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REVIEW

Efficacy, tolerability, and safety of serotonergic psychedelics for the management of mood, anxiety, and substance-use disorders: a systematic review of systematic reviews

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ABSTRACT

Introduction: Mood, anxiety, and substance-use disorders are among the most prevalent psychiatric disorders in the population. Although several pharmacological treatments are available, they are not effective for a significant proportion of patients and are associated with several adverse reactions. Therefore, new treatments should be explored. Recent studies suggest that serotonergic hallucinogens/psychedelics including ayahuasca, psilocybin, and lysergic acid diethylamide (LSD) have anxiolytic, antidepressive, and antiaddictive effects.

Areas Covered: A systematic review of systematic reviews assessing the efficacy, safety, and tolerability of serotonergic hallucinogens/psychedelic was performed using the PubMed data base until 11 April 2018. Systematic reviews with or without meta-analysis were analyzed, but only reviews that described at least one randomized controlled trial (RCT) were included.

Expert Commentary: Psilocybin and LSD reduced anxiety and depression in cancer patients and symptoms of alcohol and tobacco dependence, and ayahuasca reduced depression symptoms in treatment-resistant depression. Although the results are promising, several studies were open label, and only few were RCTs, and most had small sample sizes and a short duration. Single or few doses of these drugs seem to be well tolerated, but long-term studies are lacking. New RCTs with bigger samples and longer duration are needed to replicate these findings.

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5-HT_{2A} receptor; anxiety disorders; ayahuasca; dimethyltryptamine; lysergic acid diethylamide; mood disorders; psilocybin; substance-use disorders

1. Introduction

Mental and substance-use disorders are the fifth cause of global Disability-Adjusted Life Years (DALYs), being the leading cause of Years Lived with Disability (YLDs) worldwide. These figures correspond to 7.4% of the global DALYs, or 183.9 million DALYs. From these figures, depressive disorders accounted for 40.5% of DALYs, anxiety disorders for 14.6% (11.2–18.4), illicit drug use disorders for 10.9%, and alcohol-use disorders for 9.6% [1]. However, the available medications traditionally used to treat mental health problems are not effective for a significant proportion of patients, and many of them may induce significant adverse reactions, and in the last 40 years few novel treatments have been developed [2]. Thus, more effective and less toxic drug treatments are needed. In this context, some researchers argue that psychedelics, or serotoninergic hallucinogens, could be new psychopharmacological therapies for psychiatric and mental health disorders [3,4].

Psychedelics are experiencing a renewed interest in several disciplines in the mental health field in studies that go from understanding its neurobiological basis [5,6], to researching its psychotherapeutic potential [7], as well as the eventual neurobiological mechanisms underlying their therapeutic effects [8]. Specifically, in the field of psychology, psychedelics seem to induce positive long-term changes in personality and mood, an effect that seems to be on the basis of their therapeutic potential [9–11]. At the same time, there are evidences to considerer that psychedelics might have a beneficial effect on memory and cognitive deficits, which can open new avenues for the treatment of neurodegenerative diseases, although clinical trials are still needed [12,13]. As happens in the field of psychiatry, drug treatments in the field of neurodegenerative disorders are also experiencing a crisis, where there is a deficit of novel and effective treatments, and where the pharmaceutical industry is also withdrawing research [14].

Psychedelics, or serotoninergic hallucinogens, include substances such as LSD (lysergic acid diethylamide), psilocybin, DMT (*N,N*-dimethyltryptamine), ayahuasca (a DMT containing concoction originally from the Amazonia cultures), or mescaline. The mind-altering effects of psychedelics are due to their agonist action on 5-HT_{2A} receptors [6,15]. All serotonergic psychedelics primarily interact with this receptor [16], and the activation of this receptor induces glutamate release, increasing electrical activity at the cortex and thus increasing information processing [17]. These drugs seem to disrupt neural hierarchies, reducing top-down control and increasing bottom-up information transfer, possibly rendering the human brain more flexible/plastic [18]. At the molecular level, psychedelics stimulate c-fos expression in the medial prefrontal and anterior cingulate cortices and increase the expression of brain-derived neurotrophic factor (BDNF) in the prefrontal

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cortex, which suggests increased neuroplasticity [19]. Other evidence suggesting increased neuroplasticity by psychedelics include activation of frontal brain areas (hyperfrontality) [20–22], reduced activity of the default mode network (DMN) [23–26], and enhanced functional connectivity between normally distinct networks and brain areas [27–29].

Functionally, psychedelics reduce the amygdala response to threat [30,31] and modulate the connectivity between the amygdala, the striatum, and the frontal cortex in tasks of face discrimination [32], improving emotion processing and increasing positive mood and emotional empathy [33,34]. At the phenomenological level, psychedelics modify scores of perception, cognition, volition, affect and emotion, and interoception [35–37], and also induce mystical type experiences [38–40]. These effects are often associated with improved mood and could be mediated by 'ego dissolutive' experiences induced by these drugs (reflected in the measures 'oceanic boundlessness' and 'visionary restructuralization' factors [40,41]).

All these specific effects of psychedelics on the modulation of psychological and affective states coming from experimental research are in agreement with the preliminary results that clinicians are obtaining in the clinical trials where psychedelics are being investigated for the treatment of mood, anxiety, and addictive disorders. However, the excitement about these drugs should be tempered with hard evidence of efficacy and safety. Thus, to try to summarize the most compelling evidence from clinical research with these drugs, we performed a systematic review of systematic reviews where efficacy, tolerability, and safety of serotonergic psychedelics have been assessed regarding the management of mood, anxiety, and substance-use disorders.

2. Material and methods

Data for this review were collected in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA) [42] and a guide to identify and appraise systematic reviews systematically [43].

2.1. Search strategy

Electronic search was performed using the PubMed database. The following search terms were used: (lysergic acid diethylamide OR mescaline OR dimethyltryptamine OR psilocybin OR ayahuasca) AND (systematic review OR meta-analysis). All studies published until 11 April 2018 were included, without any language restriction. Additionally, the reference lists of all included studies identified in the database search were manually screened for relevant studies.

2.2. Selection criteria and study selection

Systematic reviews (with or without meta-analysis) of randomized controlled trials (RCTs) evaluating the safety, tolerability, and efficacy of serotonergic psychedelics for the treatment of mood, anxiety, or substance-use disorders were included. Systematic reviews (with or without meta-analysis) of observational studies assessing adverse reactions related to psychedelic drug use were also included. Systematic reviews not focused on the above-mentioned topics, published as abstracts only, and with less than one RCT were excluded.

After inspection for duplicates, the titles and abstracts of all records were reviewed. Publications that did not meet inclusion criteria after examination of titles and abstracts were excluded. The decision for inclusion or exclusion of the remaining publications was made based on the review of the full texts. All studies were screened by two independent reviewers (RGDS, JCB). In case of disagreement, reviewers discussed their reasons for initial inclusion and exclusion, and if consensus was not reached, a third reviewer (JECH) was included.

2.3. Recorded variables, data extraction, and analysis

Recorded variables included authors, year of publication, type of systematic review (RCTs, observational studies, or mixed), number of studies, number of patients (randomized in RCTs, or as reported on observational studies), specific disorder (mood, anxiety, or substance-use disorders), hallucinogenic/psychedelic drug (types), risk of bias found and other quality characteristics (see below), and main findings (positive/therapeutic effects, or negative/adverse reactions). In systematic reviews with meta-analysis, results were reported using odds ratios (OR), heterogeneity (I^2), and statistical significance (p value). In descriptive systematic reviews (without meta-analysis) and for adverse reactions, the main results are presented.

Risk of bias and methodological quality of systematic reviews was evaluated by two independent reviewers (RGS, JCB) – with disagreement being resolved by consensus or by a third reviewer (JECH) – using the six-item modified version of the Assessment of the Methodological Quality of Systematic Reviews (AMSTAR) [44,45].

3. Results

3.1. Study selection

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

The search of the literature yielded 531 separate references that were reviewed for abstract screening. Following this, 14 potentially relevant references were identified. Full-text reports of these citations were obtained for more detailed evaluation. Following detailed examination of the reports, 10 citations were included. Four citations were excluded because they did not cite any RCT [46–49]. Handsearching the bibliography of the selected citations did not increase the number of included references. Thus, 10 citations were included in the systematic review.

The studies included comprised one meta-analysis [50] and nine descriptive systematic reviews [5,7,9,51–56]. The meta-analysis evaluated specifically the effect of LSD [50], five of the descriptive systematic reviews evaluated the effects of serotonergic psychedelics in general [5,7,9,55,56], and four of the descriptive systematic reviews assessed specifically the effects of ayahuasca [51–54].

Most reviews focused on assessing (i) therapeutic effects (mood, anxiety, and substance-use disorders) [7,50,54–56];

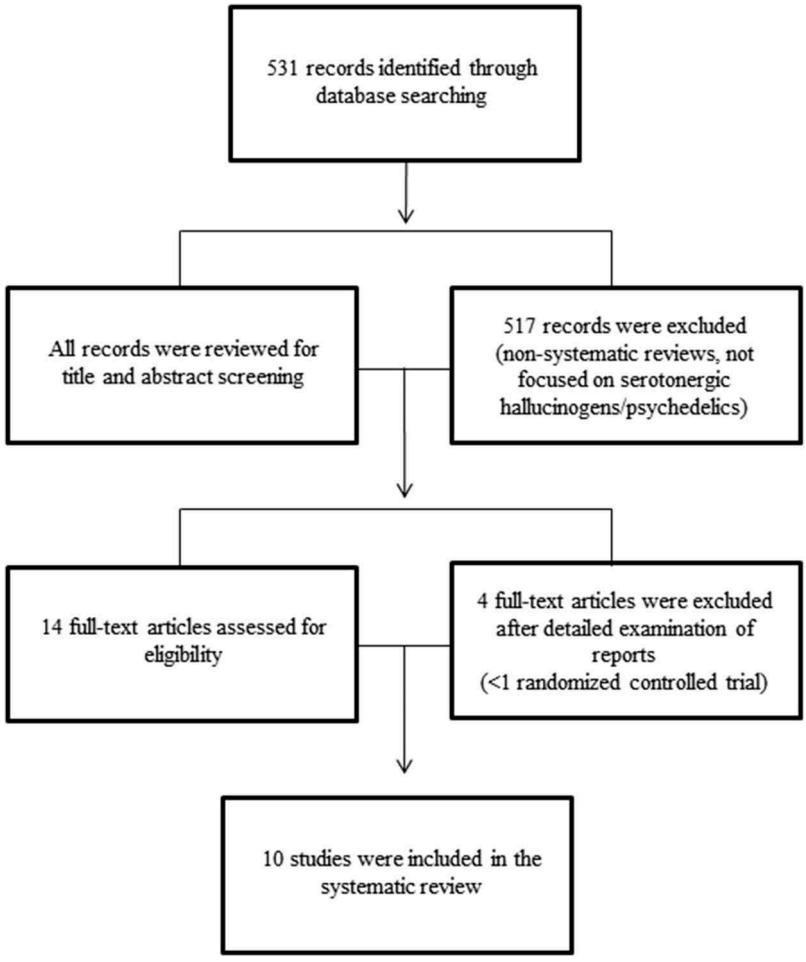

Figure 1. Flow diagram illustrating the different phases of the systematic review.

(ii) acute physiological (autonomic, neuroendocrine effects, etc.), psychological (subjective and cognitive effects, personality, etc.), and neurophysiological (neuroimaging) effects [5,9,51–53]; and (iii) long-term safety (mental health) [52,53]. Two descriptive systematic reviews focused specifically on adverse effects associated with ayahuasca and its alkaloids [51–53].

The main characteristics and results of each citation are presented in Table 1.

3.2. Overview of the results

Although the number of included reviews is small, most of them (9 in 10) consist of descriptive systematic reviews including few RCTs with small sample sizes, and also considering the observational design of several reviews, the observed results suggest that administration of single doses of serotonergic hallucinogens/psychedelics to both healthy volunteers and patients is safe and is associated with antidepressive and anxiolytic effects, with less consistent results (lack of RCTs) regarding substance-use disorders. Moreover, the results also suggest that these compounds act differently from traditional antidepressive and anxiolytic drugs both in their mechanism of action and in their therapeutic efficacy: these drugs act as agonists/partial agonists on 5-HT_{2A} receptors expressed in brains regions related to emotional processing, mood regulation, introspection, and self- and body-consciousness, and single doses of these substances are associated with rapid and persistent therapeutic effects, which can last for several weeks/months.

Further, observational studies suggest that although recreational use of hallucinogens/psychedelics such as LSD and psilocybin is associated with adverse reactions with anxiety- and psychotic-like features, these reactions are more common in the recreational context. In experimental and clinical settings, these reactions are less common and receive an appropriate approach (usually without the need of psychiatric drugs). Moreover, long-term ritual consumption of the natural hallucinogen/psychedelic ayahuasca is not consistently associated with significant increases in mental health problems.

All these results will be discussed in detail below.

3.3. Therapeutic effects

Table 2 shows the therapeutic indications with the most robust evidence of efficacy until the moment of preparation of this manuscript (May 2018). Results are described in detail below for anxiolytic, antidepressive, and antiaddictive effects of DMT, ayahuasca, psilocybin, and LSD.

Table 1. Characteristics and main results of included systematic reviews.

Systematic review	Type	Core topic	Subgroup	Number of studies/RCTs	Number of patients/ cases	Meta-analysis	Modified AMSTAR score[1]	Main findings	Limitations
Gable, 2007 [51]	Mixed[2]	Ayahuasca/DMT/β-carboline toxicity	Experimental studies of ayahuasca administration and observational studies of ayahuasca users	~140[3] RCTs: 1	(see text)	No	3	Animal studies suggest DMT and the β-carbolines have low toxicity Adverse effects related to ritual ayahuasca intake are uncommon and include the following: risk of interactions with serotonergic drugs (serotonin syndrome), transient anxiety/psychotic episodes, and prolonged psychotic reactions (rare) Ayahuasca/oral DMT have a low abuse potential	Studies conducted from 1969 to 2005 Lack of basic studies on the toxicity and abuse potential of ayahuasca Only one RCT (multiple IV doses of DMT or placebo to healthy volunteers)
Barbosa et al., 2012 [52]	Mixed[2]	Subacute and prolonged effects of ayahuasca on mental and physical health of ayahuasca users	Experimental studies of ayahuasca administration and observational studies of ayahuasca users	15 RCTs: 1	437	No	3	Ritual ayahuasca intake (subacute and long-term effects) is not associated with increases in psychiatric symptoms or disorders or cognitive deficits Ritual ayahuasca intake (subacute and long-term effects) is associated with improvements on personality traits, psychosocial status and well-being, and mood, anxiety, and substance-use disorders	Studies conducted from 1953 to 2010 Most citations are observational and/or retrospective studies conducted among ayahuasca ritual users, which could be biased toward a beneficial representation of ayahuasca Only one RCT (single oral ayahuasca dose or placebo to healthy volunteers)
Krebs and Johansen, 2012 [50]	RCTs	LSD in the treatment of alcoholism	Alcoholic patients	6	536	Yes	5	*Overall impression* In alcoholic patients, single-dose LSD was significantly associated with decreases in alcohol misuse and increases in alcohol abstinence In controlled settings, LSD was well tolerated *Quantitative results* Alcohol misuse Pooled OR (favoring LSD): First follow-up (1–3 months, $n = 6$): 1.96 (95% CI, 1.36–2.84; $p = 0.0003$) Short-term follow-up (2–3 months, $n = 3$): 1.85 (95% CI, 1.14–3.00; $p = 0.01$). Medium-term follow-up (6 months, $n = 5$): 1.66 (95% CI, 1.11–2.47; $p = 0.01$) Long-term follow-up (12 months, $n = 4$): 1.19 (95% CI, 0.74–1.90; $p = 0.47$) Pooled benefit difference (favoring LSD, $n = 5$): 16% (95% CI, 8%–25%; $p = 0.0003$) NNT = 6 I^2[b]: First, short-, and medium-term follow-ups (pooled): 0% ($p \geq 0.60$) Long-term follow-up: 15% ($p = 0.32$) Alcohol abstinence Pooled OR (favoring LSD, $n = 3$): First follow-up: 2.07; 95% CI, 1.26–3.42; $p = 0.004$) Short-term follow-up: 1.80; 95% CI, 1.07–3.04; $p = 0.03$), Medium-term follow-up: 1.42; 95% CI, 0.65–3.10; $p = 0.38$) I^2: First and short-term follow-ups (pooled): 0% ($p \geq 0.38$) Long-term follow-up: 44% ($p = 0.41$)	Studies conducted from 1966 to 1970 Small number of RCTs Differences regarding therapeutic interventions and LSD dose Overrepresentation of males Varied levels of risk of bias

(*Continued*)

Table 1. (Continued).

Systematic review	Type	Core topic	Subgroup	Number of studies/RCTs	Number of patients/ cases	Meta-analysis	Modified AMSTAR score[1]	Main findings	Limitations
Dos Santos et al., 2016 [5]	RCTs/ NRTs	Effects of psychedelics on neuroimaging	Experimental studies of psychedelic-drug administration on humans	25 RCTs: 5	222	No	5	*Acute effects* The effects of serotonergic hallucinogens/ psychedelics on perception, mood, and emotion was significant associated with increased activation of frontal, temporal, parietal, and occipital cortices, and decreased activation on the DMN Significant increases in blood perfusion on the Nac, insula, and SGA were observed in an open-label study involving administration of a single ayahuasca dose to patients diagnosed with treatment-resistant MDD In controlled settings, psilocybin, LSD, and ayahuasca were well tolerated *Long-term effects* Long-term ritual use of ayahuasca was significantly associated with cortical thinning of the PCC and thickening of the ACC, but there was no evidence of increases in psychiatric symptoms/disorders or cognitive deficits Long-term use of serotonergic hallucinogens/ psychedelics was significantly associated with decreased neocortical 5-HT_{2A} receptor binding	Small number of RCTs Sample sizes in most studies is small Lack of studies with adolescents Overrepresentation of males Few studies with long-term follow-up
Dos Santos et al., 2016 [53]	Mixed[2]	Effects of ayahuasca on psychiatric symptoms, cognition, and neuroimaging	Experimental studies of ayahuasca administration and observational studies of ayahuasca users	28 RCTs: 6	1529	No	5	Uncontrolled and controlled studies of acute administration of a single ayahuasca dose (or two consecutive doses) to healthy volunteers suggests a good safety and tolerability profile regarding subjective effects, psychological/psychiatric status, and cognitive functions Ritual ayahuasca intake (subacute and long-term effects) is not associated with increases in psychiatric symptoms or disorders or cognitive deficits Ritual ayahuasca intake (subacute and long-term effects) is associated with improvements on personality traits, psychosocial status, and well-being, and mood, anxiety, and substance-use disorders Open-label administration of a single ayahuasca dose to patients diagnosed with treatment-resistant MDD was safe and associated with enduring (21 days) significant antidepressive and anxiolytic effects Neuroimaging studies showed that the effects of ayahuasca are associated with modulation of brain areas involved in emotional processing, interoception, memory, and self-consciousness (Nac, insula, SGA, DMN) Long-term ritual use of ayahuasca was significantly associated with cortical thinning of the PCC and thickening of the ACC, but there was no evidence of increases in psychiatric symptoms/disorders or cognitive deficits	Several citations are observational and/or retrospective studies conducted among ayahuasca ritual users, which could be biased towards a beneficial representation of ayahuasca Small number of RCTs Sample sizes in most studies is small Few studies with adolescents Few neuroimaging studies Varied levels of risk of bias

(*Continued*)

Table 1. (Continued).

Systematic review	Type	Core topic	Subgroup	Number of studies/RCTs	Number of patients/ cases	Meta-analysis	Modified AMSTAR score[1]	Main findings	Limitations
Dos Santos et al., 2016 [54]	Mixed[2]	Antidepressive and anxiolytic effects of ayahuasca and its alkaloids	Experimental studies of ayahuasca administration and observational studies of ayahuasca users	21 RCTs: 2	287	No	5	*Animal studies* Evidence of anxiolytic effects of harmaline and antidepressive effects of harmine and ayahuasca *Human studies* Experimental evidence (RCT) of relaxation and increased positive mood after DMT administration Observational and clinical (open-label) evidence of antidepressive and anxiolytic effects of ayahuasca In controlled settings (ritual and clinical), ayahuasca intake seem to be well tolerated	No animal studies with DMT and only one with harmaline Only one RCT (multiple IV doses of DMT or placebo to healthy volunteers) Sample sizes in most studies is small Most human studies (7 in 11) are observational and/or retrospective studies conducted among ayahuasca ritual users, which could be biased toward a beneficial representation of ayahuasca
Dos Santos et al., 2016 [55]	RCTs/ NRTs	Antidepressive, anxiolytic, and antiaddictive effects of ayahuasca, psilocybin, and LSD	Patients with mood, anxiety, or substance-use disorders	6 RCTs: 3	54	No	5	Administration of a single dose (or few doses) of psilocybin was significantly associated with beneficial effects in patients diagnosed with OCD, anxiety associated with advanced-stage cancer, and tobacco and alcohol dependence (50% open-label studies) Administration of a single dose of LSD was significantly associated with anxiolytic effects in patients diagnosed with anxiety associated with life-threatening diseases (RCT) Administration of a single dose of ayahuasca was significantly associated with antidepressive and anxiolytic effects in patients diagnosed with treatment-resistant MDD (open-label) In controlled settings, psilocybin, LSD, and ayahuasca were well tolerated	Small number of RCTs (50% open-label studies) Sample sizes in most studies is small (smallest total sample of the review: $n = 54$) No studies with adolescents Overrepresentation of males Few studies with long-term follow-up Differences regarding therapeutic interventions and drug dose
Rucker et al., 2016 [7]	RCTs/ NRTs	Psychedelics in the treatment of unipolar mood disorders	Experimental studies of psychedelic-drug administration	21 RCTs: 1	423	No	4	Combined results of 19 trials showed a clinician-judged improvement of 79.2% (range 40–95%) in patients treated with LSD or mescaline In controlled settings, LSD and mescaline were well tolerated	Studies conducted from 1949 to 1973 Lack of studies with psilocybin Differences in the definitions of UMDs and "improvements" Inclusion of patients with other disorders Absence of a control group in most studies Only one RCT (multiple oral doses of LSD or placebo to patients with "severe chronic neuroses") Sample sizes in most studies is small Differences regarding therapeutic interventions and drug doses Varied levels of risk of bias

(*Continued*)

Table 1. (Continued).

Systematic review	Type	Core topic	Subgroup	Number of studies/RCTs	Number of patients/ cases	Meta-analysis	Modified AMSTAR score[1]	Main findings	Limitations
Bouso et al., 2018 [9]	Mixed[2]	Effects of psychedelics on personality	Experimental studies of psychedelic-drug administration and observational studies of psychedelic drug users	18[4] RCTs: 10	9786	No	5	*Acute/subacute effects* Administration of single doses of psilocybin and LSD to healthy volunteers was significantly associated with acute and enduring (weeks/months) increases in openness Some personality traits, such as neuroticism, sociability, experience/sensation seeking, disinhibition, absorption, and self-transcendence, seem to influence the effects of hallucinogens/ psychedelics In controlled settings, psilocybin and LSD were well tolerated *Long-term effects* Observational evidence that ritual ayahuasca use was associated with significant and positive personality changes (Harm Avoidance, Reward Dependence, Novelty Seeking, and Self-Transcendence) that were related to anxiolytic, antidepressive, and antiaddictive effects Long-term consumption of ayahuasca in ritual contexts was not associated with personality disorders	Several citations are observational and/or retrospective studies conducted among ayahuasca ritual users, which could be biased towards a beneficial representation of ayahuasca Sample sizes in most studies is small Differences regarding personality measures and drug doses Some studies included poly-drug users Inconsistent long-term changes in personality after in controlled settings Few studies with long-term follow-up
Reiche et al., 2018 [56]	RCTs	Anxiolytic and antidepressant effects of psychedelics in patients suffering with life-threatening diseases	Experimental studies of psychedelic-drug administration	11 RCTs: 4	445	No	4	Uncontrolled and controlled studies of acute administration of a single dose of LSD or DPT to patients suffering with life-threatening diseases showed significant antidepressive and anxiolytic effects, improvements in quality of life, and reduced fear of death All RCTs were recently performed (2011–2018) and replicated the results from previous studies with improved methodology	Studies conducted from 1964 to 1980 were all open-label (n = 7), with differences regarding therapeutic interventions and drug doses, and with varied levels of risk of bias Small number of RCTs

[1]Possible scores range from 0 to 6, with higher scores representing lower risk of bias.
[2]Observational studies and RCTs.
[3]As reported by the author. Includes preclinical, observational, and experimental studies.
[4]As reported by the authors. Included a study reporting the pooled data of 23 placebo-controlled experimental studies with healthy volunteers (n = 261).
ACC: anterior cingulate cortex; DMN: default mode network; DMT: dimethyltryptamine; DPT: dipropyltryptamine; I^2: heterogeneity; IV: intravenous; LSD: lysergic acid diethylamide; MDD: major depressive disorder; Nac: nucleus accumbens; NNT: number needed to treat; NRT: non-randomized trial; OCD: obsessive-compulsive disorder; OR: odds ratio; PCC: posterior cingulate cortex; RCT: randomized controlled trial; SGA: subgenual area; UMD: unipolar mood disorder.

Table 2. Main therapeutic indications found in the systematic reviews and level of evidence.

Therapeutic effect	Drug	Level of evidence	Justification
Anxiolytic	DMT[1]	Low	Experimental evidence (one open-label trial and one RCT in healthy volunteers)
	Ayahuasca	Moderate	Preclinical (animal models), observational (ritual use), experimental (one RCT in healthy volunteers), and clinical (one open-label trial in patients with treatment-resistant MDD) evidence
	Psilocybin	Moderate/High	Clinical evidence (three RCTs in patients with advanced-stage cancer and nonmalignant life-threatening diseases)
	LSD	Moderate	Clinical evidence (two open-label trials and one RCT in patients with advanced-stage cancer and nonmalignant life-threatening diseases)
Antidepressive	DMT[2]	Low	Experimental evidence (one open-label trial in healthy volunteers)
	Ayahuasca	Moderate	Preclinical (animal models), observational (ritual use), experimental (one RCT in healthy volunteers), and clinical (one open-label trial in patients with treatment-resistant MDD) evidence
	Psilocybin	Moderate/High	Clinical evidence (three RCTs in patients with advanced-stage cancer and nonmalignant life-threatening diseases)
	LSD	Moderate	Clinical evidence (four open-label trials and one RCT in patients with advanced-stage cancer and nonmalignant life-threatening diseases)
Antiaddictive	Ayahuasca	Low	Observational evidence (ritual use)
	Psilocybin	Low/Moderate	Clinical evidence (two open-label trials: one with tobacco dependence and another with alcohol dependence)
	LSD	Moderate/High	Clinical evidence (six RCTs in patients with alcohol dependence)
Other effects	Ayahuasca (improvements in personality traits)	Low-Low/Moderate-Low	Observational evidence (ritual use)
	Psilocybin (improvements in personality traits; OCD)		Experimental (personality, healthy volunteers) and clinical (one RCT with patients with OCD) evidence
	LSD (improvements in personality traits)		Experimental evidence (personality, healthy volunteers)

[1]Pure, intravenous.
[2]Pure, smoked.
DMT: dimethyltryptamine; LSD: lysergic acid diethylamide; MDD: major depressive disorder; OCD: obsessive-compulsive disorder; RCT: randomized controlled trial.

3.3.1. Anxiolytic effects

3.3.1.1. DMT. Evidence of relaxant effects from one open-label (n = 15 [57], extracted from [54]) and one RCT of intravenous DMT administration to healthy volunteers (n = 15 [58], extracted from [54]).

3.3.1.2. Ayahuasca. Preclinical studies show that ayahuasca and its alkaloids have anxiolytic properties [54]. Observational studies of ritual ayahuasca intake suggest that participation on these rituals is associated with remission of anxiety disorders [52–54]. One RCT with healthy experienced ayahuasca users (n = 9) [53,54,59] and one open-label clinical trial with patients with treatment-resistant major depressive disorder (n = 17) [60,61] extracted from [53,55]) showed evidence of anxiolytic effects of a single ayahuasca dose.

3.3.1.3. Psilocybin. Evidence from three RCTs (n = 92 [62–64], extracted from [55,56]) showed that psilocybin reduced the anxiety of patients with advanced-stage cancer and non-malignant life-threatening diseases.

3.3.1.4. LSD. Evidence from open-label studies (n = 53 [65,66], extracted from [56]) and one RCT (n = 12 [67,68], extracted from [55,56]) showed anxiolytic effects of LSD in patients with anxiety associated with advanced-stage cancer and nonmalignant life-threatening diseases.

3.3.2. Antidepressive effects

3.3.2.1. DMT. Evidence of increased positive mood from one open-label study with smoked DMT in healthy volunteers (n = 6 [69], extracted from [54]).

3.3.2.2. Ayahuasca. As with anxiolytic effects, preclinical evidence suggests that ayahuasca and its alkaloids have antidepressive properties [54], and observational studies of ritual ayahuasca intake report remission of mood disorders [52–54]. One RCT with healthy experienced ayahuasca users (n = 9) [59], extracted from [53,54]) and one open-label clinical trial with patients with treatment-resistant major depressive disorder (n = 17) [60,61], extracted from [53,55]) showed evidence of antidepressive effects of a single ayahuasca dose.

3.3.2.3. Psilocybin. Evidence from three RCTs (n = 92 [62–64], extracted from [55,56]) of antidepressive effects of psilocybin in patients with depressive symptoms associated with advanced-stage cancer and nonmalignant life-threatening diseases.

3.3.2.4. LSD. Evidence from open-label studies (n = 261 [65,66,70,71], extracted from [56]) and one RCT (n = 12 [67,68], extracted from [55,56]) showed mood improvements associated with LSD intake in patients with advanced-stage cancer and non malignant life-threatening diseases.

3.3.3. Antiaddictive effects

3.3.3.1. Ayahuasca. Observational studies of ritual ayahuasca intake report remission of substance-use disorders [52,53].

3.3.3.2. Psilocybin. Evidence from two open-label studies showed improvements in symptoms of tobacco (n = 15 [72], extracted from [55]) and alcohol (n = 10 [73], extracted from [55]) dependence with administration of two psilocybin doses.

3.3.3.3. LSD. Evidence from a meta-analysis of six RCTs (n = 536 [50]) shows that single-dose LSD was associated with decreases in alcohol misuse and increases in alcohol abstinence in alcoholic patients.

3.3.4. Other therapeutic effects

A double-blind, randomized, dose-escalation study with nine patients with obsessive-compulsive disorder showed that psilocybin significantly reduced their symptoms ([74], extracted form [54]). Acute administration of serotonergic psychedelics and long-term ritual ayahuasca use were associated with positive effects on personality measures [15].

3.4. Safety and tolerability

3.4.1. Ritual context

Descriptive systematic reviews reported that observational studies of long-term ritual ayahuasca use is not associated with increased psychiatric symptoms or disorders (including personality and substance-use disorders) or deficits in neuropsychological functioning [9,51–54]. In the ritual context, the most common adverse reactions seem to be nausea, gastrointestinal discomfort, vomiting, diarrhea, transient dysphoric reactions with anxiety- and psychotic-like features, and prolonged psychotic-like reactions (a rare reaction with low incidence but high morbidity) ([51,53] see also the systematic review by Dos Santos [48], which was not included in the present review because it did not report any RCT).

3.4.2. Experimental/clinical context

Experimental and clinical studies involving administration of single or few doses of serotonergic hallucinogens/psychedelics (DMT, ayahuasca, psilocybin, LSD) in controlled setting suggest that these drugs have a good safety and tolerability profile [5,7,9,50,53–56]. The most common adverse reactions observed in RCTs include transient dysphoric reactions with anxiety- and psychotic-like features. Prolonged psychotic-like reactions were not described in any of the RCTs performed in the last 25 years. In the specific case of ayahuasca, the adverse reactions also include those observed in the ritual context: nausea, gastrointestinal discomfort, vomiting, and diarrhea ([60,61], extracted from [5,52–55]).

3.5. Risk of bias and methodological quality assessment

Complete details of the risk of bias and methodological quality assessment are provided in Table 3.

The mean modified AMSTAR risk of bias score for all 10 systematic reviews was 4.4 (3 to 5). Overall, scores were moderate to high, with eight reviews showing a score >4 (six reviews scored 5, two scored 4, and other two scored 3). The most common reason for reduced scores was lack of quality assessment, observed in nine reviews. The other most common reasons were lack of a clear declaration of conflicts of interest (three reviews) and lack of/unclear information regarding the performance of study selection and data extraction by dual reviewers (three reviews).

It is important to note that at the time of preparation of the manuscript, one of the reviews was available only as an unedited manuscript accepted for publication [56]. In this specific case, we do not know if a clear declaration of conflicts of interest will be present in the final version of the manuscript.

Table 3. Quality assessments for the 10 selected systematic reviews.

	AMSTAR questions[1]						
Systematic review	1	2	3	4	5	6	Total score
Gable, 2007 [51]	0	1	1	0	1	0	3
Barbosa et al., 2012 [52]	0	1	1	0	1	0	3
Krebs and Johansen, 2012 [50]	1	1	1	1	1	0	5
Dos Santos et al., 2016 [5]	1	1	1	0	1	1	5
Dos Santos et al., 2016 [53]	1	1	1	0	1	1	5
Dos Santos et al., 2016 [54]	1	1	1	0	1	1	5
Dos Santos et al., 2016 [55]	1	1	1	0	1	1	5
Rucker et al., 2016 [7]	0	1	1	0	1	1	4
Bouso et al., 2018 [9]	1	1	1	0	1	1	5
Reiche et al., 2018[2] [56]	1	1	1	0	1	0	4
Mean quality	0.7	1	1	0.1	1	0.6	4.4

[1]The modified version of the AMSTAR score uses its six most relevant questions: *Question 1*: Were study selection and data extraction performed by dual reviewers? *Question 2*: Was the literature search comprehensive? *Question 3*: Were the included study characteristics described? *Question 4*: Was the quality of the included studies assessed and reported? *Question 5*: Were the methods used to combine results appropriate? *Question 6*: Were conflicts of interest reported?
Questions were scored as 1 (done appropriately) or 0 (unclear or not done) and summed to reach a total score where higher scores indicate lower risk of bias.
[2]Unedited manuscript accepted for publication.

4. Discussion

In the present systematic review, we analyzed 10 systematic reviews covering a wide variety of topics related to the efficacy, safety, and tolerability of classical or serotonergic hallucinogens/psychedelics in the treatment of anxiety, mood, and substance-use disorders. Broadly, these topics basically included therapeutic effects and acute and long-term safety. Overall, these systematic reviews suggest that these substances have anxiolytic, antidepressive, and antiaddictive properties, and a good safety and tolerability profile.

However, included studies comprised a single meta-analysis of the effects of LSD on alcoholic patients [50], and several studies described in the reviews were observational studies of ritual ayahuasca use or open-label studies with ayahuasca, LSD, or psilocybin involving few volunteers [5,7,9,52–55]. Moreover, the number of RCTs in most reviews was small (1 to 10), with three reviews reporting a single RCT [7,50,51], with two of these trials being performed with a small number of healthy volunteers (n = 15–22) [58,75].

Furthermore, not all drugs showed the same level of evidence. For instance, the higher level of evidence was found for the antiaddictive effects of LSD in patients with alcohol dependence (with six RCTs) and for the anxiolytic and antidepressive effects of psilocybin in patients with advanced-stage cancer and nonmalignant life-threatening diseases (with three RCTs), while evidence for the antidepressive effects of LSD was found in only one RCT in patients with advanced-

stage cancer and nonmalignant life-threatening diseases. However, studies with LSD and alcoholism were conducted from 1966 to 1970, while the psilocybin and LSD studies for existential anxiety and depression were performed from 2011 to 2016. This difference in time could induce bias regarding diagnosis criteria and the psychometric validity of the instruments used to measure the subjective/clinical outcomes in older LSD studies. Moreover, LSD studies had more heterogeneity regarding therapeutic techniques and drug doses. Therefore, although the literature on LSD was the only subjected to a meta-analysis and showed promising results, new RCTs are needed to replicate these findings.

In the case of psilocybin, the available evidence shows that this compound can be an effective treatment for patients with existential anxiety and depression. Indeed, a recent open-label study showed that a single dose of psilocybin induced rapid (1 week) and sustained (3 months) antidepressive and anxiolytic effects in 12 patients with unipolar treatment-resistant depression [76]. The next steps would be to perform RCTs for depressed patients and to compare psilocybin with other antidepressive/anxiolytic drugs. Indeed, new RCTs covering these topics are being planned or are already being conducted (ClinicalTrials.gov Identifier: NCT03181529, NCT03380442, NCT03429075).

Moreover, future studies should also compare different therapeutic interventions associated with the administration of psilocybin and other serotonergic hallucinogens/psychedelics, since it still not known neither if the therapeutic effects of these drugs are increased by the inclusion of psychotherapy nor which psychotherapeutic approach would be the most effective. This is especially relevant in the case of ayahuasca, since in the open-label study with 17 patients with treatment-resistant MDD, no psychotherapeutic intervention was used before, during, or after the experimental sessions, and the results were significant, rapid (hours/days), and sustained (21 days), and were also evident in changes in blood perfusion (SPECT) [60,61]. Furthermore, these results were recently replicated in a RCT with 29 patients with treatment-resistant MDD in which no psychotherapeutic intervention was used (different from the open-label study, a predefined music playlist was used in this RCT): compared with placebo, single-dose ayahuasca administration was associated with rapid (24 h) and sustained (7 days) significant antidepressant effects [77]. Thus, future studies should investigate the role of different psychotherapeutic techniques and music in the therapeutic effects of serotonergic hallucinogens/psychedelics.

Among the different therapeutic effects, the lowest level of evidence of efficacy was found for the antiaddictive properties of ayahuasca and psilocybin, where only observational (ayahuasca) and open-label (psilocybin) studies were described. In the case of ayahuasca, one systematic review reported evidence from animal studies that this complex mix of substances and its isolated alkaloids have antiaddictive effects in studies using drugs such as cocaine, amphetamine, and alcohol [47]. However, this descriptive review was excluded from the preset text because it did not report any RCT. Thus, the next step would be to perform such trial in patients with substance-use disorders. In the case of psilocybin, new RCTs are being planned or are already being conducted (ClinicalTrials.gov Identifier: NCT02037126, NCT02061293).

Some observational studies of ritual ayahuasca use and experimental studies with psilocybin and LSD with healthy volunteers showed positive and significative changes in personality measures [9]. In observational studies, these changes often paralleled the reports of therapeutic effects. For example, ritual ayahuasca users reported reductions in anxiety and depressive symptoms and in the use of drugs such as alcohol, tobacco, and psychostimulants, and also described reduced impulsivity and novelty seeking and increased spirituality. The experimental data with LSD and psilocybin reported increases in openness, but the evidence is mixed and inconsistent [11,78,79]. Therefore, the next step would be the performance of new RCTs to try to replicate these results.

Regarding adverse effects, three descriptive systematic reviews focused specifically on the adverse effects associated with ayahuasca and its alkaloids [51–53], and all showed observational, experimental, or clinical evidence of good safety and tolerability when used in controlled settings (ritual, experimental, or clinical). In fact, observational studies of ritual use showed the first evidence of possible anxiolytic, antidepressive, and antiaddictive effects of ayahuasca, which were subsequently observed both in animal models and in clinical trials [5,47,53–55]. A descriptive systematic review excluded from our analysis (because it did not report any RCT) reported three case series and two case reports describing psychotic episodes associated with ayahuasca intake and three case reports describing psychotic episodes associated with smoked DMT ([48]; also reported in [51]). Several reports described subjects with a personal and possibly a family history of psychotic disorders and/or concomitant use of other drugs. However, in experimental, open-label, and RCTs, the most common observed adverse reactions were transient and moderate increases in blood pressure and heart rate, nausea, gastrointestinal discomfort and vomiting, and less commonly transient anxiety- and psychotic-like reactions [24,60,61]. We are not aware of any controlled study of ayahuasca (or LSD and psilocybin) with healthy volunteers or patients in which a prolonged psychotic reaction happened. Inclusion of a psychiatric screening to exclude individuals with a personal or family history of any psychotic illness or nonpsychotic mania seems to significantly reduce the possibility of such adverse reactions in controlled settings of hallucinogen/psychedelic research. However, patients with these characteristics are common in psychiatric clinics. Thus, this is an important limitation in the possible clinical use of hallucinogens/psychedelics.

Regarding adverse effects of LSD and psilocybin, most studies described in the systematic reviews reported data from controlled experimental and/or clinical settings, where these drugs showed a good safety and tolerability profile, with transient adverse effects such as anxiety- and psychotic-like reactions, transient, moderate increases in systolic and diastolic blood pressure, headaches, nausea, or vomiting [5,7,9,50,53,54,55,56; see also 37,80]. None of the studies reported cases of prolonged psychosis.

5. Conclusion

Classic or serotonergic hallucinogens or psychedelics such as ayahuasca/DMT, psilocybin, and LSD showed in experimental,

open-label, and (less frequently) in RCTs anxiolytic, antidepressive, and antiaddictive potentials. However, evidence from controlled trials is limited to few studies with small samples and short duration. Thus, the clinical evidence for using these compounds is still far from being conclusive. Nevertheless, it is important to note that the observed effects were rapid and sustained and were induced by only one or just a few doses of these drugs, contrasting with the daily intake of traditional antidepressants and anxiolytics, which can take several weeks to achieve their therapeutic effects and are often associated with significant adverse reactions. Therefore, although research with these drugs is limited, their potential benefits should be better investigated.

Administration of serotonergic hallucinogens/psychedelics in controlled settings (experimental and clinical) showed a good safety and tolerability profile, with few transient and moderate adverse reactions. Indeed, one of the most significant adverse reactions associated with administration of these drugs is the possible induction of prolonged psychotic symptoms, and this was not observed in any of the controlled studies described in this review. We attribute this to the cautious and rigorous screening process in these studies. However, it must be acknowledged that this is an important limitation of these compounds, since in most psychiatric clinics, several patients have not only a history of psychotic disorders but also co-morbid psychotic symptoms. Therefore, any clinical use of these compounds will need to take that into consideration.

Long-term ritual ayahuasca use was not associated with increases in psychopathology or cognitive deficits in the reviewed observational studies, although prospective studies with new ayahuasca users are needed to overcome the possible bias associated with the almost exclusive participation of members of these religious groups. Moreover, rare cases of prolonged psychotic episodes were observed not only in the recreational context with smoked DMT, but also in ritual context. These cases could become even rarer if people with history of psychotic disorders are advised not to take ayahuasca or DMT.

Serotonergic hallucinogens/psychedelics, especially ayahuasca for MDD and psilocybin and LSD for existential anxiety and depression, seem to be promising treatments, but the small number of studies with few patients and short duration are important limitations that need to be overcome by new RCTs with more patients, different dosing schemes, longer duration, and, when possible, that can be conducted in multicenter trials. Thus, although the reviewed studies showed promising results, the evidence is still preliminary, and these compounds still need to be investigated in Phase II/III trials.

6. Expert commentary

Anxiety, mood, and substance-use disorders are some of the most prevalent psychiatric disorders in the population. Several antidepressive, anxiolytic, and antiaddictive drugs are available, but a significant proportion of patients do not respond to one or more of these medications, which are often associated with several adverse reactions. Moreover, these drugs are always used daily, and usually for months or years. Importantly, in the case of most traditional anxiolytic and antidepressive drugs, several weeks are necessary to achieve their therapeutic effects, and anxiety symptoms may increase during this period. Therefore, new pharmacological treatments with better efficacy and less adverse reactions should be investigated.

The pharmacological mechanisms of traditional anxiolytic, antidepressive, and antiaddictive drugs are mostly based on agonist/antagonist actions on monoaminergic neurotransmission, especially involving serotonergic, dopaminergic, GABAergic, and noradrenergic neural systems. However, despite decades investigating this monoaminergic theory and using these compounds clinically, their efficacy is still limited, and their adverse reactions are still significant. It seems that further exploration of these neurotransmitter systems is not leading to new and significant innovations on pharmacological treatments.

The therapeutic potentials of classical hallucinogens or serotonergic psychedelics such as DMT, ayahuasca, LSD, and psilocybin are mediated by an agonist action of these drugs on cortical 5-HT_{2A} serotonergic receptors expressed in frontal and paralimbic brain structures involved in mood and emotion regulation, introspection, interoception, daydreaming and mind-wandering, and self-consciousness. Stimulation of cortical 5-HT_{2A} receptors leads to increases in glutamatergic tone and synthesis of brain-derived neurotrophic factor, stimulating neuroplasticity. These effects are accompanied by reduced amygdala and DMN activity, reducing anxiety and rumination. Contrary to traditional anxiolytic, antidepressive, and antiaddictive drugs, serotonergic hallucinogens/psychedelics do not need to be taken daily and are usually administered in single or few doses, and their therapeutic effects are achieved from hours to days and are sustained for several weeks or months. When used in controlled settings, with proper screening and preparations of volunteers, these drugs have a good safety and tolerability profile.

To take serotonergic hallucinogens/psychedelics into mainstream psychiatry as new treatments, new Phase II/III RCTs will need to be developed in the following years, and the scheduling of these drugs will soon need to be reevaluated in countries where restrictive regulations render the investigation of these compounds difficult (such as in the United States and some European countries). If these studies are performed and the results are significant and positive, it is possible that in the next 5 to 10 years we will see psilocybin and LSD (and maybe other similar drugs) being recognized as official treatments in some countries, associated or not with different psychotherapeutic approaches.

In the case of natural substances with significant ethnobotanical and religious/ritual importance and a controlled context of use, such as ayahuasca, no patent can be made of the plants or their alkaloids, and both the botanical and genetic patrimony of the countries where the plants are endogenous and the traditional indigenous and religious knowledge/culture associated with ayahuasca use must be respected. Ayahuasca has been used therapeutically by Northwestern Amazonian indigenous groups for centuries, and by non-indigenous people in organized religions in Brazil and abroad for decades. Ethnomedicinal use of ayahuasca is already happening.

Future studies should explore the effects of these drugs on obsessive-compulsive and related disorders, personality disorders, aggressive behavior, post-traumatic stress disorder, and social anxiety disorder. Furthermore, the possible beneficial use of these drugs in other areas not necessarily related to psychiatry should also be explored, such as in creative enhancement and in religious or meditative practices.

7. Five-year view

In the next 5 years, new RCTs with serotonergic hallucinogens/psychedelics will be performed, especially with psilocybin, LSD, and ayahuasca, and it is possible that psilocybin will be the first of these compounds to be regulated for clinical use, most probably for unipolar depression, anxiety, and depression associated with terminal cancer and other life-threatening diseases, and substance-use disorders (alcohol, tobacco, and cocaine). LSD will probably follow the same way as psilocybin and will probably be regulated in the following years. Further clinical trials will be performed with ayahuasca, which is already used therapeutically in ethnomedicinal and ritual contexts.

Key issues

- Serotonergic hallucinogens/psychedelics such as ayahuasca, psilocybin, and LSD have anxiolytic, antidepressive, and antiaddictive effects.
- Several observational or open-label studies reported those effects, but only few randomized controlled trials were performed.
- Trials with these drugs usually administer only one or few doses of these compounds, but their therapeutic effects are rapid (hours/days) and sustained (weeks/months).
- These drugs can be safely administered in controlled settings and appear to be promising treatments for mood anxiety, and substance-use disorders.

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