerebellar toxicity (Molinari et al., 1996).

Concerns over possible cardiac toxicity have come from reports of human fatalities associated with the ingestion of ibogaine (Hoe-len et al., 2009). Ibogaine is typically administered at a dosage of 10–25 mg/kg of body weight (Alper et al., 2008). According to a recent medical review of ibogaine fatalities, 19 individuals (15 men and 4 women, all between the ages of 24 and 54) are known to have died within 1.5 and 76 hours of taking ibogaine. Of the 19 total cases, 14 included adequate postmortem data with which to infer cause of death for researchers to determine that preexisting medical comorbidities or concurrent substance abuse contributed to or explained the cause of death (Alper et al., 2012). For additional medical case-reports of human ibogaine consumption see Paling et al. (2012); Papadodima et al. (2013), and Pleskovic et al. (2012).

Preclinical data. Ibogaine has shown promise as an antiaddictive agent in animal models of drug self-administration and drug withdrawal. Ibogaine has been shown to attenuate signs of opiate withdrawal in rodents (Cappendijk et al., 1994; Dzoljic et al., 1988; Frances et al., 1992; Glick et al., 1992; Leal et al., 2003; Maisonneuve et al., 1991; Parker et al., 2002; Popik, Layer, Fossom, et al., 1995), and primates (Aceto et al., 1992). Ibogaine has also been shown to reduce animal self-administration of morphine (Glick et al., 1991, 1994); cocaine (Cappendijk & Dzoljic, 1993; Glick et al., 1994); amphetamine (Maisonneuve et al., 1992); methamphetamine (Pace et al., 2004); and alcohol (Rezvani et al., 1995), possibly by dampening dopamine efflux in the nucleus accumbens in response to opiates (Glick et al., 1994; Maisonneuve et al., 1991) and nicotine (Benwell et al., 1996; Maisonneuve et al., 1997).

Furthermore, many of these findings have been replicated with a synthetic ibogaine congener, 18-Methoxycoronaridine (18-MC), which was first synthesized in 1996 and has not shown evidence of cerebellar toxicity or tremors in animals (Glick et al., 1996, 1999; 2001). 18-MC has been shown to attenuate acute opiate withdrawal in rats (Panchal et al., 2005; Rho & Glick, 1998); and decrease self-administration of morphine (Maisonneuve & Glick, 1999; Pace et al., 2004); methamphetamine (Glick et al., 2000); alcohol (Rezvani et al., 1997); and nicotine (Glick et al., 1998, 2000).

Finally, 18-MC has also been shown to dampen dopamine efflux in the nucleus accumbens in response to opiates and tobacco (Glick et al., 1998, 2000; Taraschenko et al., 2007).

Ibogaine has also shown sex differences in rodent models, with female rats showing higher levels of ibogaine metabolite and greater antagonism of morphine-induced locomotor activity than male rats (Pearl et al., 1997). However, it is not known whether such sex differences generalize to humans.

Clinical research. To date there are three published case studies of ibogaine treatment. The first characterizes 3 ibogaine treatments including one opioid detoxification (Luciano, 1998). The second describes the use of ibogaine by 33 opioid dependent individuals in the care of a psychiatrist, who reported that withdrawal signs were observed to be markedly decreased in 29 (88%) of the sample (Alper et al., 1999). Finally, an open-label prospective study of ibogaine for opioid detoxification ($N = 32$) noted both resolution of withdrawal as determined by participant administered rating scales as well as sustained improvements in depression scores one month after treatment (Mash et al., 2001). These results, though preliminary, suggest feasibility of ibogaine as a treatment for opioid dependence. However, concerns over toxicity and adverse events remain.

A recent retrospective analysis reported on 75 alcohol, cannabis, cocaine, and crack cocaine users (72% poly drug users) who sought treatment at a Brazilian substance abuse clinic using cognitive behavior therapy in combination with ibogaine treatment (Schenberg et al., 2014). In total, the 75 individuals underwent 134 ibogaine sessions, with no fatalities or serious medical adverse events reported. This suggests that ibogaine may be safely administered by experienced professionals in a hospital environment to medically screened volunteers. The data also suggest that ibogaine may be helpful in the treatment of substance abuse. At the time of contact, all women ($n = 8$) were found to be abstinent as well as 51% of men ($n = 34$). Median length of abstinence after only one ibogaine session was 5.5 months, while those treated multiple times remained sober for a median 8.4 months. As a condition of their treatment, all volunteers were required to be abstinent from all drugs for 30 to 60 days before receiving ibogaine. It is unclear from the published report whether this abstinence was biologically verified or self-reported. All participants were given the choice of completing this abstinence period at home or at their inpatient facility. Given the potentially volatile combination between concomitant physiological withdrawal and acute ibogaine exposure (Alper, 2001; Alper et al., 2012) these precautions seem reasonable, however, that participants were able to maintain such long periods of drug abstinence preibogaine treatment calls into question the conclusiveness of posttreatment findings.

Salvia Divinorum

Background. J.B. Johnson, the first anthropologist to observe a traditional mushroom ceremony in 1939, was also the first scientist to write on the indigenous Mazatec use of another sacred plant drug, the leaves of a flowering plant that in 1962 was identified as *Salvia divinorum* (SD), a new member of the mint family (Johnson, 1939; Wasson, 1962). The psychoactive compound contained therein, salvinorin A (SA) was not successfully isolated from the leaves of SD until 1982 (Ortega et al., 1982) and the psychoactive effects of SA were not confirmed until 1994

(Siebert, 1994). SA is active in doses as small as 500 µg, putting its potency on par only with that of LSD (Cunningham et al., 2011; Siebert, 1994).

SD is controlled in 20 U.S. states (Drug Enforcement Administration, 2012) and is listed as a “drug of concern” by the US DEA (Perron et al., 2012). SD is legally and commercially available in many states and countries, which likely contributes to its popularity (Khey et al., 2008). SD is most often procured from local “head shops” or the Internet (Baggott et al., 2010; Sumnall et al., 2011) and is usually used either in residential settings with small groups of friends or else at music festivals (Sumnall et al., 2011). Recreational SD use tends to be sporadic, with most users reporting fewer than 20 lifetime uses (Baggott et al., 2010; Nyi et al., 2010) and the majority of recreational SD users surveyed report fewer than one use per year (Khey et al., 2008; SAMHSA, 2013). Most recreational use occurs via smoking commercial preparations of SD leaves fortified with additional SA, known as “enhanced leaves” (Baggott et al., 2010). The typical course of effects for inhaled SA is less than 20 min, with peak subjective effects achieved approximately two minutes after inhalation (Addy, 2012; Johnson et al., 2011, 2016).

Pharmacology. Unlike many compounds thus far mentioned, SA has no affinity for the 5-HT_{2A}R receptor, and contains no nitrogen (Roth et al., 2002). Both in vivo and in vitro studies suggest SA acts selectively as an agonist at the kappa opioid receptor (KOR) (Roth et al., 2002). Recent work using animal models of drug discrimination have further confirmed these findings (Butelman et al., 2010; Butelman et al., 2004; Killinger et al., 2010). This has been additionally demonstrated in humans in a double-blind placebo-controlled study showing that the nonspecific opioid receptor antagonist naltrexone, but not the selective 5-HT_{2A} antagonist ketanserin, blocked the subjective and physiological effects of vaporized SA (Maqueda et al., 2016).

Acute KOR activation by SA leads to decreased synaptic dopamine within the nucleus accumbens and caudate-putamen (Ebner et al., 2010). This effect is opposite to that of drugs of abuse such as cocaine and alcohol, which acutely increase dopamine in this “reward circuitry” and lead to euphoria, conditioned place preference, and compulsive use (Volkow et al., 2002). SA, in contrast, leads to conditioned place aversion and decreased intracranial self-stimulation (Carlezon et al., 2006; Sufka et al., 2014). Dynorphins, the endogenous ligands for the KOR have been implicated in many adverse behaviors including stress-induced drug relapse in animal models (Beardsley et al., 2005) and have been proposed as important therapeutic targets for addiction treatments (Butelman & Kreek, 2015; Chavkin, 2011). SA may also have downstream effects on the endocannabinoid system (Braidia et al., 2007, 2008), but this has not yet been demonstrated in primates. Animal research has shown greater antinociceptive response to KOR agonists in males than females, and sex differences in the ability of KOR agonists like SA to attenuate administration of various drugs of abuse (Rasakham & Liu-Chen, 2011). Although these sex differences in SA effects have not yet been observed in human subjects, they require examination in future research. Nevertheless, preclinical evidence suggests some promise for SA as an anti-addiction agent (e.g., Freeman et al., 2014).

Contemporary research. Several controlled studies have been published recently describing behavioral, subjective, and physiological effects of SA (Addy, 2012; Addy et al., 2015;

Johnson et al., 2011; MacLean et al., 2013; Maqueda et al., 2015, 2016; Mendelson et al., 2011; Pichini et al., 2005; Siebert, 1994). None of these studies reported serious adverse events or sustained negative effects. Inhaled SA leads to acute psychotomimetic effects (Ranganathan et al., 2012), intense perceptual alterations (Addy, 2012; Addy et al., 2015; MacLean et al., 2013; Ranganathan et al., 2012), dissociative effects (MacLean et al., 2013; Maqueda et al., 2015), elevated cortisol and prolactin, and decreased resting state EEG spectral power (Ranganathan et al., 2012). Peak plasma levels of inhaled SA were found to occur 2 min after inhalation, and to directly correspond with participant and observer ratings of subjective effects (Johnson et al., 2016). Inhaled SA has not been shown to lead to anxiogenic effects (MacLean et al., 2013), or significant changes in physiology such as heart rate or blood pressure (Addy, 2012; Johnson et al., 2011; Ranganathan et al., 2012). Auditory hallucinations and the sensed presence of other entities in the room have also been observed in human SA laboratory research (Addy et al., 2015; MacLean et al., 2013).

Given the effects of SA on reward circuitry, it is perhaps no surprise that recreational SD use is not associated with dependence. One Internet-based survey assessed 155 SD users with the Severity of Dependence Scale (SDS). No respondents met criteria for SD use disorders based on self-report (Sumnall et al., 2011). Another Internet-based survey assessed 500 SD users for *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (*DSM-IV*) criteria for substance abuse and dependence. Nine respondents (1.8%) endorsed such criteria, most commonly endorsing craving to use, but no respondents qualified for DSM substance misuse disorders (Baggott et al., 2010). Consistent with these data, research subjects given SA in the laboratory do not report experiencing euphoria or craving to use, and do not seek out SD subsequent to experimental SA exposure (Addy, 2012; Ranganathan et al., 2012).

Consistent with indigenous SD use for religious purposes, laboratory data indicate that SA administration can lead to experiences with mystical or spiritual qualities as measured by the Hood Mysticism Scale and States of Consciousness Questionnaire (MacLean et al., 2013). Several surveys of recreational SD users report “spiritual purposes” as a common reason for use (Baggott et al., 2010; Nygård, 2007; Sumnall et al., 2011). The most commonly reported spiritual experiences included (a) “shamanic experiences” such as “out of body travel” (Nygård, 2007, p. 133) and “contact with other entities” (p. 134), and (b) perception of a greater or more accurate understanding of reality. Many of the alterations of consciousness attributed to SD including contact with entities and interoceptive disturbances have been characterized by users as unique to SD (Addy et al., 2015), and represent an important area for further research on the functions of the KOR system and its role in mediating subjective awareness.

Cannabinoids

Background. *Cannabis sativa* (cannabis) is among the oldest of cultivated plants known to mankind, with the earliest evidence for cultivated use going back to northeast China over 5,000 years ago where it was used medicinally, as a food source, but most importantly as a source of fiber (Li, 1973). The oldest sample of paper known to archeology dates to the early Han dynasty of China

approximately 100 BC and is made of hemp, a nonpsychoactive member of the cannabis genus (Li, 1974). Throughout the ages, cannabis has held a prominent role in the medicine of cultures as diverse as ancient China, ancient Greece and Victorian England (Clendinning 1843; Mikuriya, 1973; Russo, 1998). Cannabis as a psychoactive drug has played a prominent role in the religious and ceremonial life of many peoples both past and present, including recognition as a sacred plant in Hindu scripture dating back more than 3,000 years (Touw, 1981), and religious use in Jamaican Rastafari since the 1930s (Semaj, 1980). Although a comprehensive discussion of cannabis' risks and therapeutic potentials is outside the scope of this paper, a brief review will highlight some key points here.

Pharmacology. The plant genus *Cannabis* is commonly divided in two species, *Cannabis sativa* and *Cannabis indica*, with some distinguishing a third species as *Cannabis ruderalis* (Hillig, 2004). Cannabis is commonly smoked, or prepared in food or beverage form (Vandrey et al., 2015), and cannabinoids can also be extracted from the plant or synthesized in the laboratory (Haze-kamp et al., 2013). In *Cannabis sativa* the number of cannabinoids identified now exceeds 100 with more continually being cataloged (ElSohly & Gul, 2014). The cannabinoid primarily responsible for the psychoactive effects of the drug is Δ^9 -tetra-hydrocannabinol (THC), was first isolated in 1963 (Gaoni & Mechoulam, 1964). Additionally, cannabidiol (CBD) a nonpsychoactive cannabinoid, has emerged as a potential therapeutic agent of interest (Mechoulam et al., 2002). In the human organism there are two cannabinoid receptors (CB1 and CB2) and two endogenous cannabinoids N-arachidonylethanolamin (anandamide) and 2-arachidonoylglycerol (2AG; Battista et al., 2012). The CB1 receptor is most commonly found within the central and peripheral nervous system and is one of the most commonly expressed G-Protein coupled receptors (GPCRs) in the mammalian nervous system (Devane et al., 1988), whereas CB2 preponderates in the immune system and other peripheral organs (Klein & Cabral, 2006; Mackie, 2008).

Cannabis has demonstrated some significant sex differences in preclinical and human research, including greater sensitivity to the rewarding effects of cannabis, and greater vulnerability to cannabis dependence in females (Fattore, 2013). In humans, similar trends have been observed, with women reporting significantly greater abuse-related drug effects such as "good" and "take again" compared with men, although both sexes reported comparable levels of intoxication (Cooper & Haney, 2014). These differences will be important to take into account in considering both medical and recreational cannabis use, and in implementing appropriate gender-tailored treatments for cannabis use disorders (Fattore, 2013).

Contemporary research. The medical conditions for which cannabis has been used, both historically and presently, are diverse, including neuropathic pain, cancer related pain, headache, epilepsy and multiple sclerosis (Baron, 2015; Friedman & Devinsky, 2015; Whiting et al., 2015). Some cannabinoids have been made available as approved medications, including dronabinol (synthetic THC) and nabilone (synthetic cannabinoid mimicking THC) as capsules, and nabiximols (synthetic THC and CBD) as oromucosal spray (Haze-kamp et al., 2013). A recent meta-analysis of 79 randomized clinical trials (total $N = 6462$), found a significant therapeutic effect of cannabinoids in treating nausea and vomiting due to chemotherapy, chronic neuropathic or cancer pain,

and spasticity due to multiple sclerosis, with potential benefits for weight gain in HIV patients, Tourette syndrome, and treatment of sleep disorders (Whiting et al., 2015). The review also found an increased risk of short-term adverse effects including balance problems, confusion, dizziness, euphoria, and drowsiness (Whiting et al., 2015).

Several other therapeutic applications of cannabinoids have garnered interest and demonstrated some preliminary or preclinical evidence of feasibility, including as an anticancer agent (Velasco et al., 2016), for epilepsy (Alexander, 2016), mood disorders (Bambico et al., 2007), and PTSD (Greer et al., 2014). Additionally, medical access to cannabis in the U.S. has been linked to a significant 24.8% decrease in average opioid overdose mortalities from 1999 to 2010 as compared to states without medical cannabis access, consistent with data on efficacy of cannabinoids for treating pain, and suggesting a potential role for cannabis as a means of reducing opioid abuse (Bachhuber et al., 2014).

Regarding cancer, animal models have shown that cannabinoids can reduce tumor growth, potentially through inhibition of tumor angiogenesis and metastasis, and induction of cancer cell death (Galve-Roperh et al., 2000; Guzman, 2003; Velasco et al., 2016). However, clinical research applying cannabinoids as a cancer treatment is still lacking.

Preclinical evidence, case reports, and preliminary human data indicate that cannabinoids, and particularly CBD, may be useful in reducing seizures in epilepsy with limited adverse effects (Cunha et al., 1980; Devinsky et al., 2014; Maa & Figi, 2014). Effects of CBD on the G-protein-coupled receptor GPR55, serotonin 1A receptor, $\alpha 3$ and $\alpha 1$ glycine receptors, vanilloid type-I Channel, and equilibrative nucleoside transporter are among the hypothesized mechanisms by which CBD may exert acute anticonvulsant effects (Devinsky et al., 2014), though data from well controlled trials are still forthcoming.

Cannabis and the endocannabinoid system have also been implicated in the neurobiology of anxiety and depression (Viveros et al., 2005; Witkin et al., 2005). Synthetic CB1 agonists have shown powerful antidepressant effects in rodent models (Bambico et al., 2007; Hill & Gorzalka, 2005), as have enzyme inhibitors that prevent the normal breakdown of anandamide (Bortolato et al., 2007). The CB1 receptor has also demonstrated a mediating relationship with anxious behavior (Haller et al., 2002, 2004; Uriguen et al., 2004). Several earlier studies suggested the potential of smoked cannabis for the management of depressive symptoms in cancer patients (Regelson et al., 1976; Gruber et al., 1996), though this remains to be tested in larger controlled trials.

Similarly, individuals with PTSD often self-medicate with cannabis (Akirav, 2013; Bonn-Miller et al., 2011; Cogle et al., 2011; Passie et al., 2012; Potter et al., 2011), and have reported decreased PTSD symptoms as a result (Greer et al., 2014). Recent human neuroimaging studies have shown pronounced differences in CB1 receptor densities and anandamide signaling in sufferers of PTSD as compared to healthy controls and traumatized individuals without PTSD (Hauer et al., 2013; Neumeister et al., 2013). Cannabinoids have also been shown to reduce traumatic nightmares in sufferers of PTSD (Fraser, 2009). One small study of 10 chronic PTSD patients showed that twice a day supplementation with THC led to significant improvements in sleep quality and nightmares (Shalev et al., 2013).

These data offer a compelling glimpse of some of the diverse therapeutic potentials of cannabis that will likely be explored in more depth over the coming years and decades, especially as greater access to medical cannabis, and development of cannabinoid-based treatments continue to proliferate. Despite such broad potential, further clinical research with cannabinoids are necessary before definite conclusions can be drawn, with the current lack of evidence attributable in part to cannabis' current Schedule I status (Grinspoon & Bakalar, 1998; Nutt et al., 2013).

Discussion

The data presented here provide a review of potential therapeutic applications of hallucinogenic drugs, many of which have been dismissed as drugs of abuse with no clinical utility. The psychedelics, including LSD, psilocybin, mescaline, DMT, and the DMT containing admixture ayahuasca, have shown promise in treating a range of psychological disorders for which currently available treatments are often insufficient, such as mood, substance use, and anxiety disorders (see Table 2). These studies have mostly been conducted in small, relatively homogeneous samples, limiting the generalizability of their findings. However, safety and feasibility of psychedelic-facilitated treatment models have been established by these initial studies, paving the way for further investigation in larger, more diverse samples, using randomized controlled designs.

This also holds true for the entactogens, specifically MDMA, which has shown promise as a treatment for PTSD (see Table 3), and whose other therapeutic potentials are beginning to be systematically investigated for conditions such as social anxiety in individuals with autism spectrum disorder (Danforth et al., 2015), and psychological distress associated with life-threatening illness. While some concerns may remain about possible neurotoxicity or adverse cognitive effects associated with chronic abuse of 'Ecstasy' (Parrott, 2013, 2014), such effects have not been observed in individuals undergoing limited exposure to pure MDMA in controlled settings (Doblin et al., 2014). Nevertheless, ongoing clinical MDMA research should continue to address these concerns through rigorous monitoring of acute and persisting adverse effects as assessed in previous studies (Mithoefer et al., 2011). It should also be noted that at low to moderate doses, classic psychedelics such as LSD or psilocybin may serve as reasonable alternatives to MDMA, with similar mood elevating and prosocial effects (e.g., Schmid et al., 2015). Although classic psychedelics have not been examined in clinical trials for PTSD, preclinical evidence (Catlow, Song, Paredes, Kirstein, & Sanchez-Ramos, 2013), and neuroscience findings (Kraehenmann et al., 2015), indicate feasibility.

The dissociatives have been classified less restrictively than the psychedelics and entactogens. As such, they have been studied more thoroughly over the past several decades. In particular, ketamine's antidepressant properties have been well-established (Abdallah, Averill, & Krystal, 2015; Abdallah, Sanacora, et al., 2015). Ketamine has also shown considerable promise as an anti-addictive agent in conjunction with psychotherapy (Krupitsky et al., 1992, 2002, 2007). However, translation to clinical practice has not been widely adopted, in part due to concerns about durability of treatment effects, and potential adverse effects of repeated, chronic administration (Schatzberg, 2014). Other dissociatives like DXM (Doody et al., 2015) and nitrous oxide (Nagele et al., 2015)

are currently being revisited as potential treatments for mood disorders (see Table 4), an area that will likely see further research in coming years.

Finally, the atypical hallucinogens discussed here have shown varying degrees of clinical potential. Ibogaine has demonstrated good preclinical evidence as an antiaddictive agent (Glick et al., 1991, 1994), as well as anecdotal reports and preliminary clinical findings showing promise as an aid in opioid detoxification and substance use disorder treatment (Alper et al., 1999; Lotsof, 1995; Schenberg et al., 2014). However, concerns remain about safety and toxicity of ibogaine, tempering the widespread implementation of ibogaine research and treatment for the time being (Alper et al., 2012; Hoelen et al., 2009). Preclinical data and basic human research on Salvinorin A (SA) suggest an important role for the Kappa opioid receptor system in modulating addiction, mood, and consciousness (Addy et al., 2012; Addy et al., 2015; Freeman et al., 2014; Johnson et al., 2011, 2016); though clinical research has yet to provide evidence for therapeutic use of SA, which remains an important direction for future research (Butelman & Kreek, 2015; Chavkin, 2011). Cannabis and the cannabinoids have shown therapeutic value as a treatment for chronic pain, spasticity in multiple sclerosis, and chemotherapy induced nausea (Whiting et al., 2015), with a number of other conditions such as cancer, epilepsy, sleep disorders, and PTSD implicated as possible targets for cannabis-based treatments. Given the growing interest in cannabis-based treatments and expanding access to medicinal cannabis, these areas will more than likely see significant growth in the years ahead (Russo et al., 2015).

With the advent of the medical cannabis movement, which has become increasingly widespread over the past two decades, citizens and lawmakers alike are beginning to reconsider the therapeutic potentials of a variety of once taboo illicit drugs. At the state level, medical cannabis is now legal in 25 states, as well as Washington D.C., and recreational cannabis use has been legalized in Colorado, Oregon, Alaska, and Washington state. Nevertheless, cannabis remains a Schedule I substance at the federal level, and thus poses an ongoing conundrum regarding the ultimate legality and safety of both medical and recreational use. Additionally, with the ever-growing availability of novel hallucinogenic drugs, such as the synthetic phenethylamines (2-CB, etc.), and synthetic cannabinoids (e.g., 'Spice'; Spaderna et al., 2013), the potential risks and benefits of such substances pose a very real and timely public health issue that warrants serious consideration.

The convergence of these historic events have brought us to the verge of a new scientific framework that is presently taking shape within which to consider all drugs, both scheduled and unscheduled. This new approach ought to take into account not only the adverse effects of various drugs, but should also acknowledge their possible beneficial uses (Werb et al., 2016). This conceptual shift is further accompanied by the realization that the legal status of a drug does not always accurately reflect its actual harm to the user or to society (Nutt et al., 2007, 2010, 2013; Van Amsterdam et al., 2010, 2011). Current legal classification of cannabis, psychedelics, and entactogens place them in the most restricted class of drugs (Schedule I in the U.S.), indicating a high potential for abuse, no currently accepted medical use, and a lack of accepted safety for use under medical supervision (Nutt et al., 2013). Based on the evidence presented here, preliminary data indicate safety and feasibility of hallucinogen-facilitated treatments when conducted un-

der appropriately structured conditions (Johnson et al., 2008). Furthermore, a growing body of research suggests a wide range of medical uses for these drugs, particularly psilocybin, LSD, MDMA, and cannabis, thereby challenging their current legal classification.

Population data from 2010 indicate that in the U.S. alone, approximately 32 million individuals have used a psychedelic in their lifetime (Krebs & Johansen, 2013a), and a recent series of epidemiological analyses using data from the National Survey of Drug Use and Health (NSDUH) offered compelling results regarding the associations between psychedelic use and public health (Hendricks et al., 2015; Johansen & Krebs, 2015; Krebs & Johansen, 2013b). One such epidemiological study pooled NSDUH data from 2001–2004 ($N = 130,152$), revealing that lifetime psychedelic use was not associated with mental health problems of any kind, and that lifetime use of LSD or psilocybin was associated with lower rates of mental health treatment and psychiatric medication prescriptions (Krebs & Johansen, 2013b). Another study examining NSDUH data from 2008 through 2011 ($N = 135,095$) found no significant association between lifetime psychedelic use and psychological distress, depression, anxiety, or suicidality (Johansen & Krebs, 2015).

A related study using pooled NSDUH data from 2008 through 2012 provided a larger sample and thus more statistical power ($N = 191,382$), finding that lifetime psychedelic use was associated with significantly lower rates of past month psychological distress, and past year suicidality, while illicit use of other drug classes such as sedatives was generally associated with increased risk of psychological distress and suicidality (Hendricks et al., 2015). Although these findings cannot demonstrate causation, they do indicate that in nationally representative samples psychedelics do not pose enough of a public health concern to justify current Schedule I status, and may even offer some protective benefits that warrant further investigation, consistent with the fact that many psychedelic drugs have been used in religious contexts for thousands of years (Baker, 2005; Ott, 1993; Schultes et al., 2001). Currently, in the U.S., two religious organizations, the Native American Church and O Centro Espirita Beneficente Uniao do Vegetal (UDV), have won the right to use Schedule I psychedelics (peyote and ayahuasca, respectively) as a tenet of their religious life (Bullis, 2008; de Verges, 1974).

No class of drugs has undergone a more critical reappraisal in the past decade than the hallucinogens discussed in this manuscript. During the latter half of the 1960s, when prohibition of psychedelics was becoming more prominent, Pahnke and Richards offered this prescient evaluation of the situation:

We are confronted by the very real possibility that the known and unknown uses of these drugs that could prove to be legitimate and beneficial for individual persons and society may be suppressed until some future century when investigation will be permitted to proceed unhampered by popular hysteria and overrestrictive legislation. In the United States, interested and capable scientists are hesitating to investigate this field because of the abundance of unfavorable publicity and the threat of condemnation by identification with irresponsible researchers. Even among those who are willing to risk their reputations, some are finding it difficult to obtain the governmental approval now prerequisite for the legal acquisition of these drugs for research purposes. Paradoxically, a significant danger confronting our society

may lie in losing out on the values that the responsible use of these drugs may offer. (1966, p. 176)

Ultimately, at this time it is critical to take a level-headed assessment of the current state of the field, and in the scientific domain, to continue examining the harms and clinical potentials of these substances in a thorough and balanced manner. In the popular press and media, sensational reports can abound from either side, expounding on the “miraculous” healing qualities of certain compounds, or conversely demonizing the potential physical and psychological damages that they can entail. A judicious assessment, however, paints a much more nuanced and complex picture. The hallucinogens discussed here exhibit a collection of remarkable properties, some of which can elicit harm, and others which when applied skillfully, can promote healing or wellbeing. This is similar to many other classes of drugs that can be used therapeutically, or abused in destructive ways. It should also be noted that many of the hallucinogen-facilitated treatments presented here are designed as a combination of drug administration plus psychotherapy within a structured treatment context. Thus, variability in set and setting, as well as therapeutic rapport with treatment providers will undeniably affect observed outcomes, and must be taken into account when designing and conducting clinical research with hallucinogens (Johnson et al., 2008). Furthermore, sex differences in drug effects will have to be investigated more thoroughly to elucidate ramifications for hallucinogen-facilitated treatments (Fattore, 2013; Liechti et al., 2001).

It seems reasonable to assert that while individuals continue to suffer the burden of illnesses such as addiction and posttraumatic stress disorder, for which current treatment models often fall short, it is the moral responsibility of biomedical researchers and clinicians to explore every available treatment option. Public policy should be beholden to the scientific data on these substances, not vice versa. As stated by Nutt and colleagues, “It is surprising that the scientific community, particularly neuroscientists, has not protested against the effective ban of research on drugs that could offer so many insights into human brain function and such great opportunities for new treatments” (Nutt et al., 2013, p. 583). In collecting and summarizing the evidence presented here, this paper represents a tangible step toward making the case for additional basic, translational, and clinical research with hallucinogens, as well as a thorough reappraisal of their current legal status worldwide.

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