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Antidepressive, anxiolytic, and antiaddictive effects of ayahuasca, psilocybin and lysergic acid diethylamide (LSD): a systematic review of clinical trials published in the last 25 years

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***Abstract*:** To date, pharmacological treatments for mood and anxiety disorders and for drug dependence show limited efficacy, leaving a large number of patients suffering severe and persistent symptoms. Preliminary studies in animals and humans suggest that ayahuasca, psilocybin and lysergic acid diethylamide (LSD) may have antidepressive, anxiolytic, and antiaddictive properties. Thus, we conducted a systematic review of clinical trials published from 1990 until 2015, assessing these therapeutic properties. Electronic searches were performed using the PubMed, LILACS, and SciELO databases. Only clinical trials published in peer-reviewed journals were included. Of these, 151 studies were identified, of which six met the established criteria. Reviewed studies suggest beneficial effects for treatment-resistant depression, anxiety and depression associated with life-threatening diseases, and tobacco and alcohol dependence. All drugs were well tolerated. In conclusion, ayahuasca, psilocybin and LSD may be useful pharmacological tools for the treatment of drug dependence, and anxiety and mood disorders, especially in treatment-resistant patients. These drugs may also be useful pharmacological tools to understand psychiatric disorders and to develop new therapeutic agents. However, all studies reviewed had small sample sizes, and half of them were open-label, proof-of-concept studies. Randomized, double-blind, placebo-controlled studies with more patients are needed to replicate these preliminary findings.

Keywords: ayahuasca, dimethyltryptamine, hallucinogens, LSD, psilocybin, tryptamines

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Introduction

Naturally occurring classical or serotonergic hallucinogens such as the tryptamines *N*,*N*-dimethyltryptamine (DMT) and psilocybin (4-phosphoryloxy-*N*,*N*-DMT) have a long history of ritual use in Latin America [Harner, 1976; Grispoon and Bakalar, 1981; Dobkin de Rios, 1984, 1990; Schultes, 1986, 1998; Wasson *et al.* 1986; Schultes and Hofmann, 1992; Furst, 1994; Ott, 1994, 2004; Guzmán, 2008; McKenna and Riba, 2016]. DMT was first synthesized in 1931 by the Canadian chemist Richard Manske and subsequently isolated by the Brazilian chemist Oswaldo Gonçalves de Lima in 1946 from *Mimosa hostilis*, a hallucinogenic plant used by northeastern Brazilian indigenous groups for the preparation of a sacred beverage called *jurema* [Ott, 1994, 1999, 2004; McKenna and Riba, 2016]. DMT is also the main psychotropic compound of ayahuasca, a psychotropic brew used for magico-ritual and therapeutic purposes by indigenous and urban populations of Amazonian countries such as Brazil, Colombia, Peru and Ecuador [Harner, 1976; Dobkin de Rios, 1984,

1990; Schultes, 1986, 1998; Schultes and Hofmann, 1992; Furst, 1994; Ott, 1994, 2004; McKenna and Riba, 2016].

Ayahuasca is usually obtained by boiling the stems of the liana *Banisteriopsis caapi* with the leaves of the shrub *Psychotria viridis* [Harner, 1976; Dobkin de Rios, 1984, 1990; McKenna *et al.* 1984; Schultes, 1986, 1998; Schultes and Hofmann, 1992; Furst, 1994; Ott, 1994, 1999, 2004; Riba *et al.* 2001, 2003; McKenna and Riba, 2016]. *P. viridis* is rich in DMT, while *B. caapi* contains β-carboline compounds that reversibly inhibit monoamine oxidase A (MAO-A), such as harmine, tetrahydroharmine (THH) and harmaline [Buckholtz and Boggan, 1977; Dobkin de Rios, 1984; McKenna *et al.* 1984; Schultes, 1986; Schultes and Hofmann, 1992; Ott, 1994, 1999, 2004; Riba, *et al.* 2001, 2003; McKenna and Riba, 2016]. Due to peripheral (gastrointestinal and liver) MAO-A degradation, DMT is not orally active [Riba *et al.* 2001, 2003, 2015; McKenna and Riba, 2016]. Thus, MAO-A inhibition by the β-carbolines in ayahuasca allows DMT to reach systemic circulation and the central nervous system [Ott, 1999; Riba *et al.* 2001, 2003, 2015; McKenna and Riba, 2016].

Psilocybin and its active dephosphorylated metabolite psilocin (4-hydroxy-*N*,*N*-DMT) are the primary psychoactive compounds of several species of hallucinogenic mushrooms found throughout the world [Harner, 1976; Grispoon and Bakalar, 1981; Wasson *et al.* 1986; Dobkin de Rios, 1990; Schultes and Hofmann, 1992; Furst, 1994; Schultes 1998; Passie *et al.* 2002; Ott, 2004; Guzmán, 2008; Tylš *et al.* 2014; McKenna and Riba, 2016]. Some of these species, such as *Psilocybe mexicana*, have a crucial role in the religious and medicinal systems of indigenous groups in Mexico [Harner, 1976; Grispoon and Bakalar, 1981; Wasson *et al.* 1986; Dobkin de Rios, 1990; Schultes and Hofmann, 1992; Furst, 1994; Schultes, 1998; Ott, 2004; Guzmán, 2008; McKenna and Riba, 2016]. The Swiss chemist Albert Hofmann first isolated psilocybin and psilocin from *P. mexicana* in 1958 after several self-experiments, and synthetized these compounds later in the same year [Passie *et al.* 2002; Ott, 2004; Hofmann, 2005; Guzmán, 2008; Tylš *et al.* 2014; McKenna and Riba, 2016]. Although psilocybin is usually referred to as being the main psychoactive compound in hallucinogenic mushrooms, it is in fact a so-called prodrug of psilocin. Thus, after ingestion, it is rapidly dephosphorylated in the gut and liver into the active metabolite psilocin [Passie *et al.* 2002; Tylš *et al.* 2014; McKenna and Riba, 2016].

DMT and psilocybin are pharmacologically related to the ergoline D-lysergic acid diethylamide (LSD or LSD-25), a semisynthetic derivative of the naturally occurring lysergic acid moiety, present in several alkaloids found in the rye ergot fungus (*Claviceps purpurea*) [Hofmann, 2005; Passie *et al.* 2008; Hintzen and Passie, 2010; Smith *et al.* 2014; McKenna and Riba, 2016]. LSD was first synthetized by Albert Hofmann in 1938, and its psychoactive effects were discovered when the Swiss chemist accidentally ingested the drug in 1943 [Hofmann, 2005; Passie *et al.* 2008; Hintzen and Passie, 2010; Smith *et al.* 2014; McKenna and Riba, 2016].

DMT, psilocybin and LSD are agonists of serotonin 5-$HT_{1A/2A/2C}$ receptors [Pierce and Peroutka, 1989; McKenna *et al.* 1990; Glennon *et al.* 2000; Passie *et al.* 2002, 2008; Nichols, 2004; Hintzen and Passie, 2010; Hanks and González-Maeso, 2013; Tylš *et al.* 2014; Halberstadt, 2015]. Although the 5-$HT_{1A/2C}$ receptors modulate the effects of serotonergic hallucinogens, activation of frontocortical glutamate receptors secondary to 5-HT_{2A} receptor-related glutamate release appears to be the key mechanism of action of these drugs [Nichols, 2004; González-Maeso *et al.* 2008; Moreno *et al.* 2011, 2013; Hanks and González-Maeso, 2013; Santini *et al.* 2014; Buchborn *et al.* 2015; Carbonaro *et al.* 2015; Halberstadt, 2015]. The 5-HT_{2A} and the metabotropic glutamate 2/3 (mGluR2/3) receptors show an overlapping distribution in the brain cortex, and their interaction has a crucial role in the neuropsychopharmacology of classical hallucinogens [González-Maeso *et al.* 2008; Moreno *et al.* 2011].

In the last 25 years, the ritual and therapeutic use of ayahuasca has spread from small cities in the Amazonian jungle to the urban centers of South America, the United States, Europe, Asia and Africa [Labate *et al.* 2009; Labate and Jungaberle, 2011; Labate and Cavnar, 2014]. Animal research [Glick *et al.* 1994; Aricioglu-Kartal *et al.* 2003; Hilber and Chapillon, 2005; Farzin and Mansouri, 2006; Lima *et al.* 2006; Wu *et al.* 2009; Fortunato *et al.* 2009, 2010a, 2010b; Réus *et al.* 2010, 2012; Brierley and Davidson, 2012, 2013; Liester and Prickett, 2012; Owaisat *et al.* 2012; Abelaira *et al.* 2013; Oliveira-Lima *et al.* 2015; Pic-Taylor *et al.* 2015; dos Santos *et al.* 2016] and observational

and preliminary experimental studies of ayahuasca consumers [Grob *et al.* 1996; Barbosa *et al.* 2005, 2012; da Silveira *et al.* 2005; Doering-Silveira *et al.* 2005; dos Santos *et al.* 2007, 2016; Halpern *et al.* 2008; Barbosa *et al.* 2009; Labate *et al.* 2009, 2014; Fábregas *et al.* 2010; Labate and Jungaberle, 2011; Bouso *et al.* 2012; dos Santos, 2013; Thomas *et al.* 2013; Bouso and Riba, 2014; Fernández and Fábregas, 2014; Fernández *et al.* 2014; Loizaga-Velder and Loizaga Pazzi, 2014; Loizaga-Velder and Verres, 2014; Palhano-Fontes *et al.* 2014; Winkelman, 2014] suggest that ayahuasca and its isolated alkaloids have antidepressive, anxiolytic, and antiaddictive effects.

Moreover, experimental studies of acute ayahuasca administration to healthy volunteers [Riba *et al.* 2001, 2003, 2006; dos Santos *et al.* 2011, 2012; de Araujo *et al.* 2012; Palhano-Fontes *et al.* 2015; McKenna and Riba, 2016] and mental health assessments of long-term ayahuasca consumers [Grob *et al.* 1996; Barbosa *et al.* 2005, 2009, 2012; da Silveira *et al.* 2005; Doering-Silveira *et al.* 2005; Halpern *et al.* 2008; Fábregas *et al.* 2010; Bouso *et al.* 2012, 2015; dos Santos, 2013] suggest that this preparation is quite safe.

In the case of psilocybin and LSD between the mid-1950s and mid-1970s, several studies investigated the potential therapeutic use of these drugs in the treatment of neurosis, obsessive–compulsive disorder (OCD), substance dependence, and as an adjunctive therapy in the terminally ill [Kurland *et al.* 1971; McGlothlin and Arnold, 1971; Grispoon and Bakalar, 1981; Riedlinger and Riedlinger, 1994; Abraham *et al.* 1996; Delgado and Moreno, 1998; Grob, 1998; Grof, 2001; Hofmann, 2005; Dyck, 2006; Hintzen and Passie, 2010; Vollenweider and Kometer, 2010; Bogenschutz and Pommy, 2012; Krebs and Johansen, 2012; Bogenschutz, 2013; Burdick and Adinoff, 2013; Baumeister *et al.* 2014; Liester, 2014; Oram, 2014; Smith *et al.* 2014; Bogenschutz and Johnson, 2016].

However, clinical research with hallucinogens was interrupted in the late 1960s mid-1970s due to an increase in the recreational use of these substances and their association with the countercultural movements [Grispoon and Bakalar, 1981; Riedlinger and Riedlinger, 1994; Grob, 1998; Grof, 2001; Hofmann, 2005; Dyck, 2006; Hintzen and Passie, 2010; Liester, 2014; Oram, 2014; Smith *et al.* 2014; Bogenschutz and Johnson, 2016]. Moreover, new rules for investigating novel pharmacological agents were introduced in the 1960–1970s [Liester, 2014; Oram, 2014], creating many difficulties for human hallucinogen research since most of these studies had important methodological limitations, such as absence of adequate control groups and follow-up measurements; substantial variation of dose and dosing duration among studies; lack of control for confounding factors such as pre-existing mental health problems or participant sex and age; non-standardized criteria for therapeutic outcome; and use of diverse theoretical approaches for assessing beneficial effects (ranging from psychoanalysis or transpersonal psychology to hypnosis and sensorial isolation or overload) [Grispoon and Bakalar, 1981; Kurland *et al.* 1971; McGlothlin and Arnold, 1971; Riedlinger and Riedlinger, 1994; Grob, 1998; Grof, 2001; Dyck, 2006; Vollenweider and Kometer, 2010; Bogenschutz and Pommy, 2012; Krebs and Johansen, 2012; Bogenschutz, 2013; Burdick and Adinoff, 2013; Baumeister *et al.* 2014; Liester, 2014; Oram, 2014; Bogenschutz and Johnson, 2016].

Therefore, although the early clinical studies with hallucinogens showed promising results, their methodological limitations suggest caution when interpreting their results. After a halt of almost 20 years, controlled laboratory studies in humans involving the administration of hallucinogens resumed in the 1990s with the investigations in healthy volunteers of Leo Hermle and collaborators in Germany, using orally administered mescaline [Hermle *et al.* 1992], and of Rick Strassman and coworkers in the United States, administering intravenous DMT [Strassman and Qualls, 1994; Strassman *et al.* 1994].

More recent preclinical research [Delgado and Moreno, 1998; Zghoul and Blier, 2003; Matsushima *et al.* 2009; Vollenweider and Kometer, 2010; Bogenschutz and Pommy, 2012; Bogenschutz, 2013; Burdick and Adinoff, 2013; Baumeister *et al.* 2014; Buchborn *et al.* 2014; Bogenschutz and Johnson, 2016], case reports [Leonard and Rapoport, 1987; Riedlinger and Riedlinger, 1994; Hanes, 1996; Delgado and Moreno, 1998; Perrine, 1999; Wilcox, 2014] and observational [Krebs and Johansen, 2013; Hendricks *et al.* 2014, 2015; Johansen and Krebs, 2015] and preliminary experimental studies in healthy volunteers [Griffiths *et al.* 2006, 2011; Vollenweider and Kometer, 2010; Studerus *et al.* 2011; Kometer *et al.* 2012; Kraehenmann *et al.*

2016; Schmid *et al.* 2016] suggest that classical hallucinogens such as psilocybin and LSD have anxiolytic, antidepressive, and antiaddictive properties.

Moreover, early clinical research [Kurland *et al.* 1971; McGlothlin and Arnold, 1971; Grispoon and Bakalar, 1981; Strassman, 1984; Riedlinger and Riedlinger, 1994; Grob, 1998; Grof, 2001; Passie *et al.* 2002, 2008; Hofmann, 2005; Dyck, 2006; Hintzen and Passie, 2010; Vollenweider and Kometer, 2010; Bogenschutz and Pommy, 2012; Krebs and Johansen, 2012; Bogenschutz, 2013; Liester, 2014; Smith *et al.* 2014; Tylš *et al.* 2014; Bogenschutz and Johnson, 2016], and more recent observational studies [Krebs and Johansen, 2013; Hendricks *et al.* 2014, 2015; Johansen and Krebs, 2015], drug harm or risk assessments [Nutt *et al.* 2010; van Amsterdam *et al.* 2011, 2013, 2015; Morgan *et al.* 2013], and pharmacological studies of acute drug administration to healthy volunteers [Griffiths *et al.* 2006, 2011; Vollenweider and Kometer, 2010; Studerus *et al.* 2011; Kometer *et al.* 2012; Carhart-Harris *et al.* 2012a, 2012b, 2013; Kraehenmann *et al.* 2016; Schmid *et al.* 2016] suggest that these compounds have low toxicity and are reasonably safe when administered in supervised or controlled settings. Indeed, classic hallucinogens such as psilocybin and LSD are considered less toxic and harmful than most licit and illicit drugs [Nutt *et al.* 2010; van Amsterdam *et al.* 2011, 2013, 2015; Morgan *et al.* 2013].

Thus, considering this context, this study aimed to conduct a systematic literature review of clinical trials published in the last 25 years (1990–2015) that investigated anxiolytic, antidepressive, and antiaddictive effects of ayahuasca, psilocybin and LSD.

Methods

Data for this systematic review were collected in accordance with the Systematic Reviews and Meta-Analyses guidelines (PRISMA) [Moher *et al.* 2009].

Data acquisition

We intended to identify all clinical trials available for review from 1 January 1990 to 1 July 2015, in which the anxiolytic, antidepressive, or antiaddictive effects of ayahuasca, psilocybin or LSD were analyzed.

Search strategy

Electronic searches were performed using the PubMed (1 January 1990–1 July 2015), LILACS (1 January 1990–1 July 2015) and SciELO (1 January 1990–1 July 2015) databases. The following key words were used: ayahuasca OR psilocybin OR lysergic acid diethylamide AND anxiety OR depression OR dependence. References were retrieved through searching electronic databases and manual searches through reference lists of identified literature. All studies published in English, Spanish, and Portuguese up to 1 July 2015 were included.

Eligibility criteria

The following inclusion and exclusion criteria were established prior to the literature search:

Article type. For purposes of this review, only clinical trials (open-label pilot studies, single-blind trials, or double-blind placebo-controlled trials) published in peer-reviewed journals were included. Animal studies, experimental studies in healthy volunteers, observational studies, review papers, qualitative studies, opinion pieces or comments, letters or editorials, conference abstracts or posters, books or book chapters, case reports, and published abstracts were excluded.

Study design. The review included only clinical trials involving patients with a diagnosis of an anxiety, depressive, or dependence disorder based on a structured diagnostic interview [*Diagnostic and Statistical Manual of Mental Disorders* (DSM)].

Participants. Only studies that included patients with a diagnosis of an anxiety, depressive, or dependence disorder based on a structured diagnostic interview (DSM) were included.

Interventions. All clinical trials evaluating the effects of ayahuasca, psilocybin, or LSD on anxiety, depressive, or dependence symptoms were included.

Comparisons. The main comparators considered were placebo and active placebo.

Outcomes. Reductions in anxiety, depressive, or dependence symptoms measured with validated scales.

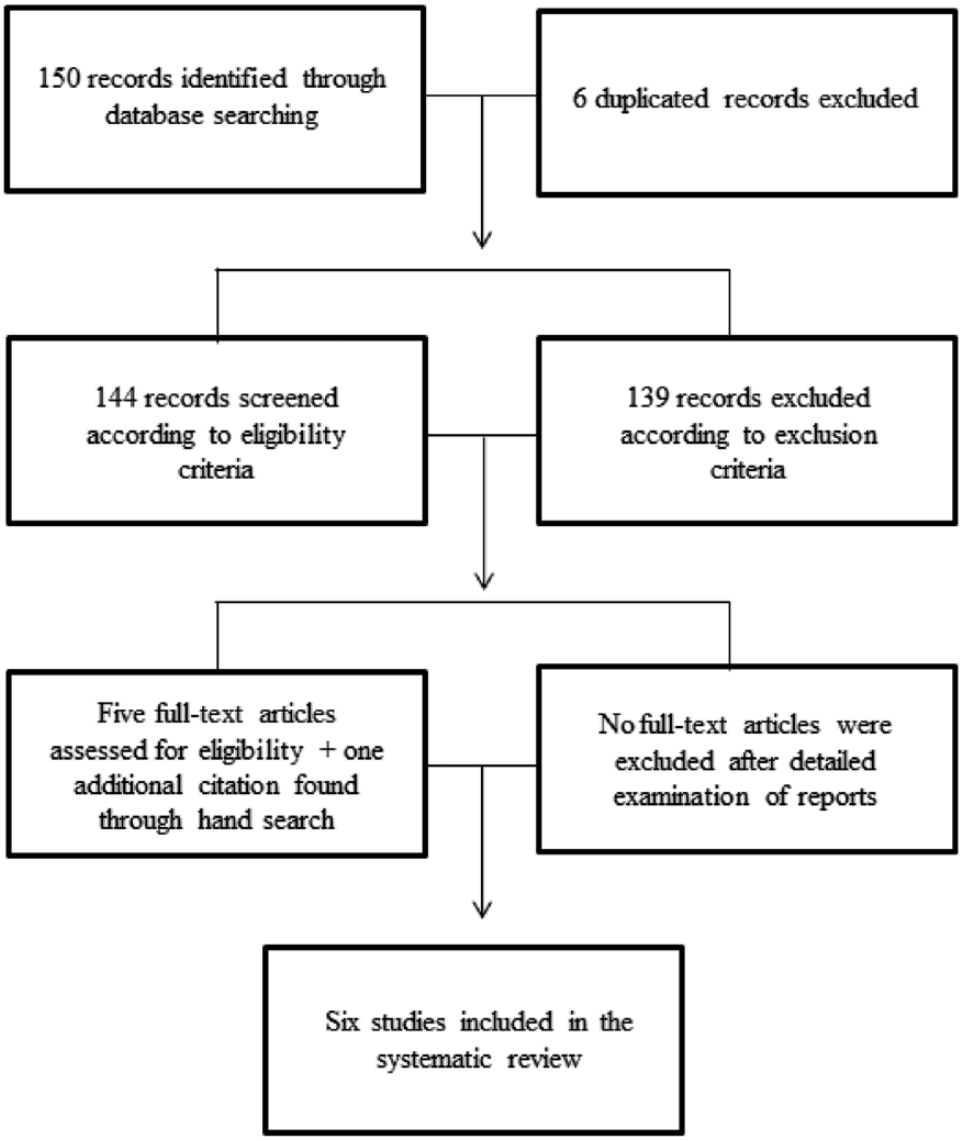

Figure 1. Flow diagram illustrating the different phases of the systematic review.

Data extraction

All studies were screened by two independent reviewers, with discrepancies resolved by a third reviewer. From the articles included we recorded names of authors, year of publication, study design (open label, single or double blind), characteristics of the participants (anxiety, depressive, or dependence symptoms, and sample size), response criteria (anxiolytic, antidepressive, or antiaddictive effect), type of intervention (drug, dose, and form of administration), and type of outcome measure (anxiety, depression, or dependence symptoms and scales).

Results

Study selection

A flow diagram illustrating the different phases of the systematic review is presented in Figure 1.

The search of the literature yielded 150 separate references. Owing to the overlap of coverage between the databases, six of the references were found to be duplicates. Thus, a total of 144 citations were reviewed for abstract screening (first pass). Following the first pass, five potentially relevant references were identified [Moreno *et al.*

2006; Grob *et al.* 2011; Gasser *et al.* 2014; Bogenschutz *et al.* 2015; Osório *et al.* 2015]. The remaining 139 studies were excluded according to the exclusion criteria. Full-text reports of the five selected citations were obtained for more detailed evaluation (second pass). Following detailed examination of the reports, all five citations were included. Another citation was found after hand search of the bibliography of the selected reports [Johnson *et al.* 2014]. Thus, six citations were included in the systematic review.

Studies were classified according to drug (ayahuasca, psilocybin, or LSD) and symptom (anxiety, depression, or dependence symptoms). The included studies comprised four studies with psilocybin (one study of OCD: Moreno *et al.* 2006; one study of anxiety associated with advanced-stage cancer: Grob *et al.* 2011; one study of tobacco dependence: Johnson *et al.* 2014; and one study of alcohol dependence: Bogenschutz *et al.* 2015], one study with LSD (anxiety associated with life-threatening diseases: Gasser *et al.* 2014], and one study with ayahuasca [Osório *et al.* 2015]. The details of the selected studies are summarized in Table 1.

Despite the small number of studies, the small sample sizes (6–15 volunteers), the high degree of heterogeneity among studies, and the lack of placebo and control groups in three of the selected citations (open-label, proof-of-concept studies), the reported results consistently show that ayahuasca, psilocybin, and LSD have anxiolytic, antidepressive, and antiaddictive properties. These findings will be further discussed in detail below.

Drugs

Psilocybin

Obsessive–compulsive disorder. In a double-blind study, nine subjects (seven men, two women) with obsessive–compulsive disorder (OCD) and at least one treatment failure with a serotonin reuptake inhibitor (mean 3.4 ± 1.9 treatment failures) received up to four different doses of orally administered psilocybin (one dose for test session) in a dose-escalation blinded design [Moreno *et al.* 2006). Low (100 μg/kg), medium (200 μg/kg), and high (300 μg/kg) doses of psilocybin were administered in that order, and a very low dose (25 μg/kg) was inserted randomly and in double-blind design at any time after the first dose (100 μg/kg). Subjects met DSM-IV criteria for OCD and had a mean baseline Yale–Brown Obsessive–Compulsive Scale (YBOCS) score of 24.1 ± 5.9. YBOCS and Visual Analog Scales (VAS) scores for overall OCD symptom severity were measured immediately before drug ingestion and at 4, 8, and 24 hours after ingestion.

All subjects received the low dose, seven received the very low and medium doses, and six received all doses. Reductions in YBOCS scores ranging from 23% to 100% were observed in all subjects during one or more sessions. Moreover, 88.9% of subjects maintained no less than a 25% decrease and 66.7% maintained no less than a 50% decrease in YBOCS scores at 24 hours with at least one psilocybin dose. Symptom improvement during the following week was reported by two subjects, and one volunteer reported improvement at the 6-month follow up. VAS scores were also reduced throughout the study period, and psilocybin was well tolerated by all volunteers.

Anxiety associated with advanced-stage cancer. A double blind, randomized, placebo-controlled study assessed the safety and potential therapeutic effects of psilocybin in the treatment of psychological distress associated with the existential crisis of terminal disease [Grob *et al.* 2011]. Twelve subjects (11 women) with advanced-stage cancer and a DSM-IV diagnosis of acute stress disorder, generalized anxiety disorder, anxiety disorder due to cancer, or adjustment disorder with anxiety, received oral psilocybin (0.2 mg/kg) or the active placebo niacin (250 mg) in a double-blind fashion. The Beck Depression Inventory (BDI), the Profile of Mood States (POMS), and the State–Trait Anxiety Inventory (STAI) were administered the day before, at the conclusion, the day after, and 2 weeks after each experimental session. The BDI, POMS, and STAI were administered again at monthly intervals for 6 months after the final session.

All 12 participants completed the 3 months of follow up, 11 completed the 4-month follow up, and eight completed the 6-month follow up. During the study, two subjects died of their cancer and two became too ill to continue the study. Significant decreases were observed in STAI scores at the 1- and 3-month follow ups, and in BDI scores at the 6-month follow up. No significant changes were observed in POMS scores, and psilocybin was well tolerated by all patients. By the time of the paper's submission in 2010, 10 of the 12 subjects had died of their cancer.

Table 1. Clinical trials assessing the anxiolytic, antidepressive, and antiaddictive effects of ayahuasca, psilocybin, and lysergic acid diethylamide (LSD).

Reference	No. of Patients/ Diagnostic	Study Design	Drug (mg/kg)	Main Findings
Moreno *et al.* [2006]	9 OCD	Double blind, randomized, dose escalation	Psilocybin 0.25–0.3	Reduction in YBOCS scores in all subjects during one or more sessions Reduction in VAS scores for overall OCD symptom severity
Grob *et al.* [2011]	12 Anxiety associated with advanced-stage cancer	Double blind, randomized, active placebo (niacin 250 mg)	Psilocybin 0.2	Reduction in STAI trait anxiety scores at 1 and 3-month follow up, and in BDI scores at 6-month follow up
Gasser *et al.* [2014]	12 Anxiety associated with life-threatening diseases	Double blind, randomized, active placebo (LSD 20 µg)	LSD 2.9×10^{-3}	Reduction in STAI state anxiety scores at 2-month follow up
Johnson *et al.* [2014]	15 Tobacco dependence	Open label	Psilocybin 0.29–0.43	Reduction in breath CO levels, urine cotinine, daily smoking (TLFB), withdrawal (WSWS), craving (QSU), and temptation to smoke (SASE), and increase in confidence to abstain (SASE) through the 6-month follow up
Bogenschutz *et al.* [2015]	10 Alcohol dependence	Open label	Psilocybin 0.3–0.4	Reduction in percent-drinking days (TLFB) at all follow up points (weeks 5–36) Reduction in drinking consequences (SIP) and craving (PACS), and improves in self-efficacy (AASE), motivation (SOCRATES 8A), and mood (POMS) at multiple time points (weeks 5–36)
Osório *et al.* [2015]	6 MDD	Open label	Ayahuasca 2.2 ml/kg[1]	Reduction in HAM-D, MADRS, and BPRS-AD scores between baseline and 1, 7 and 21 days after drug intake

AASE, Alcohol Abstinence Self-Efficacy Confidence score; BPRS-AD, Anxious–Depression subscale of the Brief Psychiatric Rating Scale; BDI, Beck Depression Inventory; CO, carbon monoxide; DSM, Diagnostic and Statistical Manual of Mental Disorders; HAM-D, Hamilton Rating Scale for Depression; LSD, lysergic acid diethylamide; MADRS, Montgomery–Åsberg Depression Rating Scale; MDD, major depressive disorder; OCD, obsessive–compulsive disorder; PACS, Penn Alcohol Craving Scale; POMS, Profile of Mood States; QSU, Questionnaire on Smoking Urges; SASE, Smoking Abstinence Self-Efficacy scale; SIP, Short Inventory of Problems; SOCRATES 8A, Stages of Change Readiness and Treatment Eagerness Scale; STAI, State–Trait Anxiety Inventory; TLFB, Time-Line Follow-Back; VAS, Visual Analog Scales; WSWS, Wisconsin Smoking Withdrawal Scale; YBOCS, Yale–Brown Obsessive–Compulsive Scale.
[1]Orally administered as a decoction; alkaloid content 0.8 mg/ml DMT, 0.21 mg/ml harmine (no harmaline was detected).

Tobacco dependence. An open-label study assessed the effects of moderate (20 mg/70 kg) and high (30 mg/70 kg) doses of psilocybin in 15 (ten men, five women; mean age of 51 years) nicotine-dependent smokers [Johnson *et al.* 2014]. Participants had a mean of six previous lifetime quit attempts, and smoked a mean of 19 cigarettes per day for a mean of 31 years. Volunteers participated in a 15-week smoking cessation treatment (cognitive behavioral therapy), with psilocybin administration occurring in weeks 5 (moderate dose), 7 (high dose), and 13 (high dose) (participants were permitted to repeat the moderate dose on sessions two and three). Changes in mean cigarettes per day were compared between the 30 days prior to study intake and the 6 months after the first psilocybin session (at week 5 of treatment). Exhaled carbon monoxide (CO) and urinary cotinine level were assessed at intake, weekly throughout the intervention, and at 6-month follow up to measure recent smoking.

All participants completed the study. According to the Time-Line Follow-Back (TLFB) and biomarker data (breath CO, urine cotinine), 80% (12 of 15) of participants were abstinent at 6-month follow up. Among the entire sample, significant reductions from intake to the 6-month follow up were observed in breath CO levels, urine cotinine, and self-reported daily smoking. Moreover, craving [Questionnaire on Smoking Urges (QSU)] and temptation to smoke [Smoking Abstinence Self-Efficacy scale (SASE)] were significantly reduced across all time points.

Significant increases were reported for confidence to abstain (SASE) from intake to the 6-month follow up, and withdrawal scores [Wisconsin Smoking Withdrawal Scale (WSWS)] peaked at 1-week postpsilocybin and decreased significantly through the 6-month follow up. No significant adverse events were reported during psilocybin sessions.

Alcohol dependence. Ten volunteers (four women, six men) with DSM-IV alcohol dependence (mean duration of dependence 15.1 ± 11.5 years, range 4–32) participated in an open-label trial that included a 12-session psychosocial intervention and two oral doses of psilocybin [Bogenschutz *et al.* 2015]. Eight of the 10 volunteers had evidence of physical dependence (tolerance or withdrawal). The psychosocial intervention included seven sessions of Motivational Enhancement Therapy (MET); three preparation sessions; two debriefing sessions; four sessions before the first psilocybin dose (0.3 mg/kg); four sessions between the first and second psilocybin dose (0.4 mg/kg); and four sessions after the second psilocybin dose. Outcome measures were collected for 36 weeks.

Nine volunteers completed all follow-up assessments; 10 completed the first psilocybin session, and seven the second session. However, only six patients were included in the analysis of the second session since one volunteer did not receive the 0.4 mg/kg psilocybin dose, receiving the 0.3 mg/kg due to meeting criteria for 'complete mystical experience' [Mystical Experience Questionnaire (MEQ)] in the first session. One patient discontinued participation and was excluded from the analysis.

According to the TLFB, percent-drinking days (consumption of any amount of an alcoholic beverage) and heavy-drinking days (consumption of four or more drinks of 14 g of alcohol) decreased significantly relative to weeks 1–4 prior to psilocybin, and also during weeks 5–12 relative to baseline. Following the first psilocybin session, percent-drinking days and heavy-drinking days were significantly lower than baseline at all follow-up points.

Significant correlations were observed between the overall intensity (Hallucinogen Rating Scale Intensity score; Altered States of Consciousness Scale summary score) and mystical quality (MEQ) of the psilocybin session and changes in percent-drinking days (TLFB), craving [Penn Alcohol Craving Scale (PACS)], self-efficacy to abstain from drinking [Alcohol Abstinence Self-Efficacy Confidence score (AASE)], and motivation [Stages of Change Readiness and Treatment Eagerness Scale (SOCRATES 8A)].

Improvements were largely maintained throughout the 36 weeks follow up. At multiple time points relative to baseline and (or) week 4, psilocybin reduced drinking consequences [Short Inventory of Problems, (SIP); weeks 8 to 36] and craving (PACS), and improved self-efficacy (AASE; weeks 5, 9, 24 and 36), motivation (SOCRATES 8A; weeks 5 to 36), and mood [Profile of Mood States, (POMS); weeks 4 and 24]. No significant adverse effects were reported after psilocybin administration.

Lysergic acid diethylamide (LSD)

Anxiety associated with life-threatening diseases. A double blind, randomized, active placebo-controlled study assessed the effects of lysergic acid diethylamide (LSD) in 12 patients (seven men, four women) with anxiety associated with life-threatening diseases (cancer, or chronic motor or inflammatory diseases) [Gasser *et al.* 2014]. Volunteers had a score of no less than 40 on the state or trait scales of the STAI and a DSM-IV diagnosis of major depressive disorder (MDD), reactive depression, dysthymia, posttraumatic stress disorder (PTSD), panic disorder, or social phobia. The study included drug-free psychotherapy sessions and two LSD-assisted psychotherapy sessions. Volunteers received either an experimental dose (200 μg, $n = 8$) or an active placebo (20 μg, $n = 3$) of LSD 2 to 3 weeks apart, with an open-label crossover to 200 μg of LSD after the initial blinded treatment ($n = 4$). Outcome data were collected at baseline, 1 week after LSD sessions, and at 2- and 12-month follow ups.

At the 2-month point, STAI state anxiety was significantly reduced, and a trend was found for reductions in STAI trait anxiety. STAI reductions were sustained for 12 months. Beneficial results were also observed in secondary outcome measures, including the European Cancer Quality of Life Questionnaire 30-item version 1.0 (EORTC-QLQ-30), the Symptom Checklist-90-Revised (SCL-90-R), and the Hospital Anxiety and Depression Scale (HADS). However, due to concerns about multiplicity, changes in secondary outcome measures were not analyzed for statistical

significance. No adverse effects or treatment-related serious adverse events were reported.

Ayahuasca

Major depressive disorder. An open-label trial assessed the antidepressive potential of ayahuasca in patients with diagnosis of recurrent major depressive disorder (MDD) [Osório *et al.* 2015]. A single dose of orally administered ayahuasca (2.2 ml/kg body weight) was administered to six volunteers (two men, four women) suffering a mild ($n = 2$), moderate ($n = 3$) or severe ($n = 1$) depressive episode. Ayahuasca administration produced statistically significant reductions of up to 82% in depressive scores between baseline and 1, 7 and 21 days after drug intake, according to the Hamilton Rating Scale for Depression (HAM-D), the Montgomery–Åsberg Depression Rating Scale (MADRS), and the Anxious–Depression subscale of the Brief Psychiatric Rating Scale (BPRS). Ayahuasca did not produce significant effects in the Young Mania Rating Scale (YMRS) scores or in the other subscales of the BPRS. Ayahuasca was well tolerated by all patients and vomiting was the only adverse effect recorded, being reported by 50% of the volunteers. Patients did not consider this emetic effect as causing severe discomfort.

Discussion

Possible mechanisms of therapeutic action

The mechanisms of action responsible for the beneficial effects produced by ayahuasca, psilocybin and LSD are not completely understood. Preclinical evidence show that ayahuasca [Lima *et al.* 2006; Pic-Taylor *et al.* 2015] and its β-carbolines harmine [Aricioglu-Kartal *et al.* 2003; Farzin and Mansouri, 2006; Fortunato *et al.* 2009, 2010a, 2010b; Réus *et al.* 2010, 2012; Brierley and Davidson, 2012; Owaisat *et al.* 2012] and harmaline [Glick *et al.* 1994; Hilber and Chapillon, 2005; Wu *et al.* 2009], as well as psilocybin [Matsushima *et al.* 2009] and LSD [Zghoul and Blier, 2003; Buchborn *et al.* 2014], have antidepressive, anxiolytic, and antiaddictive properties. Experimental studies with healthy volunteers report that acute administration of DMT [Gillin *et al.* 1976; Strassman *et al.* 1994; Riba *et al.* 2015], psilocybin [Griffiths *et al.* 2006, 2011; Studerus *et al.* 2011; Kometer *et al.* 2012; Kraehenmann *et al.* 2016], and LSD [Schmid *et al.* 2016] increase positive mood. Furthermore, observational and preliminary experimental studies of ayahuasca consumers [Grob *et al.* 1996; Barbosa *et al.* 2005, 2009, 2012; da Silveira *et al.* 2005; Doering-Silveira *et al.* 2005; dos Santos *et al.* 2007, 2016; Halpern *et al.* 2008; Labate *et al.* 2009, 2014; Fábregas *et al.* 2010; Labate and Jungaberle, 2011; Bouso *et al.* 2012; dos Santos, 2013; Thomas *et al.* 2013; Bouso and Riba, 2014; Fernández and Fábregas, 2014; Fernández *et al.* 2014; Loizaga-Velder and Loizaga Pazzi, 2014; Loizaga-Velder and Verres, 2014; Palhano-Fontes *et al.* 2014; Winkelman, 2014], as well as case reports [Leonard and Rapoport, 1987; Riedlinger and Riedlinger, 1994; Hanes, 1996; Delgado and Moreno, 1998; Perrine, 1999; Wilcox, 2014] and observational studies [Krebs and Johansen, 2013; Hendricks *et al.* 2014, 2015; Johansen and Krebs, 2015] involving psilocybin and LSD, also suggest that these drugs have therapeutic potentials.

Since DMT, psilocybin and LSD are agonists of serotonin 5-$HT_{1A/2A/2C}$ receptors [Pierce and Peroutka, 1989; McKenna *et al.* 1990; Glennon *et al.* 2000; Passie *et al.* 2002, 2008; Nichols, 2004; Hintzen and Passie, 2010; Hanks and González-Maeso, 2013; Tylš *et al.* 2014; Halberstadt, 2015], these receptors may be involved in the therapeutic effects of these tryptamines. In fact, cortical expression of 5-$HT_{1A/2A/2C}$ receptor is altered in post-mortem samples of depressed patients, suggesting that these receptors are involved in emotional processing [Vollenweider and Kometer, 2010; Baumeister *et al.* 2014]. Furthermore, animal models and clinical studies show that 5-HT_{1A} receptor agonists have anxiolytic and antidepressive properties [Nutt, 2005; Katzman, 2009; Baumeister *et al.* 2014], and 5-$HT_{2A/2C}$ receptor agonists reduce anxiety- and depression-related behavior in animals [Masuda and Sugiyama, 2000; Nic Dhonnchadha *et al.* 2003a, 2003b; Baumeister *et al.* 2014].

Another possible mechanism of therapeutic action is the modulation of glutamatergic neurotransmission induced by 5-HT_{2A}-receptor agonism [Nichols, 2004; González-Maeso *et al.* 2008; Vollenweider and Kometer, 2010; Moreno *et al.* 2011, 2013; Hanks and González-Maeso, 2013; Santini *et al.* 2014; Buchborn *et al.* 2015; Carbonaro *et al.* 2015; Halberstadt, 2015]. Activation of frontocortical glutamate networks by 5-HT_{2A} receptor agonists could lead to increases in the expression of neurotrophic factors such as brain-derived neurotrophic factor (BDNF) and glial cell line-derived neurotrophic factor (GDNF) and in the size of dendritic spines

on cortical neurons, thus enhancing neuroplasticity and neurogenesis [Vollenweider and Kometer, 2010; Bogenschutz and Pommy, 2012; Ross, 2012; Baumeister *et al.* 2014; Bogenschutz and Johnson, 2016]. For instance, depression is associated with deficient neurogenesis and neurotrophic activity, and BDNF levels are decreased in depressed patients and normalized after antidepressant treatment [Baumeister *et al.* 2014]. Furthermore, alcohol self-administration and conditioned place preference are inversely related to BDNF or GDNF expression in animal models [Bogenschutz and Pommy, 2012; Bogenschutz and Johnson, 2016]. Interestingly, a low dose (0.1 mg/kg) of psilocybin produced a trend toward increased neurogenesis in the mouse hippocampus 2 weeks after its administration, while a high dose (1 mg/kg) significantly decreased neurogenesis [Catlow *et al.* 2013]. These results suggest that the effects of psilocybin on neurogenesis are dose- and time-related.

Agonism at the 5-HT_{2A} receptor could also produce beneficial effects due to an anti-inflammatory action [Nau *et al.* 2013; Baumeister *et al.* 2014; dos Santos, 2014; Szabo *et al.* 2014]. Increased levels of pro-inflammatory cytokines such as tumor necrosis factor α (TNFα), interleukin-6 (IL-6), IL-8, and IL-1β are associated with depressive illness, while normalization of these levels are related to antidepressant effects [Baumeister *et al.* 2014; Réus *et al.* 2015]. The 5-HT_{2A} receptor is expressed in central and peripheral immune-related cells [Stefulj *et al.* 2000; Nau *et al.* 2013], and 5-HT_{2A} agonists may modulate the immune system [Forrer and Goldner, 1951; Feld *et al.* 1958; Sackler *et al.* 1963, 1966; Hollister and Sjoberg, 1964; House *et al.* 1994, 1997; Stefulj *et al.* 2000; Passie *et al.* 2002; Davydova *et al.* 2010; Hintzen and Passie, 2010; dos Santos *et al.* 2011, 2012; Frecska *et al.* 2013; Nau *et al.* 2013; Baumeister *et al.* 2014; dos Santos, 2014; Szabo *et al.* 2014]. Indeed, *in vitro* studies show that LSD inhibits the production of IL-6 [House *et al.* 1994, 1997], and the serotonergic hallucinogen 4-iodo-2,5-dimethoxyphenylisopropylamine (DOI, a 5-HT_{2A} receptor agonist) produces anti-inflammatory effects in mice by blocking TNF-α-induced expression of pro-inflammatory cell adhesion (Icam-1, Vcam-1), cytokine (IL-6, IL-1β), and chemokine (Mcp-1, Cx3cl1) genes, and expression of VCAM-1 protein [Nau *et al.* 2013]. These effects were blocked by a 5-HT_{2A} selective antagonist, implicating this receptor in the anti-inflammatory effects of DOI. Moreover, DMT and the related tryptamine 5-methoxy-DMT (5-MeO-DMT) reduced the mRNA expression and the levels of IL-6, IL-8, IL-1β, and TNF-α, increased the levels of the anti-inflammatory cytokine IL-10, and inhibited the immune responses of inflammatory T helper 1/17 (Th1/Th17) cells [Szabo *et al.* 2014]. Interestingly, gene knock-down experiments showed that the effects of both tryptamines on TNFα, IL-10, and Th1/Th17 responses were mediated by the sigma-1 receptor, and recent studies show that DMT is an endogenous agonist for the sigma-1 receptor [Fontanilla *et al.* 2009; Su *et al.* 2009; Frecska *et al.* 2013; Szabo *et al.* 2014].

The possible modulation of the sigma-1 receptor by DMT shows that other mechanisms of action that are not dependent of the 5-$HT_{1A/2A/2C}$ receptors may also be involved in the therapeutic action of classic hallucinogens. For instance, harmine, THH and harmaline reversibly inhibit MAO-A [Buckholtz and Boggan, 1977; McKenna *et al.* 1984; Ott, 1994, 1999, 2004; Riba *et al.* 2001, 2003; McKenna and Riba, 2016], and reversible inhibitors of MAO-A (RIMAs) are clinically used as anxiolytic and antidepressant drugs [Yamada and Yasuhara, 2004; Nutt, 2005]. Moreover, rodent studies show that the antidepressive effects of harmine are associated with increases in BDNF levels [Fortunato *et al.* 2009; 2010a; 2010b].

Neural oxidative stress and subsequent neuroinflammation are associated with psychiatric disorders such as depression [Réus *et al.* 2015], and several preclinical studies show that harmine and harmaline have antioxidant and neuroprotective effects that seem to be mediated by MAO inhibition [Maher and Davis, 1996; Biradar *et al.* 2013], regulation of the dual specificity tyrosine-phosphorylation-regulated kinase DYRK1A [Frost *et al.* 2011], modulation of dopaminergic [Lee *et al.* 2000; Schwarz *et al.* 2003], cholinergic [Biradar *et al.* 2013], and glutamatergic [Maher and Davis, 1996; Li *et al.* 2011; Sun *et al.* 2014] pathways, interaction with voltage-gated membrane channels [Splettstoesser *et al.* 2005], and regulation of cell-energy homeostasis, mitochondrial functions, and oxygen free radical scavenging [Moura *et al.* 2007; Réus *et al.* 2010, 2012; Abelaira *et al.* 2013]. Furthermore, harmine also has anti-inflammatory properties that seem to be mediated at least in part by DYRK1A [Khor *et al.* 2015].

The antiaddictive effects of ayahuasca, psilocybin and LSD could also be related to the activation of

the dopaminergic system. For instance, preclinical studies show that LSD [Nichols, 2004; Passie *et al.* 2008; Hintzen and Passie, 2010], psilocybin [Tylš *et al.* 2014; Sakashita *et al.* 2015], and ayahuasca [de Castro-Neto *et al.* 2013] may indirectly stimulate dopaminergic pathways, probably through 5-HT_{2A}-receptor activation (LSD, psilocybin, and DMT) or MAO inhibition (β-carbolines). Moreover, acute psilocybin administration indirectly increased (through 5-$HT_{1A/2A}$ receptors) the release of dopamine in the ventral striatum in humans [Vollenweider *et al.* 1999]. Animal studies suggest that the antiaddictive potentials of harmine and harmaline appear to involve imidazoline, glutamate, and dopamine pathways [Glick *et al.* 1994; Iurlo *et al.* 2001; Aricioglu-Kartal *et al.* 2003; Schwarz *et al.* 2003; Brierley and Davidson, 2012, 2013; Owaisat *et al.* 2012].

Recent neuroimaging studies in humans suggest that the mood-enhancing properties of ayahuasca and psilocybin could be related to modifications in the activity of brain regions such as the amygdala and the anterior cingulate cortex (ACC), involved in emotional processing, and the default mode network (DMN), a group of brain regions associated with introspection and other internally focused functions [Riba *et al.* 2006; Araujo *et al.* 2012; Carhart-Harris *et al.* 2012a, 2014; Tagliazucchi *et al.* 2014; Bouso *et al.* 2015; Palhano-Fontes *et al.* 2015; Alonso *et al.* 2015; Kraehenmann *et al.* 2016; McKenna and Riba, 2016]. Psilocybin reduced amygdala reactivity, which correlated with increases in positive mood [Kraehenmann *et al.* 2016]. Increased activity of the DMN is associated with intensification of the self-reference process of rumination, which is an important depressive symptom, and acute administration of ayahuasca [Palhano-Fontes *et al.* 2015] and psilocybin [Carhart-Harris *et al.* 2012a] reduces brain activity in key regions of the DMN, such as the posterior cingulate cortex (PCC). Moreover, regular ayahuasca use is associated with cortical thinning in the PCC [Bouso *et al.* 2015].

Early human research with classical hallucinogens suggests that the therapeutic properties of these compounds are related at least in part to their effects on perceptions, emotions, and thoughts [Kurland *et al.* 1971; McGlothlin and Arnold, 1971; Grispoon and Bakalar, 1981; Riedlinger and Riedlinger, 1994; Abraham *et al.* 1996; Delgado and Moreno, 1998; Grob, 1998; Grof, 2001; Hofmann, 2005; Dyck, 2006; Hintzen and Passie, 2010; Vollenweider and Kometer, 2010; Bogenschutz and Pommy, 2012; Krebs and Johansen, 2012; Bogenschutz, 2013; Burdick and Adinoff, 2013; Baumeister *et al.* 2014; Liester, 2014; Oram, 2014; Majić *et al.* 2015; Bogenschutz and Johnson, 2016]. The subjective experience produced by these drugs would create a 'window of opportunity' in which changes in unhealthy thoughts, emotions, and behaviors could take place in a psychotherapeutic context [Kurland *et al.* 1971; McGlothlin and Arnold, 1971; Grispoon and Bakalar, 1981; Riedlinger and Riedlinger, 1994; Abraham *et al.* 1996; Delgado and Moreno, 1998; Grob, 1998; Grof, 2001; Hofmann, 2005; Dyck, 2006; Hintzen and Passie, 2010; Vollenweider and Kometer, 2010; Bogenschutz and Pommy, 2012; Krebs and Johansen, 2012; Bogenschutz, 2013; Burdick and Adinoff, 2013; Baumeister *et al.* 2014; Liester, 2014; Oram, 2014; Majić *et al.* 2015; Bogenschutz and Johnson, 2016]. Recent neuroimaging studies with ayahuasca and psilocybin seem to corroborate these early ideas by suggesting that the altered state of consciousness produced by these drugs would create a disruption or interruption of the repetitive, rigid, and pathological pattern of negative and compulsive thoughts present in anxiety and mood disorders and in drug dependence, contributing to mental flexibility and changes in perspective, values, and behavior [Carhart-Harris *et al.* 2012a, 2014; Tagliazucchi *et al.* 2014; Palhano-Fontes *et al.* 2015; McKenna and Riba, 2016].

Furthermore, the ability of classical hallucinogens to elicit religious, mystical, transcendent, or peak experiences has also been proposed as a possible psychological mechanism associated with the beneficial effects of these drugs [Kurland *et al.* 1971; McGlothlin and Arnold, 1971; Grispoon and Bakalar, 1981; Riedlinger and Riedlinger, 1994; Abraham *et al.* 1996; Delgado and Moreno, 1998; Grob, 1998; Grof, 2001; Hofmann, 2005; Dyck, 2006; Griffiths *et al.* 2006, 2008, 2011; Hintzen and Passie, 2010; Vollenweider and Kometer, 2010; MacLean *et al.* 2011; Bogenschutz and Pommy, 2012; Krebs and Johansen, 2012; Bogenschutz, 2013; Burdick and Adinoff, 2013; Baumeister *et al.* 2014; Liester, 2014; Oram, 2014; Majić *et al.* 2015; Bogenschutz and Johnson, 2016]. Indeed, recent studies in healthy individuals show that acute psilocybin administration induces highly meaningful and spiritually significant experiences with sustained positive

changes in attitudes, mood, personality, and behavior [Griffiths *et al.* 2006, 2008, 2011; MacLean *et al.* 2011]. Moreover, a secondary analysis of the data from the study of psilocybin and tobacco dependence reported that the mystical-type effects of psilocybin and their personal meaning, spiritual significance, and impact on well-being were correlated with improvements in smoking cessation [Garcia-Romeu *et al.* 2014; Johnson *et al.* 2014]. A qualitative follow-up assessment of the patients enrolled in the study of LSD-assisted psychotherapy for anxiety associated with a life-threatening disease also suggested that the intense emotional experiences with mystic-like features produced by LSD could mediate the observed long-term beneficial changes in perspectives, attitudes, values, and quality of life [Gasser *et al.* 2014, 2015].

Interestingly, these findings are consistent with studies that suggest that the dissociative, psychotomimetic, and mystical-type effects produced by the *N*-methyl-D-aspartate (NMDA) antagonist ketamine may mediate the anxiolytic [Kolp *et al.* 2007], antidepressive [Sos *et al.* 2013; Luckenbaugh *et al.* 2014], and antiaddictive [Krupitsky *et al.* 1992, 2002, 2007; Krupitsky and Grinenko, 1997; Jansen, 2001; Kolp *et al.* 2006; Krupitsky and Kolp, 2007; Dakwar *et al.* 2014a, 2014b] properties of this nonclassic hallucinogen. Moreover, some authors suggested that the temporary mental state produced by classic hallucinogens might induce profound long-term effects by producing an 'inverse post-traumatic stress disorder (PTSD)-like effect' in which a highly significant and positive experience would cause lasting beneficial changes, as opposed to chronic negative mood and other detrimental symptoms caused by a single traumatic event, which characterizes PTSD [MacLean *et al.* 2011; Young 2013; Garcia-Romeu *et al.* 2014].

Human hallucinogenic research performed in the 1960s and 1970s also suggests that the context and the psychotherapeutic approach used in combination with classic hallucinogens are also important components of the beneficial effects produced by these drugs [Kurland *et al.* 1971; McGlothlin and Arnold, 1971; Grispoon and Bakalar, 1981; Riedlinger and Riedlinger, 1994; Abraham *et al.* 1996; Delgado and Moreno, 1998; Grob, 1998; Grof, 2001; Hofmann, 2005; Dyck, 2006; Hintzen and Passie, 2010; Vollenweider and Kometer, 2010; Bogenschutz and Pommy, 2012; Krebs and Johansen, 2012; Bogenschutz, 2013; Burdick and Adinoff, 2013; Baumeister *et al.* 2014; Liester, 2014; Oram, 2014; Majić *et al.* 2015; Bogenschutz and Johnson, 2016]. The methodology of the clinical trials included in the present systematic review are very diverse regarding this topic: three studies assessed the effects of single-dose exposures without psychotherapeutic approaches [Moreno *et al.* 2006; Grob *et al.* 2011; Osório *et al.* 2015] and three trials included some form of psychological intervention over a few weeks [Gasser *et al.* 2014; Johnson *et al.* 2014; Bogenschutz *et al.* 2015]. The studies without psychotherapy suggest that biochemical mechanisms may be involved in the beneficial effects observed. On the other hand, the inclusion of psychological interventions in the other studies suggests that at least some part of the therapeutic results is related to nondrug factors. Placebo effects and enhanced suggestibility may also play a role as adjuncts in hallucinogen-assisted psychotherapy [Young, 2013; Carhart-Harris *et al.* 2015].

Future research should investigate the possible influence of different psychotherapeutic approaches or other nondrug factors – such as patient preparation before drug administration and integration of the drug session afterwards – in mediating the therapeutic properties of classic hallucinogens.

Safety

No serious adverse reactions were reported in any of the clinical trials reviewed in the present systematic review, suggesting that classic hallucinogens can be safely administered to patients suffering anxiety, depression, or drug dependence. Previous experimental studies of acute ayahuasca administration to healthy volunteers [Riba *et al.* 2001, 2003, 2006; dos Santos *et al.* 2011, 2012; de Araujo *et al.* 2012; Palhano-Fontes *et al.* 2015; McKenna and Riba, 2016] also suggest that this drug can be safely administered in controlled experimental settings. Observational studies of long-term ayahuasca consumers [Grob *et al.* 1996; Barbosa *et al.* 2005, 2009, 2012; da Silveira *et al.* 2005; Doering-Silveira *et al.* 2005; Halpern *et al.* 2008; Fábregas *et al.* 2010; Bouso *et al.* 2012, 2015; dos Santos, 2013] also suggest that this brew has a low toxicity profile when consumed in ritual contexts. Previous clinical research [Kurland *et al.* 1971; McGlothlin and Arnold, 1971; Grispoon and Bakalar, 1981; Strassman, 1984;

Riedlinger and Riedlinger, 1994; Grob, 1998; Grof, 2001; Passie *et al.* 2002, 2008; Hofmann, 2005; Dyck, 2006; Hintzen and Passie, 2010; Vollenweider and Kometer, 2010; Bogenschutz and Pommy, 2012; Krebs and Johansen, 2012; Bogenschutz, 2013; Liester, 2014; Smith *et al.* 2014; Tylš *et al.* 2014; Bogenschutz and Johnson, 2016] and recent observational studies [Krebs and Johansen, 2013; Hendricks *et al.* 2014, 2015; Johansen and Krebs, 2015], drug harm or risk assessments [Nutt *et al.* 2010; van Amsterdam *et al.* 2011, 2013, 2015; Morgan *et al.* 2013], and experimental studies with healthy volunteers [Vollenweider and Kometer, 2010; Carhart-Harris *et al.* 2012a, 2012b, 2013] also suggest that psilocybin and LSD can be safely administered in controlled settings.

Limitations

A main limitation of the present systematic review is the inclusion of a small number of studies (six) with small sample sizes (6–15 volunteers), which limits the generalization of the reported results. Included studies also show a high degree of heterogeneity, and three of the selected citations did not include placebo or a control group (open-label, proof-of-concept studies). Another important limitation is the difficulty in disentangling placebo effects, drug effects, and the influence of the psychological intervention included in the clinical trial.

However, despite these important limitations, results consistently showed that ayahuasca, psilocybin, and LSD produced anxiolytic, antidepressive, and antiaddictive effects in patients, and these results were also observed in animal studies and with healthy volunteers. Given the low success rates of current pharmacological and non-pharmacological treatments for drug dependence and anxiety and mood disorders, and considering the high morbidity and mortality associated with these disorders, it is necessary to perform more studies with these drugs, even if only a small portion of patients may reduce their suffering with these drugs. Future studies should include more patients, placebo or active placebo, randomized and double-blind designs, and multiple doses during treatment. Moreover, the influence of psychological interventions and the possible increases in therapeutic efficacy proportionated by these psychotherapeutic approaches should be better explored.

Conclusion

Currently available pharmacological treatments for drug dependence and anxiety and mood disorders have limited efficacy and often produce important adverse reactions that may limit treatment continuation. Classic tryptamine hallucinogens such as ayahuasca/DMT, psilocybin, and LSD are safely administered in controlled settings and several basic, experimental, and clinical studies suggest that these drugs have anxiolytic, antidepressive, and antiaddictive effects. Such beneficial properties seem to be mediated by an agonist action of these compounds on 5-$HT_{1A/2A/2C}$ receptors, which are involved in emotional processing, regulation of neurotrophic factors, anti-inflammatory actions, and modulation of frontal and medial brain structures. Other mechanisms of action not related to serotonergic receptors, such as regulation of cell energy homeostasis, mitochondrial functions, and oxidative stress, also appear to mediate these therapeutic effects.

The reviewed studies suggest that the therapeutic use of classic hallucinogens may offer to some patients fast-acting and prolonged beneficial effects after a single dose, producing few adverse effects. Indeed, interest in the medicinal uses of this class of drugs is increasing: new clinical trials investigating the effects of psilocybin in the treatment of alcoholism, cocaine dependence, tobacco dependence, and anxiety and depression associated with cancer are currently underway [ClinicalTrials.gov identifiers: NCT02061293, NCT02037126, NCT01943994, NCT00957359, NCT00465595]. Moreover, our group recently replicated the results of the original open-label, proof-of-concept study [Osório *et al.* 2015] but including an increased sample size (n =17) and single-photon emission computed tomography (SPECT), showing that ayahuasca antidepressive properties may be associated with increased blood perfusion in brain areas related to depressive symptoms (Sanches *et al.* 2016 "This reference was not included in the review because it was not published at the time of the electronic search"). Our group is currently performing randomized, double blind, placebo-controlled studies assessing the antidepressive and anxiolytic potentials of ayahuasca [Frood, 2015].

Further studies are urgently needed to better understand the effects of classical tryptamine hallucinogens in psychiatric disorders.

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Conflict of interest statement

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