Research Article

Hallucinogens and Their Therapeutic Use: A Literature Review

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The exploration of possible therapeutic benefits of hallucinogenic substances has undergone a revitalization in the past decade. This literature review investigated the published literature regarding the psychotherapeutic uses of hallucinogens in psychiatric disorders. The results showed that a variety of substances have been evaluated in the treatment of psychiatric disorders, including ayahuasca, ibogaine, ketamine, lysergic acid diethylamide, 3,4-methylenedioxymethamphetamine, and psilocybin. The conditions treated ranged from depression to autism, with the largest volume of research dedicated to substance use disorders. The majority of studies that were reviewed demonstrated significant associations with improvement in the conditions investigated. However, it was difficult to draw definitive conclusions as most studies suffered from small sample sizes, inconsistent measures, and poor study design. To properly assess the risks and potential benefits of hallucinogens in psychiatric treatment, there is a need for well designed, standardized studies that demonstrate the impact of hallucinogenic substances on psychiatric conditions.
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Hallucinogens are classified by the fifth edition of the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) as a diverse group of substances that, despite having different chemical structures and possibly involving different molecular mechanisms, produce similar alterations of perception, mood, and cognition in users.[1] Multiple substances comprise this category ranging from naturally occurring plants to synthetically produced compounds. Examples include ayahuasca, ibogaine, ketamine, lysergic acid diethylamide (LSD), 3,4-methylenedioxymethamphetamine (MDMA), and psilocybin (the active ingredient in "magic mushrooms").

Although hallucinogens have been used in spiritual rituals among multiple cultures for nearly 2500 years, they were largely unknown to western society until the discovery of LSD's mind altering effects in 1943.[2] In 1947, the first clinical paper published about LSD discussed possible applications in the field of psychiatry.[2] Subsequently, LSD was sold under the name Delysid. The first indication listed in its information packet was "analytical psychotherapy, to elicit release of repressed material and provide mental relaxation, particularly in anxiety states and obsessional neuroses."[2] Although now disproven, the second indication encouraged self-experimentation to perform studies on the nature of psychoses, advising "by taking Delysid himself, the psychiatrist is able to gain an insight into the world of ideas and sensations of mental patients."[2] Research with psychedelics occurred for 2 decades until widespread misuse, political pressures, stigmatization, and eventual illegalization ended the investigations. However, these same adverse factors that stopped academic research have not curtailed illicit exploration and abuse.

The 2015 National Survey on Drug Use and Health estimates that > 40 million people (15.3% of the US population) have used hallucinogens at least once in their lifetime.[3] Given increasingly lax substance control laws, the increasing availability of hallucinogenic substances on the Internet, and travel to experience ritualistic hallucinogenic use becoming more frequent,[4] the number of hallucinogenic users is predicted to increase. These factors

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make psychiatrists' knowledge about hallucinogens more than a matter of academic curiosity, but rather valuable in daily patient management.

After decades of obscurity, the field of psychedelic research is reemerging. In 2012, the University of Pennsylvania hosted "Psychedemia," a weekend event attended by researchers, clinicians, and other scientists to discuss the impact of hallucinogens in a variety of fields.[5] In April 2017, the largest reported gathering of professionals to discuss hallucinogenic research took place in California, boasting an attendance of 3000.[6] Most recently, in September 2017, the United States Food and Drug Administration (FDA) approved a phase 3 trial for MDMA-assisted psychotherapy for patients with posttraumatic stress disorder (PTSD).[7] Despite increasing awareness of and revitalized interest in hallucinogens, their safety and usefulness have been debated and challenged in the medical literature.[8–10]

While the use of hallucinogens remains controversial, investigation of clinical applications of illicit substances is not a novel idea. Many illicit substances are classified by the FDA to allow their use in specific clinical scenarios. Examples include the use of cocaine for nose bleeds and anesthetic eye drops, opioids for pain, and cannabinoids for pain, glaucoma, and appetite stimulation. Hallucinogens are unique, however, as their therapeutic use is believed to go beyond their physiological actions, many of which are just beginning to be discovered. Rather, the therapeutic value of hallucinogens is attributed to their distinct ability to alter consciousness and invoke new insights, thereby creating fundamental changes in mental schema.[11,12] While some argue that one experience cannot produce life changing effects, research has shown at 14 months after receiving a psychedelic dose of psilocybin, 50% of subjects rated the experience as "the most personally meaningful and spiritually significant of their lives," with 64% reporting "increased well-being or life satisfaction."[13]

SUBSTANCES AND ASSOCIATED PROPERTIES

This review includes ayahuasca, dipropyltryptamine (DPT), diethyltryptamine (DET), ibogaine, ketamine, LSD, MDMA, and psilocybin. All of these substances possess hallucinogenic properties, but their mechanisms of action and proposed therapeutic attributes vary.

LSD

LSD is theorized to enable access to thoughts, associations, feelings, and inner processes that are usually excluded from consciousness.[14] When patients compare the effects of LSD-assisted psychotherapy with those of traditional psychotherapy, they mention facilitated access to emotions, important insights, faster progress, and accessing feelings of safety and facilitation of "letting go" as the most prominent differences.[15] It seems that the core of these deeply affecting experiences is a tension-free state of well-being or a positive experience of "pure existence in the here and now" accompanied by a relative freedom from concerns about the past as well as from guilt, depression, and anxiety. The biological effects are secondary to primary affinity for 5-HT_{2A} receptors, as well as significant modulation of 5-HT_{2C} and 5-HT_{1A} receptors, which may lead to cascades creating excess neuronal excitability in key areas of the brain including the prefrontal cortex and ventral tegmental nucleus.[15]

Amid investigations into the therapeutic potential of hallucinogens in the 1960s and 1970s, researchers hoped to find substances that could produce similar effects, but would possess a shorter duration of effect and allow for a more abrupt return to baseline consciousness than LSD, the most commonly researched hallucinogen at the time.[14] Three tryptamine derivatives were found to have hallucinogenic properties: dimethyltryptamine (DMT), DET, and DPT.[14] Similar to LSD, these compounds act upon $5HT_{1A/2A}$ receptors.[16]

Ketamine

Ketamine is a prescription medication that when administered in subanesthetic dosages produces hallucinations and dissociative effects.[12] Because of its established legal status, classification, safety profile, and availability, ketamine has been at the forefront of experimental study designs over the past several years. Ketamine also has a significant advantage over other hallucinogens because of its significantly shorter duration of effect of 45 to 60 minutes when administered intramuscularly.[17] Ketamine has been studied for the treatment of addiction and mood disorders. Ketamine exerts its anticraving effects by acting on N-methyl-D-aspartate (NMDA) ligands, similar to acamprosate and ibogaine.[17] The antidepressant effects of ketamine

may be secondary to increased serotonin or glutamate in the prefrontal cortex caused by the diversion of glutamate signaling to alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA) receptors as a result of ketamine's antagonistic activity at NMDA receptors.[18]

Psilocybin

Psilocybin is a naturally occurring hallucinogen found in various types of "magic mushrooms." Psilocybin's effects are similar to those of LSD, but they are considered to be more strongly visual, more euphoric, and less emotionally intense with fewer related panic and paranoid reactions.[19] Once digested, psilocybin is metabolized to psilocin, a potent 5-$HT_{1A/2A/2C}$ receptor agonist.[20] In clinical trials, psilocybin is often used to target anxiety-related disorders and depression. Therapeutically, psilocybin increases the vividness of memories and promotes an overall feeling of well-being.[21] Imaging studies have also shown that psilocybin reduces amygdala reactivity to negative and neutral stimuli. Amygdala hyperactivity in response to negative stimuli has been consistently demonstrated in depressed patients.[22]

Ayahuasca

Ayahuasca is an Amazonian botanical hallucinogenic brew containing DMT and B-carboline alkaloids including harmine.[23] Harmine produces peripheral reversible monoamine oxidase A (MAO-A) inhibition, while DMT is a $5HT_{1A/2A/2C}$ receptor agonist.[24] The MAO-A inhibition and global elevation of serotonin may give the substance antidepressant properties. It is also theorized that the alkaloids, which are unique to ayahuasca, balance dopamine levels in the mesolimbic dopamine pathway through both direct and indirect actions.[25] This unique action may contribute to ayahuasca's potential to alleviate addiction feedback loops.[25]

Ibogaine

Ibogaine is an alkaloid extracted from plants that is often classified as a hallucinogen given its strong psychoactive properties when consumed in certain quantities. It acts as an agonist at $5HT_2$ and $5HT_3$ receptors, as well as other receptors including glutamate NMDA and acetylcholine muscarinic receptors.[25] Ibogaine may also inhibit adenylyl cyclase; an effect opposite to the activation of adenylyl cyclase that is classically associated with opioid withdrawal.[26] This corresponds with reports suggesting that illicit ibogaine users most frequently obtain the substance for relief from opioid withdrawal.[26]

MDMA

In contrast to other hallucinogens, MDMA is believed to have a distinct ability to affect the emotional sphere without altering visual perception or sense of self.[27] MDMA, also known as "ecstasy," inhibits the reuptake of serotonin and stimulates the release of dopamine and norepinephrine.[28] By reducing anxiety and fear and enhancing empathy, MDMA is postulated to strengthen the therapeutic alliance while allowing patients to process troubling or disturbing memories.[29] It is hypothesized that these properties may augment PTSD treatment by enhancing the patient's ability to share traumatic experiences with the therapist that will hasten and facilitate recovery.

OBJECTIVE

Theories abound about the potential therapeutic utility of hallucinogens for treating patients with mental illness. The purpose of this review was to critique actual clinical trials measuring the value of hallucinogens in psychiatric practice. We identified clinical studies investigating the psychotherapeutic use of hallucinogens, classified those studies using established levels of an evidence grading system, and critiqued the reported clinical efficacy and safety.

METHODS

We identified relevant articles published between 1946 and September 2017 using OVID MEDLINE. We used the search term *hallucinogens,* which was then limited to the subheading "therapeutic use." We selected only articles that investigated the use of hallucinogens in human subjects as treatment for psychiatric diagnoses. We excluded duplicate articles and articles that were not available in English.

TABLE 1. Levels of Evidence Grading System

*Level of Evidence**	*Study Type*
I	High-quality, properly powered and conducted randomized controlled trial; systematic review or meta-analyses of these studies
II	Well-designed controlled trial without randomization; prospective comparative cohort trial
III	Retrospective cohort study, case-control study, or systematic review of these studies
IV	Case series with or without intervention; cross-sectional study
V	Expert opinion, case report, or bench research

**All studies were considered for downgrade if they exhibited poor design, insufficient number of subjects (N < 10), or other methodological flaws. Studies not meeting the above criteria, including case reports and expert opinion papers, were excluded entirely.*
Adapted with permission from the The Oxford Levels of Evidence 2 developed by the Oxford Centre for Evidence-Based Medicine (https://www.cebm.net/index.aspx?o=5653) and from Ishii 2015.[30]

We excluded reports on cannabinoids as these are distinguished from hallucinogens in DSM-5.

Each author reviewed and classified the selected articles in accordance with the levels of evidence grading system above (Table 1).[30] Differences between the authors' ratings were resolved through discussion. Only class I, II, and III studies were eligible for inclusion. Table 2 documents the study design, hallucinogen administered, exposure parameters, detailed outcome measures, and summary of significant findings. All outcomes documented in Table 2 were statistically significant unless otherwise stated. Funding sources, if present, were primarily nonprofit agencies or research grants, and no trial was funded by a pharmaceutical company or private entity.

RESULTS

Sixteen of 214 abstracts met criteria for review. We identified class I (n = 3), class II (n = 6), and class III (n = 7) studies. Fifteen of the 16 studies found that the therapeutic use of hallucinogens led to reduction in symptomatology. Substance use disorders were the most commonly studied conditions. No long-term adverse outcomes were reported, and the hallucinogens were generally well tolerated with acute increases in blood pressure and vomiting being the most common side effects.

Ayahuasca

Our review identified 1 class II and 1 class III study. Both studies were small, open-label, crossover trials with subjects serving as their own controls. They investigated the antidepressant effects of ayahuasca on patients diagnosed with recurrent major depressive disorder (MDD), mild to severe. In the class II study,[23] after completing a 2-week washout of medications, patients with MDD unresponsive to standard medications (N = 17) took a single dose of ayahuasca. Reductions in depression were reported from 80 minutes up to 21 days after consumption on all 3 depression rating scales used, with a mean reduction of 61% recorded between baseline and day 21.[23] In a similar, class III study[24] (N = 6) performed by the same investigators, patients reported an average 62% reduction in depression on day 1, and ~72% reduction on days 7 and 21.[24] Ayahuasca was generally well tolerated with the exception of vomiting which was reported by 50% of participants.[23,24]

DET and DPT

Our review identified 1 class II and 1 class III study investigating the effects of tryptamine derivatives on alcohol use disorder. In a class II, open-label, nonrandomized, pilot study, using subjects as their own controls, patients with alcohol use disorder (N = 51) were administered a high dose of DPT during a multiweek course of psychotherapy in an inpatient setting.[14] Subjects were in treatment for an average of 8 weeks and participated in an average of 1.86 unguided DPT sessions that were both preceded and followed by drug-free therapy sessions. Nearly all patients reported profound esthetic

TABLE 2. Reviewed Studies Investigating the Therapeutic Use of Hallucinogens

Study and Design	*Study Class*	*Participants*	*Exposure Parameters*	*Dosage*	*Outcome Measures*	*Significant Findings*
Ayahuasca						
Sanches et al, 2016[23] Open-label, crossover with subjects as their own controls	II	N = 17 (14 F, 3 M, mean age 42.7 y) with mild to severe recurrent MDD	1 unguided session in inpatient setting	2.2 mL/kg	BPRS, CADSS, HAM-D, MADRS, SPECT, YMRS	Increased blood flow in brain regions that regulate mood and emotion per SPECT, decreased depression up to 21 d after administration per HAM-D and MADRS
Osório et al 2015[24] Open-label, crossover with subjects as their own controls	III	N = 6 (4 F, 2 M, mean age 44.2 y) with mild to severe recurrent MDD	1 unguided session in inpatient setting	2.2 mL/kg	BPRS, HAM-D, MADRS, YMRS	Decreased depression at 1, 7, and 21 d after administration per HAM-D and MADRS
Tryptamine derivatives: dipropyltryptamine (DPT), diethyltryptamine (DET)						
Grof et al 1973[14] Open-label, crossover with subjects acting as their own controls	II	N = 51 (sex not specified, mean age 38.6 y) with alcohol use disorder for an average of 10.4 y	~2 DPT sessions during several weeks of psychotherapy in inpatient rehabitation setting	DPT 60-150 mg	MMPI, POI, PEP, Raven Progressive matrices, social history questionnaire, Benton visual retention test	Depression and social introversion, self-regard, insight, and distress all improved per MMPI, POI, and PEP, respectively, 3-5 d after session. 6-mo follow-up with 47 subjects found abstinence achieved by 18 subjects (32.8%), and marked improvement in occupational and interpersonal relations achieved by 22 subjects (46.8%) per social history questionnaire
Faillace et al 1970[31] 2-y follow-up of single-blind, crossover study with subjects acting as their own controls	III	N = 12 (sex not specified, mean age 38.2 y) with alcohol use disorder and history of multiple hospitalizations	5 guided weekly sessions during psychotherapy 2×/wk in inpatient setting	DPT, DET 0.7 mg/kg, 1.0 mg/kg, 1.3 mg/kg	Survey response	Only 2 of 12 patients reported improvement in drinking behavior or social adjustment per survey response at 2-y follow-up
Ibogaine						
Schenberg et al 2014[32] Retrospective analysis, non-controlled	III	N = 75 (67 M, 8 F, mean age 33.67 y) with various substance use disorders, and 30-60 d abstinence before session	1-9 unguided sessions in inpatient setting with elective postsession treatment options	17-20 mg/kg	Interview response	37.3% of users maintained abstinence after 1 session, with an additional 22.7% maintaining sobriety after the second session; a median of 5.5 mo of abstinence was obtained after the first session, and a median of 8.4 mo of abstinence was obtained after all subsequent sessions per interview response
Ketamine						
Krupitsky et al 2002[17] Double-blind, randomized, active-placebo controlled	I	N = 70 (15 F, 55 M, mean age 22.3 y) with heroin use disorder who completed detoxification before the trial	1 guided session during 15 total hours of psychotherapy in inpatient setting	2.0 mg/kg, 0.2 mg/kg	ZDS, SAS, VAS, SA, MMPI, LCS, CTA, PLT, SCS, HRS, interview response, physical exam, UDS	High dose ketamine (2.0 mg/kg) produced greater rates of abstinence within the first 2 y of follow-up per interview response and UDS, longer lasting reduction in craving at 2-y follow-up per VAS, and greater positive change in unconscious emotional attitudes per CTA compared with low dose ketamine (0.2 mg/kg)
Sos et al 2013[18] Double-blind, crossover, placebo controlled	I	N = 30 (15 F, 15 M, mean age 43.7 y) with MDD, single episode or recurrent, and MADRS > 20; all ketamine naive. Analyses were based upon the 27 who completed both arms of the trial	1 ketamine and 1 placebo session at 1 wk intervals in combination with antidepressant medication in inpatient setting	0.54 mg/kg	MADRS, BPRS, serum analysis	Patients in the ketamine group demonstrated greater response than those in the placebo group, with mean MADRS reductions of 5.7 on day 1, 4.7 on day 4, and 4.0 at day 7. Correlation was found between intensity of ketamine's effects and lessening of depression symptoms per MADRS and BPRS. No differences were found between responders and nonresponders in ketamine serum levels
Krupitsky et al 1997[12] Open-label, nonrandomized, controlled	II	N = 211 (211 M, mean age 37.5 y) with alcohol use disorder	1 guided ketamine session during inpatient rehabilitation treatment	2.5 mg/kg	MMPI, LSI, LCS, CTA, PD, QTLV, MVRG, MCRG, written and interview response	Total abstinence for > 1 y was observed in 73 of 111 patients receiving ketamine vs. 24 of 100 patients in the conventional treatment control group. Ketamine was associated with positive changes in psychological attributes that contribute to sobriety per LCS, QTLV, MVRG, and MCRG

TABLE 2. Reviewed Studies Investigating the Therapeutic Use of Hallucinogens (*continued*)

Study and Design	*Study Class*	*Participants*	*Exposure Parameters*	*Dosage*	*Outcome Measures*	*Significant Findings*
Lysergic acid diethylamide (LSD)						
Krebs and Johansen 2012[33] Meta-analysis of 6 randomized, double-blind, controlled trials	I	N = 536 (2 F, 534 M, mean age unquantified) with alcohol use disorder, and previous admission to alcohol-treatment programs	1 LSD session, guidance varied, during 7-90 d treatment programs consisting of individual therapy, group therapy, or both, in inpatient setting	210-800 μg (median 500 μg)	Odds ratio (OR)	Compared with the group who received placebo, the group treated with LSD reported decreased rates of alcohol misuse at 2-3 mo and 6-month follow-up, but the effect did not reach significance at 12 mo per OR; the rates of alcohol abstinence also favored the LSD group at 1-3 mo follow-up, but did not reach significance at 6 mo follow-up per OR
Kurland et al 1967[34] Open-label, nonplacebo controlled, crossover trial	II	N = 69 (69 M, age not specified) with alcohol use disorder, unspecified	1 high-dose, guided LSD session incorporated into ~3 wk of psychotherapy in inpatient setting, with optional outpatient and inpatient follow-up	450 μg	MMPI, EEG	Decreased levels of depression and psychasthenia after LSD treatment per compiled MMPI of all participants; 33% of patients maintained abstinence at 6-mo follow-up
Gasser et al 2015[15] Prospective follow-up of a double-blind, randomized, active-placebo controlled, with optional crossover trial	II	N = 10; (4 F, 6 M, mean age 51.1 y) with anxiety disorder related to life threatening conditions	6-8 psychotherapy sessions with 2 guided LSD experiences embedded at 4-6 wk intervals in an outpatient setting	200 μg, 20 μg	STAI, interview response	Sustained reduction in anxiety and less fear of death reported by 7 of 9 subjects and improved quality of life and positive personality changes reported by 6 of 9 subjects at 12-month follow-up per STAI and interview response
Itil et al 1969[35] Open-label, nonrandomized, placebo controlled, crossover trial	III	N = 17; (sex and age not specified) with 3 y history of schizophrenia and minimum 1 continuous year hospitalization	4-15 LSD administrations at 1-2 wk intervals amid conventional antipsychotic medication treatment in inpatient setting	LSD, 5-840 μg	7-point global rating scale, EEG, psychopathological ratings scale	Patients who exhibited marked EEG changes after hallucinogenic drugs responded best to subsequent conventional medication treatment; 3/6 patients who received LSD and completed the trial eventually met discharge criteria
3, 4-Methylenedioxymethamphetamine (MDMA)						
Bouso et al 2008[29] Double-blind, randomized, placebo controlled trial	III	N = 6 (6 F, mean age 35.7 y) with posttraumatic stress disorder, chronic, with ≥ 1 standard treatment failure	1 guided MDMA session amid 7 weekly psychotherapy sessions	50 mg, 75 mg	SSSPTSD, STAI, BDI, HAM-D, MFS, MS, SE/R, HRS, UKU Scale of Secondary Effects, HAq	Improvement in PTSD and anxiety symptoms was evidenced in a dose-dependent manner per SSSPTSD and STAI, but due to early termination secondary to political pressure, this study lacked enough data to calculate statistical significance
PSILOCYBIN						
Grob et al 2011[19] Double-blind, placebo controlled, crossover trial	II	N = 12 (11 F, 1 M, mean age not provided) with illness anxiety disorder related to cancer diagnoses	1 unguided psilocybin session and 1 placebo session several weeks apart, in a hospital setting	0.2 mg/kg	BDI, POMS, STAI, 5D-ASC, BPRS	30% reduction in depression 2 wk after the psilocybin session, which was sustained and reached significance at 6-month follow-up per BDI; anxiety was reduced by 15% and reduction was sustained at 1 and 3 mo after treatment per STAI

TABLE 2. Reviewed Studies Investigating the Therapeutic Use of Hallucinogens (*continued*)

Study and Design	*Study Class*	*Participants*	*Exposure Parameters*	*Dosage*	*Outcome Measures*	*Significant Findings*
Moreno et al 2006[20] Modified double-blind, active-placebo controlled, crossover trial	III	N = 9 (2 F, 7 M, mean age 40.9 y) with obsessive-compulsive disorder (OCD) and history of ≥ 1 treatment failure	4 unguided sessions of increasing dosage, with 1 very low dose randomly inserted, all separated by at least 1 wk in inpatient setting	25 μg/kg, 100 μg/kg, 200 μg/kg, 300 μg/kg	YBOCS, VAS, HRS	Decrease of 23%-100% in OCD symptoms observed in all subjects during 1 or more sessions per YBOCS; 88.9% of subjects maintained ≥ 25% decrease and 66.7% maintained ≥ 50% decrease in OCD symptoms at 24 h postingestion per YBOCS; 1 subject achieved long-term remission at 6-mo follow-up; 1 subject did not complete study due to transient hypertension
Garcia-Romeu et al 2015[11] Secondary analysis of an open-label, uncontrolled trial	III	N = 15 (5 F, 10 M, mean age 51 y) with tobacco use disorder, unspecified, with an average of 6 previous attempts to quit	1 moderate and 2-3 high doses administered in the course of 15 wk of cognitive-behavioral therapy, mindfulness exercises, and imagery exercises in an outpatient setting	286 μg/kg, 429 μg/kg	Breath carbon monoxide (CO), urine samples, TLFB, QSU, SASE, HRS, Mysticism Scale, SOCQ, Personal Meaning, Spiritual Significance, and Well-being rating scales	12/15 participants maintained abstinence at 6-mo follow-up per TLFB, breath CO, and urine samples. Quitting was positively correlated with ratings of spiritual and personal meaning of the psilocybin session and not with drug intensity, per the SOCQ, Personal Meaning, Spiritual Significance, and Well-being rating scales. Thus, abstinence was found to be associated with the subject's interpretation of the session (via their ratings on personal meaning and spiritual significance) and not with their rating of the intensity of the drug. The more meaning the session was interpreted to have, the more likely the patient was to maintain abstinence

5D-ASC indicates 5-Dimension Altered States of Consciousness profile; BDI, Beck Depression Inventory; BPRS, Brief Psychiatric Rating Scale; CADSS, Clinical Administered Dissociative States Scale; CTA, Color Test of Attitudes; EEG, electroencephalogram; F, female; HAM-D, Hamilton Depression Rating Scale; HAq, Penn Helping Alliance Questionnaire; HRS, Hallucinogen Rating Scale; LCS, Locus of Control Scale; LSI, Plutchik's Life Style Index; M, male; MADRS, Montgomery-Asberg Depression Rating Scale; MDD, major depressive disorder; MFS, Modifed Fear Scale, MMPI, Minnesota Multiphasic Personality Inventory; MCRG, Mean color repertory grid; MS, Maladjustment scale; MVRG, Mean verbal repertory grid; PD, personality differential; PEP, Psychiatric Evaluation Profile; PLT, Purpose-in-Life Test; POI, Personality Orientation Inventory; POMS, Profile of Mood States; QSU, Questionnaire on Smoking Urges; QTLV, Questionnaire of Terminal Life Value; SA, Scale of Anhedonia Syndrome; SAS, Spielberger Self-rating State-Trait Anxiety Scale; SASE, Smoking abstinence scale; SCS, Spirituality Change Scale; SE/R, Rosenberg Self-Esteem scale; SOCQ, States of Consciousness Questionnaire; SPECT, single photon emission tomography; SSSPTSD, Severity of Symptoms Scale for PTSD; STAI, State-Trait Anxiety Inventory; TLFB, Timeline Follow-Back; UDS, urine drug screen; VAS, visual analog scale; YBOCS, Yale-Brown Obsessive Compulsive Scale; YMRS, Young Mania Rating Scale; ZDS, Zung Self-rating Depression Scale.

experiences, including the reliving of emotionally salient memories with abreaction or catharsis, and experiences that were religious or mystical in nature. Immediate posttesting demonstrated significant improvement on multiple rating scales, including depression, self-regard, and insight. At 6-month follow-up, 47 patients were contacted and 46.8% reported reductions in alcohol use, and improvements in occupational functioning and interpersonal relations ($t = 8.02, P = 0.001$), occupational adjustment ($t = 3.05$, $P = 0.01$), and interpersonal functioning ($t = 4.14$, $P = 0.001$); 38.2% were totally abstinent and 53.2% reported minimal departure from total abstinence. A brief psychotic episode was experienced by 1 subject 3 weeks after the last DPT session.[14]

In a smaller, class III, placebo-controlled study, subjects with alcohol use disorder (N = 12) were randomly treated with mild, moderate, or high dosages of tryptamine derivatives DPT, DET, or the nonhallucinogenic derivative 6-fluoro-DET.[31] Five weekly experimental sessions took place after 2 weeks of psychotherapy. At 1- and 2-year follow-up, only 3 of 12 subjects showed improvement in drinking behavior and social adjustment. One subject denied that the hallucinogens had any impact on his recovery, while the remaining 2 were actively engaged in therapy and Alcoholics Anonymous. The success of these last 2 patients was attributed to the ability of the hallucinogens to bring awareness to personal problems, which in combination with continued treatment, allowed them to find new meaning in life and remain sober. Side effects were not reported in this study.

Ibogaine

Our review identified 1 class III study investigating ibogaine. Investigators retrospectively studied the abstinence rates of subjects (N = 75) with alcohol, cannabis, and cocaine use disorders (72% polysubstance users) treated with ibogaine during dialectical behavioral therapy.[32] The treatments ranged from 1 (44% subjects) to 9 (1% subjects) unguided, 10-hour ibogaine sessions. The authors reported that 61% of the sample were abstinent for a median of 5.5 months for those treated with 1 session and for a median of 8.4 months for those treated with multiple sessions. Most subjects attributed abstinence to ibogaine but acknowledged the possible contribution of therapy. Abstinence rates in the ibogaine treatment group (56%) were markedly greater compared with rates in those who received psychotherapy alone (26%).[32] Side effects frequently included nausea, ataxia, headaches, mental confusion, tremors, and vomiting during intoxication.

Ketamine

Our review identified 2 class I studies and 1 class II study investigating ketamine. In a class I, randomized, active-placebo controlled, double-blind study, detoxified subjects with opioid use disorder (N = 70) underwent ketamine-assisted psychotherapy.[17] Thirty-five subjects received 1 hallucinogenic dose and 35 subjects received a comparison nonhallucinogenic lower dose of ketamine. While both dosages reduced cravings, the reduction in craving was markedly greater in the group who received the hallucinogenic dose at 1-month (74% vs. 44%) and 3-month (82% vs. 22%) follow-up. In addition, the hallucinogenic dose group's reduction in craving was significant at 24 months, versus only the first month in the low dose group. The difference in both abstinence and relapse rates also favored the hallucinogenic dose group in all months of follow-up, reaching clinical significance in 22 of 24 months. When comparing subjects' responses at the conclusion of the study, those who received the psychedelic dose reported greater positive change in emotional attitudes. No long-term adverse outcomes, including psychosis, flashbacks, or addiction, were found. An acute 20% to 30% elevation in blood pressure was noted in all subjects.

In a class I double-blind, placebo-controlled, crossover trial, subjects with MDD (N = 30) received 1 ketamine and 1 placebo session in randomized order.[18] All subjects continued their established antidepressant medication regimen throughout the trial. The statistical analyses included only subjects who completed both arms of the trial (n = 27). One session of ketamine was associated with ~30% reduction of core depressive symptoms versus placebo. These responses persisted at days 1, 4, and 7. Five subjects reported depressive symptom reductions of 50% or greater at all 3 follow-ups after receiving ketamine compared with none in the placebo group. Ketamine serum levels did not correlate with depressive symptom reduction. Rather, reduction correlated with the

intensity of the ketamine experience. This relationship was maintained and most pronounced 7 days after treatment ($r = -0.40$, $P = 0.04$). Side effects were limited to those associated with subanesthetic dosages of ketamine, including perceptual disturbances, confusion, mild elevation of blood pressure, and emotional blunting. The majority of side effects lasted ~30 minutes with none lasting beyond 60 minutes.

In a class II, open-label, nonrandomized, controlled trial performed over the course of 10 years, researchers investigated the incorporation of ketamine psychotherapy into a standard 3-month treatment course for patients with alcohol use disorder (N = 211).[12] Subjects were divided into 2 groups, those who consented to receive an experimental ketamine treatment and those who did not consent to ketamine, but underwent the same 3-month psychotherapy course. Seventy-three of 111 (65.8%) subjects in the ketamine group obtained total abstinence for > 1 year compared with 24 of 100 (24%) in the nonketamine group. Personality rating scales of subjects who underwent ketamine psychotherapy demonstrated significant improvement in multiple areas including decrease in regression defense mechanism, internal locus of control with increased confidence to manage difficult situations, self-perception, spiritual contentment, appreciation of the importance of achieving life goals, and a deeper understanding of the meaning of life. The authors reported treating over 1000 patients with ketamine psychotherapy without any reports of prolonged psychosis, flashbacks, agitation, or ketamine abuse.

LSD

Our review identified 4 articles investigating LSD: class I (n = 1), class II (n = 2), and class III (n = 1). A class I meta-analysis was performed on 6 randomized controlled trials using LSD as a treatment for alcohol use disorder (N = 536).[33] A single dose of LSD showed greater benefit and a lower number needed to treat to maintain abstinence (NNT = 7) than daily use of naltrexone (NNT = 33), acamprosate (NNT = 9), or disulfiram (NNT = 9).[33] Common reports of improvement in patients included increased insight into their problems, a sense of having "a new lease on life," and building a stronger resolution to discontinue drinking. The benefit of a single dose of LSD was reported up to 6 months after treatment, but the effect was no longer significant by 12 months. Two of 3 trials that reported employment data found higher rates of employment in those receiving LSD. Acute adverse reactions included "acting bizarrely" (n = 2), agitation (n = 1), unspecified adverse reaction (n = 2), and a seizure by a patient with a history of alcohol withdrawal seizures and recent abstinence (n = 1). In the days after the session, transient moderate confusion (n = 1) and a transient "adverse reaction" (n = 1) were recorded. One study reported acute side effects of nausea, vomiting, and "moderate agitation" relieved by support in a small number of subjects. Another study reported episodes of "vivid perceptual thoughts or feelings clearly related to the LSD experience" in approximately one third of 18 subjects. These effects were commonly experienced in the context of alcohol consumption. In a different study, similar experiences were specifically denied by subjects (n = 13) at 6-month follow-up.

The first class II nonrandomized, crossover controlled trial we identified incorporated a single LSD-guided session into a structured 3-week psychotherapy regimen for subjects with alcohol use disorder (N = 69).[34] Subjects received 12 to 15 hours of therapy over the 2-week period preceding the LSD session. Depression, social inversion, and severe personality disturbances improved. Tests of intellectual functioning before and after sessions trended toward enhancement. At 6-month follow-up, 33% of subjects maintained abstinence. Adverse outcomes were not reported in this study. There were no significant electroencephalogram (EEG) changes in 20 randomly selected subjects.

The second class II, nonrandomized, crossover controlled trial (N = 10), incorporated 2 LSD sessions within 8 psychotherapy sessions over the course of 3 months for the treatment of anxiety.[15] Anxiety decreased by 27% at the end of the study and this decrease was maintained at 12-month follow-up. Seventy-eight percent (n = 7/9 subjects) reported reduction in anxiety and less fear of death, and 67% (n = 6/9 subjects) reported an improved quality of life. Personality changes such as increased openness and deepened awareness were subjectively reported.

The class III, open-label, nonrandomized, pilot study examined the benefits of LSD for subjects with schizophrenia (N = 17) who were administered 4 to

15 increasing dosages of LSD or Ditran (a hallucinogen chosen for its ability to desynchronize EEGs) at 1 to 2 week intervals.[35] After evidencing EEG changes or after being nonresponsive after 3 months, the agents were discontinued. Subjects were then re-started on psychotropic medications for 2 to 12 months. Twelve subjects completed the study, 6 of whom received LSD and 6 of whom received Ditran. Upon conclusion of the study, all subjects had improved from baseline according to a 7-point global functioning rating scale. Three of 6 subjects treated with LSD and 4 of 6 subjects treated with Ditran met criteria for discharge. The most significant improvements were found in areas of attention and concentration, comprehension, insight and judgment, aggressive behavior, and uncooperativeness in the LSD group after starting the second antipsychotic. The authors concluded that subjects demonstrating marked EEG changes after hallucinogenic drugs responded better to subsequent conventional treatment. All 12 subjects demonstrated worsening of symptoms during the experimental drug phase, with subjects receiving LSD experiencing increased depersonalization, perceptual disturbances, and disturbed motor behavior.

N-Methyl-3,4-Methylenedioxy-Amphetamine (MDMA)

Our review identified 1 class III study investigating MDMA. In a small (N = 6) double-blind, randomized, placebo-controlled study, women with chronic PTSD from sexual trauma were assigned to 3 groups; 1 receiving 75 mg MDMA, 3 receiving 50 mg MDMA, and 2 receiving placebo.[29] Each subject underwent 3 therapy sessions before and after the therapist-guided experimental session. Immediate posttreatment rating scales measuring the severity of PTSD symptoms demonstrated a mean reduction of 24% with MDMA versus 10% with placebo. At 1-month follow-up this reduction improved to 33%. The reduction in PTSD symptoms seemed to correlate with dosage, with the subject receiving 75 mg reporting the greatest reductions in symptoms; 35% at 1 month follow-up, and 42% at 3-month follow-up. Neither the 75 or 50 mg dose increased symptomatology. All of the subjects, except 1 who was receiving placebo, reported an improved therapeutic alliance. At 24-hour follow-up, side effects including headache, palpitations, photosensitivity, and sedation, were scored as mild by 2 subjects receiving MDMA.

Psilocybin

Our review identified 3 studies investigating psilocybin: class II (n = 1) and class III (n = 2). In a double-blind, placebo-controlled, crossover study, subjects with varying cancers and a comorbid anxiety-related diagnosis (N = 12) received a moderate dose (0.2 mg/kg) of psilocybin and were assessed monthly for 6 months for improvement in anxiety.[19] Subjects did not receive counseling before, during, or after the experimental session. Although improvements in anxiety and depression were reported 1 month after the session, reductions only reached clinical significance at remote time frames during the 6-month follow-up. Depression symptoms decreased by 30% at 1-month follow-up and reached statistically significant improvement at 6-month follow-up ($t = 2.71$, $P = 0.03$) when symptoms were reduced by 55% from baseline. Administration of psilocybin was associated with statistically significant peak increases in heart rate (mean increase of 11.1 beats per minute), systolic blood pressure (mean increase of 21.9 mm Hg), and diastolic blood pressure (mean increase of 6.3 mmHg). These elevations all returned to baseline after 6 hours and did not produce long term sequelae. Heart monitoring demonstrated no sustained tachyarrythmias or heart block.

In a class III, modified double-blind, nonrandomized, active-placebo crossover trial, subjects with obsessive-compulsive disorder (OCD) (N = 9) participated in up to 4 individual nonguided psilocybin sessions with dosages ranging from very low (25 μg/kg), low (100 μg/kg), medium (200 μg/kg), and high (300 μg/kg).[20] Subjects must have failed to respond to at least one trial of standard treatment for OCD and tolerated at least one prior hallucinogenic experience. OCD symptoms decreased by 45% for all dosages at 24 hours postingestion. While not prospectively followed, 1 subject who completed all 4 dosage sessions reported sustained remission of symptoms at 6-month follow-up. One subject experienced transient hypertension 24 hours after ingestion, and 2 subjects dropped out due to discomfort with the hospital setting.

In the second class III trial, a secondary analysis of an open-label, crossover, uncontrolled trial, researchers studied the relationship between psilocybin and smoking cessation. In the original trial, patients with tobacco use disorder (N = 15) were treated with 2 or 3 psilocybin sessions during a 15-week course of cognitive-behavioral therapy, mindfulness practices, and imagery exercises.[11] Subjects then received weekly follow-up to reinforce treatment techniques. At 6-month follow-up, 12 of 15 (80%) subjects demonstrated laboratory confirmed abstinence. Those in remission reported significantly higher ratings of meaningfulness, spiritual significance, and impact on well-being of the psilocybin experience compared to those unable to quit smoking. Significant correlations were also identified between the personal meaning of the experience and both confidence to abstain ($r = 0.68$, $P = 0.005$) and reduced temptation to smoke ($r = -0.70$, $P = 0.004$). Ratings of intensity of the psilocybin session were not significantly different between the 2 groups. No lasting significant adverse events were reported, but 40% of subjects experienced at least 1 psilocybin session characterized by transient fear and feelings of being trapped that resolved by end of session.

DISCUSSION

This literature review identified 16 studies examining the potential benefits of 7 different hallucinogens for augmenting the treatment of 8 different psychiatry diagnoses: MDD, anxiety, PTSD, OCD, schizophrenia, alcohol use disorder, nicotine use disorder, and opioid use disorder. This broad, but thin, yield coupled with quality design issues (only 7 studies had a placebo or comparison group) and low power (only 6 studies had 50 or more participants) make it difficult to draw significant inferences. However, we can conclude that this body of pilot literature suggests the possibility of therapeutic benefit that could outweigh adverse events and warrants more rigorous, definitive investigation.

In 15 of the 16 studies, it was reported that hallucinogen monotherapy or augmentation therapy produced clinically significant reduction in symptomatology. Many of these improvements occurred in subjects who had previously failed to respond to traditional treatments. Furthermore, many studies demonstrated improvement in less time than commonly observed with traditional psychopharmacology or therapy. For example, psilocybin was reported to have reduced OCD symptoms by 45% within 24 hours of ingestion and 1 patient maintained remission at 6-month follow-up.[20] By comparison, serotonin reuptake inhibitors reduce OCD symptoms by 30% in 40% to 60% of patients.[36] In another study, 12 of 15 smokers treated with psilocybin achieved 6-month cessation compared with typical cessation rates of 35% for those treated with traditional medications.[11]

Ironically, 8 of the 16 studies, including a meta-analysis, examined the benefit of hallucinogens for substance use disorders and all but one reported significant benefits.[11,12,14,17,31–34] Ketamine's effectiveness in the treatment of alcohol use disorder was particularly noteworthy given the extensive history of drinking in the selected subjects.[12] The investigators attributed ketamine's success to its ability to improve unconscious emotional attitudes. However, another contributing factor may be that it reduced depression and anxiety independent of sobriety. LSD was theorized to help subjects obtain abstinence by alleviating rumination and preoccupation with negative thought content.[34] Regardless of cause, these pilot trials support investigators' advocacy for more studies to examine the potential benefit of hallucinogens and determine the mechanism of action that facilitates the restoration of sobriety.

Despite feared side effects, most subjects tolerated the treatments. The most notable adverse effects were that ayahuasca caused vomiting in half of those ingesting it and LSD exacerbated psychotic symptoms in subjects with schizophrenia.[35] Contemporary clinical trials of hallucinogens now exclude subjects with psychosis as treatment through symptom provocation is no longer practiced.

The known common side effects of hallucinogens include transient paranoia, mood changes, anxiety, sleep disturbances, headaches, and memory deficits.[1,37] In the studies discussed in this review, the most common side effects reported were acute increases in blood pressure and vomiting. Although a few instances of mood irritability did occur, these were able to be resolved by the treatment team. Reports of long-term side effects of hallucinogens also vary in the literature.[38,39] For example, MDMA is associated with persistent depression, anxiety, low self-esteem, as well as neuroendocrine

impairments, and memory deficits.[10] No studies reviewed in this study reported long-term adverse outcomes, including the DSM-5 condition of hallucinogen-persisting perception disorder. This may suggest that factors beyond the hallucinogen itself, such as genetics, comorbid substance abuse, additives, and setting contribute to adverse outcomes. Regardless, this finding also supports the need for longer term studies before these substances could ever be recommended or approved for therapeutic use.

In addition to the small sample sizes, multiple other limitations must be addressed in future studies. Many trials lacked quality, parallel control groups, making it impossible to determine to what extent the hallucinogen led to improvement versus the extensive time spent in therapy and the therapeutic treatment settings. Compounding this limitation was lack of feedback from subjects in some studies regarding the impact the hallucinogen had on their improvement. Comprehensive side effect rating scales were also not included in some studies, which may have led to an underrepresentation of side effects experienced. The side effects may have also been affected by selection bias, as some studies selected only subjects who had previously used hallucinogens. Individual studies also suffered from poor control, with subjects predicting which substance they were receiving, while the retrospective nature of other studies made causal relationships indeterminate.

The number of hallucinogenic sessions was not always standardized, and data correlating number of sessions with improvement was not documented. One ketamine trial also utilized 3 compounds in addition to ketamine.[12] These were bemegride to enhance emotional experience and visions, aethimizol to enhance storage of experiences in long-term memory, and nimodipine to improve memory of the psychedelic experience. The impact of these additives on the success of the trial is uncertain.

While the successes reported in the studies reviewed here are intriguing, they should not be misinterpreted as an endorsement for the use of hallucinogens to medicate any of the above conditions. This review was inherently biased by the selection criteria, and dangers of hallucinogenic drug use were not the focus of this review. This should not, however, distract from the potential benefits described. The improvements reported warrant further investigation into the mechanisms of action, duration of effects, and frequency of treatments needed to bring about improvement, as well as into the detailed side effect profiles of these agents. The impact of cultural stigma of a substance may also be of interest in determining if the results reported with native substances such as ayahuasca are reproducible across multiple cultures.

Future clinical trials must use parallel treatment groups as well as placebo-controlled comparison groups to draw meaningful conclusions despite the inherent challenge of finding a "blinded" placebo. Larger sample sizes will improve statistical power for detecting benefits and adverse events, and comparing subjects naive to hallucinogen use with those who have had previous hallucinogen experience may delineate efficacy and acute side effect profiles.

Despite promising findings in therapeutic hallucinogen trials, current factors, including funding, laws, and stigma, continue to impose limitations on further research. Schedule 1 classification makes study development difficult, costly, and prolonged. Funding by both government and pharmaceutical companies is nonexistent. The field does receive support from foundations such as the Heffter Institute and the Multidisciplinary Association for Psychedelic Studies, but these organizations rely on public donations. At some point, the field must overcome these barriers if we are to advance our knowledge about the impact of hallucinogenic agents on the treatment of serious mental conditions.

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