From Venerable Cultural Practices to Modern Psychological Solutions: Enter Entheogens into Mainstream Medicine

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Abstract

Entheogens, a class of psychoactive substances with profound cultural and religious significance, have been utilized for centuries across diverse traditions for healing, spiritual exploration, and communication with the divine. Their historical usage spans continents, from the pre-Columbian Americas to traditional African practices and Ayurvedic medicine in India. While entheogens offer potential therapeutic benefits, their use entails inherent risks, including physiological and psychological adverse effects.

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Recent research has increasingly focused on elucidating the mechanisms of action and therapeutic potential of entheogens such as psilocybin, N,N-dimethyltryptamine (DMT), mescaline, lysergic acid diethylamide (LSD), ayahuasca, ibogaine, and *Salvia divinorum*. These substances exhibit diverse pharmacological profiles, acting primarily on serotonin receptors and other neurotransmitter systems, resulting in alterations in perception, mood, and cognition.

Clinical studies have demonstrated promising results for entheogens in the treatment of psychiatric disorders, including depression, anxiety, addiction, and post-traumatic stress disorder (PTSD), and, to a lesser extent, pain management and cluster headaches. However, regulatory constraints, limited participant numbers, and ethical considerations hinder comprehensive research.

Safety considerations are paramount in administering entheogens, necessitating proper dosing, individual risk assessment, supportive set and setting, and medical supervision. Adherence to rigorous clinical trial standards and transparent methodologies is essential for advancing research and harnessing the therapeutic potential of entheogens.

Despite obstacles, continued investigation into entheogens is imperative for unlocking their therapeutic potential and developing safe and effective mental health treatments. Key research avenues include elucidating mechanisms of action, standardizing administration protocols, determining optimal dosages, and assessing long-term effects and associated risks.

While cannabis is commonly recognized as an entheogen, it was not encompassed in this review. The authors omitted it due to its unique status, ongoing discourse, and the need for a separate dedicated analysis.

Keywords: *Addiction, Bad Trips, Cluster Headaches, Flashbacks, Psychiatric Disorders, Psychoactive.*

Abbreviations: CNS: Central Nervous System; DMT: N,N-Dimethyltryptamine; DMN: Default Mode Network; IM: Intramuscular; IP: Intraperitoneally; IV: Intravenously; LSD: Lysergic acid diethylamide; MAO: Monoamine Oxidase; NMDA: N-methyl-D-aspartate; PNS: Peripheral Nervous System; PTSD: Post-Traumatic Stress Disorder; T_{max}: Time to Maximum Plasma Concentration; VTA: Ventral Tegmental Area

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Introduction

Entheogens are a class of psychoactive substances that have been used for centuries in various cultures and religious practices to produce altered states of consciousness and spiritual experiences. The term "entheogen" was first coined in the late 1970s by botanists and scholars who wanted to distinguish these substances from recreational drugs and emphasize their spiritual and religious significance (Kime, 2018; Thoricatha, 2015).

Entheogens play vital roles in diverse cultural and religious traditions. They have been used as tools for healing, divination, communication with spirits and ancestors, and connecting with the divine or experiencing mystical states of consciousness. In many traditional cultures, the use of entheogens is deeply intertwined with their cultural and spiritual heritage (Arce & Winkelman, 2021).

The earliest reported usage of entheogens dates back thousands of years and includes substances such as cannabis, opium, and the peyote cactus. In pre-Columbian America, entheogens were widespread and included sacred plants such as ayahuasca, San Pedro, and psilocybin-containing mushrooms (Carod-Artal, 2015). In Africa, iboga has been used for healing and spiritual purposes for centuries (Corkery, 2018). In India, Ayurvedic medicine has long used a variety of psychoactive plants (Alrashedy & Molina, 2016).

The use of ayahuasca by indigenous people in South America has spread to the West and other parts of the world, where it is used in spiritual communities and by individuals seeking healing and personal transformation (Frecska, Bokor, & Winkelman, 2016). The use of peyote by Native American communities has a controversial history, including persecution by the US government and struggles for religious freedom (Calabrese, 2013).

While entheogens offer potential therapeutic benefits, their usage also entails inherent risks. These risks include panic attacks, psychotic episodes, dehydration, heat stroke, or interactions with other medications (Schifano, Vento, Scherbaum, & Guirguis, 2023). However, recent research has shown that some of these substances may have therapeutic potential, particularly in the treatment of mental health disorders such as depression, anxiety, and addiction (Tupper, Wood, Yensen, & Johnson, 2015).

Studies on entheogens have increased in recent years, with a focus on substances such as psilocybin, ayahuasca, and lysergic acid diethylamide (LSD). Research on psilocybin has shown promising results in the treatment of depression and anxiety, with some studies showing that a single dose can produce lasting improvements in mood and well-being. Ayahuasca has been studied for its potential to treat addiction and has been shown to have antidepressant effects. LSD has also been studied for its potential therapeutic applications, particularly in the treatment of anxiety and end-of-life distress (Nichols, 2016).

The term "entheogen" is derived from the Greek words "entheos," meaning "full of the divine," and "genesthai," meaning "to generate" or "to bring forth." Entheogens are believed to facilitate experiences perceived as sacred or transcendent, leading to a deeper understanding of oneself, the universe, or spiritual realms (Thoricatha, 2015).

Discussion

Entheogens Trending in Medical Research

The most commonly reported entheogens include psilocybin, N,N-dimethyltryptamine (DMT), mescaline, lysergic acid diethylamide (LSD), ayahuasca, ibogaine, and *Salvia divinorum* (Garcia-Romeu et al., 2016). These substances vary widely in their chemical structure and pharmacological properties.

Psilocybin is the primary psychoactive compound found in certain species of mushrooms, particularly those in the genus *Psilocybe*. It is classified as a tryptamine alkaloid and has structural similarities to the neurotransmitter serotonin—carrying messages between nerve cells in the brain (central nervous system [CNS]) and throughout the peripheral nervous system (PNS). Psilocybin is rapidly dephosphorylated to psilocin, which produces its characteristic effects by acting as an agonist at serotonin receptors in the brain (Lowe et al., 2021). These effects are alterations in consciousness, mood, and perception, resulting in subjective experiences characterized by visual distortions and enhanced emotional processing.

DMT is a tryptamine alkaloid that occurs naturally in many plants and animals, including humans. It is a highly potent psychedelic compound that is typically smoked or brewed in a tea known as ayahuasca. DMT produces its effects by acting as a partial agonist at serotonin receptors, particularly the 5-HT_{2A} receptor, widely distributed in the CNS, especially in the brain region. DMT elicits rapid and intense alterations in consciousness characterized by vivid visual hallucinations, dissociative experiences, and profound changes in perception (Barker, 2018).

Mescaline is a psychoactive alkaloid found in the peyote cactus and certain other cactus species. It is structurally similar to amphetamines and produces its effects by acting as an agonist at several serotonin receptor subtypes, as well as at the dopamine receptor. Mescaline has a long history of use in Native

American religious traditions. Mescaline alters perception, mood, and cognition, often accompanied by sensory enhancement, synesthesia, and profound introspection (Dinis-Oliveira, Pereira, & Da Silva, 2019).

LSD is a synthetic compound derived from ergot fungus. It belongs to the class of compounds known as lysergamides. LSD acts as an agonist at serotonin receptors, particularly the 5-HT_{2A} receptor. It is recognized for inducing profound changes in perception and thought (Jastrzębski, Kaczor, & Wróbel, 2022; Passie, Halpern, Stichtenoth, Emrich, & Hintzen, 2008).

Ayahuasca is a traditional South American brew made from the Amazonian vine *Banisteriopsis caapi* and the leaves of the *Psychotria viridis* (chacruna) or *Diplopterys cabrerana* (chaliponga) plants. The active compounds in ayahuasca are DMT and beta-carboline alkaloids. Beta-carbolines are believed to inhibit the action of monoamine oxidase (MAO), allowing DMT to be orally active. Ayahuasca has been associated with alterations in serotonin receptor activity, modulation of brain connectivity, and subjective experiences encompassing heightened introspection, emotional processing, and potential therapeutic effects on mood disorders (Frecska et al., 2016; White, Kennedy, Ruffell, Perkins, & Ruffell, 2024).

Ibogaine is a psychoactive and indole alkaloid found in the roots of the iboga plant, which is native to Africa. It is used in traditional African religious practices and has gained attention in recent years for its potential to treat addiction. Ibogaine produces its effects by acting as an antagonist at the kappa-opioid receptor and a partial agonist at the serotonin 5-HT_2 receptor. Ibogaine alters mood, perception, and cognitive processes. Additionally, it has been shown to stimulate the production of growth factors that may contribute to its anti-addictive effects (Bouso et al., 2020; Corkery, 2018; Obembe, 2012).

Salvia divinorum is a plant native to Mexico that contains the psychoactive compound salvinorin A. Salvinorin A is a potent kappa-opioid receptor agonist and produces dissociative and often intense hallucinogenic effects. *Salvia divinorum* has been used in traditional Mazatec shamanic practices and has gained popularity in recent years as a recreational drug (Maqueda et al., 2015).

Table 1 provides an overview of where the receptors mentioned above are distributed in the human body.

Table 1. Specific Receptors and Their Distributions in the Human Body

Receptor	Distribution in Human Body
Serotonin	Central Nervous System (CNS): Found in various brain regions including the cortex, hippocampus, amygdala, and basal ganglia. Also present in the spinal cord.
	Peripheral Nervous System (PNS): Found in the gastrointestinal tract, blood vessels, platelets, and various other organs such as the liver, kidneys, and lungs.
5-HT_{2A}	Predominantly located in the cerebral cortex, particularly in areas associated with sensory perception, cognition, and mood regulation.
Dopamine	Central Nervous System (CNS): Concentrated in the substantia nigra and ventral tegmental area (VTA), with projections to various brain regions including the striatum.
	Peripheral Nervous System (PNS): Present in sympathetic ganglia and adrenal medulla, influencing functions such as heart rate, blood pressure, and renal blood flow.
5-HT_2	Mainly distributed in the brain, particularly in areas associated with mood regulation, such as the limbic system and frontal cortex.
Kappa-opioid	Central Nervous System (CNS): Found in regions involved in pain modulation, including the spinal cord and brain areas such as the periaqueductal gray and amygdala.
	Peripheral Nervous System (PNS): Present in peripheral sensory neurons and immune cells, contributing to analgesic effects and modulation of inflammatory responses.

Mechanisms of Action and General Psychological Effects

Psilocybin

Psilocybin is commonly ingested orally by eating the mushrooms directly or brewing them in tea.

After ingestion, psilocybin is primarily metabolized in the liver by cytochrome P450 enzymes, particularly CYP2D6, to the active metabolite psilocin—the actual active compound responsible for the effects of psilocybin—which then undergoes further metabolism by MAO enzymes before being excreted in the urine. Psilocybin and psilocin bind primarily to serotonin receptors in the brain, inducing a wide range of perceptual, cognitive, and emotional alterations (Dinis-Oliveira, 2017; Lowe et al., 2021).

The onset of action of psilocybin is typically 20 to 40 minutes after oral administration, with peak effects occurring within 60 to 90 minutes. The duration of effects is usually 4 to 6 hours, depending on the dose and route of administration. Psilocin and other metabolites have a half-life of approximately 50 minutes and are cleared from the body within 24 hours after ingestion (MacCallum, Lo, Pistawka, & Deol, 2022).

The clearance of psilocybin and its metabolites occurs mainly through the kidneys via excretion in urine, followed by bile and stool. The ratio of unchanged psilocybin to psilocin varies depending on the dose and route of administration, with psilocin being the dominant metabolite after oral administration (Matsushima, Eguchi, Kikukawa, & Matsuda, 2009).

Psilocybin is mainly administered orally in capsules or tablets under medical supervision. The doses range from 10 to 30 mg, with most of the trials using a standard dose of 25 mg (MacCallum et al., 2022; Matsushima et al., 2009; Ziff, Stern, Lewis, Majeed, & Gorantla, 2022).

DMT

DMT is most commonly self-administered through inhalation; other routes are injection, oral ingestion, and sublingual absorption. Inhalation is considered the most common and effective route, providing the most rapid onset of effects and the highest bioavailability (Barker, 2018). After inhalation, DMT is readily absorbed into the bloodstream and rapidly crosses the blood-brain barrier to reach the CNS (Barker, 2018).

The mechanisms of action of DMT are not yet fully understood. However, it is thought to act through multiple receptors, including 5-HT_{2A}, sigma-1, and trace amine-associated receptors, causing a wide range of perceptual, cognitive, and emotional changes (Barker, 2018).

DMT has a rapid onset of action, typically within seconds to minutes. Peak effects occur 5 to 10 minutes after inhalation and last less than one hour, depending on dose and route. DMT has a short half-life of 9 to 12 minutes, and the metabolites are eliminated mainly via renal excretion (Barker, 2018; Brito-Da-Costa, Da Silva, Gomes, Dinis-Oliveira, & Madureira-Carvalho, 2020; Good et al., 2022).

The clearance rate of DMT is rapid, estimated to be 26 L/min, suggesting that the elimination of DMT is independent of blood flow (Eckernäs, Timmermann, Carhart-Harris, Röshammar, & Ashton, 2022).

In medical trials, DMT has been mainly administered intravenously (IV) via bolus or infusion or intraperitoneally (IP) under medical supervision. IV doses range from 0.2 to 0.4 mg/kg, with most trials using 0.4 mg/kg as the highest dose (Vogt et al., 2023). In animal studies, the IP dose was 10 mg/kg (Barker, 2018).

Mescaline

Mescaline is commonly ingested orally by chewing the dried cactus buttons or brewing them in tea. After oral administration, mescaline is slowly absorbed from the gastrointestinal tract and metabolized mainly in the liver afterward.

Mescaline is a partial agonist of serotonin 5-HT_{2A} and 5-HT_{2C} receptors, resulting in cognitive, sensory, and affective alterations.

The onset of mescaline's effects is within 30 minutes after ingestion, with peak effects occurring within about 2 hours and a duration of up to 12 hours. Mescaline has a relatively long half-life of 6 hours.

It is metabolized mainly by oxidation and excreted in the urine. The majority of the dose is eliminated unchanged. The remaining dose is converted into inactive metabolites, primarily 3,4,5-trimethoxyphenylacetic acid.

In medical studies, there are no standardized routes of administration for mescaline. However, synthetic mescaline is usually administered orally. It has an effective oral dosage range of 200 to 400 mg, with most studies using a standard dose of 200 mg (Dinis-Oliveira et al., 2019; Thomann, Ley, Klaiber, Liechti, & Duthaler, 2022).

LSD

LSD is commonly ingested orally in a tablet, capsule, or blotter paper (Couper, 2016). Following oral administration, LSD is rapidly absorbed from the gastrointestinal tract and then distributed throughout the body with concentrations in organs such as the liver, gallbladder, lungs, kidneys, adipose tissue, blood plasma, and brain (Passie et al., 2008).

The brain stem and cortex contain LSD concentrations similar to each other, and LSD is equally distributed between white and gray matter in the brain (Passie et al., 2008).

LSD is thought to act primarily through binding to serotonin 5-HT_{2A} receptors, leading to altered sensory, emotional, and cognitive experiences (Jastrzębski et al., 2022; Passie et al., 2008).

The onset of effects of LSD is usually within 30 to 45 minutes after ingestion, with peak effects occurring within 1 to 2 hours and lasting up to 12 hours. LSD has a plasma half-life of 3 to 4 hours and is metabolized primarily in the liver. The major metabolite in urine is 2-oxylysergide (Okumuş, Metin, & Kariper, 2023; Passie et al., 2008).

LSD is excreted in urine within 24 hours, depending on dose, with only a small amount of LSD (1% or less) eliminated unchanged. The majority of LSD is metabolized to inactive compounds, such as O-H-LSD, and then excreted in the urine. However, it is reported that metabolites can still be detected in the urine after 4 days after ingestion (Passie et al., 2008).

In clinical research, LSD is administered through various routes, such as oral, IV, and intramuscular (IM) injection. Most studies using LSD involved oral administration of the drug, usually in a tablet or capsule. The dosage of LSD in these studies ranges from 20 to 800 mcg, with most studies using a standard dose of 100 to 200 mcg (Fuentes, Fonseca, Elices, & Farré, 2020; Liechti, 2017).

Ayahuasca

Ayahuasca is commonly ingested orally and contains compounds such as DMT and harmine, which can interact with different neurotransmitter systems in the human body.

After oral ingestion of ayahuasca, DMT and harmine are rapidly absorbed from the gastrointestinal tract and distributed throughout the body. DMT acts on serotonin 5-HT_{2A} and sigma-1 receptors, leading to psychedelic and clinically significant psychoactive effects. Harmine acts as an MAO inhibitor and increases the bioavailability of DMT, thus potentiating its pharmacological effects (Frecska et al., 2016; White et al., 2024).

DMT and harmine affect various target organs, such as the brain, heart, liver, and kidneys. Ayahuasca can modulate neuronal activity by activating the default mode network (DMN) and other cortical and subcortical regions. Ayahuasca's psychoactive effects include changes in mood, perception, and ego-death experiences (Frecska et al., 2016; White et al., 2024).

The onset of effects of ayahuasca is usually within 30 to 60 minutes after ingestion, with peak effects occurring within 1.5 to 2 hours. The duration of action is approximately 4 to 6 hours. DMT and harmine have a relatively short plasma half-life of 10 to 25 minutes and about 2 hours, respectively. After metabolism in the liver, harmine is excreted through the kidneys, while DMT is rapidly metabolized to inactive metabolites via MAOs and excreted in urine within 24 hours (Barker, 2018; Brito-Da-Costa et al., 2020; Campagnoli, Pereira, & Bueno, 2020).

Ayahuasca is typically administered orally in medical research. The dose of ayahuasca used in research can vary. According to specific reviews, the average ceremonial dose of DMT in ayahuasca preparations is about 27 mg, with an average ritual/ceremonial oral dose of ayahuasca being 100-150 mL for a 70 kg

person (Frecska et al., 2016; White et al., 2024). However, clinical studies have administered an oral dose of ayahuasca of 2.2 mL/kg (De Morais Santos et al., 2023). In the first-in-human clinical trial, 50 mg of DMT and harmine was administered as a capsule (Dornbierer et al., 2023).

Ibogaine

Ibogaine is commonly ingested orally in the form of capsules, tablets, or a crude extract. It is rapidly absorbed from the gastrointestinal tract and has a time to maximum plasma concentration (T_{max}) of approximately 2 to 6 hours (Luz & Mash, 2021).

The exact mechanisms of ibogaine's actions are not well understood, but it has been suggested to act on various neurotransmitter systems, including dopamine, serotonin, and glutamate. It acts as a non-competitive antagonist at the N-methyl-D-aspartate (NMDA) receptor, a partial agonist at the mu-opioid receptor, and an agonist at the kappa-opioid receptor. Ibogaine alters mood, perception, and cognitive processes (Luz & Mash, 2021).

The onset of effects of ibogaine is 1 to 3 hours and typically lasts from 24 to 72 hours, depending on the dose and individual metabolism. The active metabolite noribogaine is formed by the O-demethylation of ibogaine and has a considerably longer half-life than ibogaine, up to 30 hours (Dickinson et al., 2016; Luz & Mash, 2021).

Ibogaine and its metabolites are mainly excreted in urine, with small amounts being eliminated in feces and expired air. Ibogaine is primarily metabolized by oxidation through cytochrome P450 enzymes, particularly the CYP2D6 isoform, into various metabolites, including noribogaine and O-desmethylibogaine. Most of the dose of ibogaine is excreted in the urine and feces in 24 hours (Luz & Mash, 2021; Martins et al., 2022; Mash, Duque, Page, & Allen-Ferdinand, 2018).

In clinical research studies, ibogaine has been administered through various routes, such as oral, IM, and IV injection. The most common method of administration is oral ingestion, usually in the form of tablets, capsules, or a crude extract. The dose of ibogaine used in clinical research studies ranges widely, from 1 to 29 mg/kg, but most studies use a dose of 10 mg/kg (Martins et al., 2022).

Salvia divinorum

Salvia divinorum is commonly smoked, vaporized, or chewed, with smoking being the most common route of administration.

Salvinorin A, the primary psychoactive compound in *Salvia divinorum*, is rapidly absorbed through the oral mucosa or the respiratory tract into the bloodstream through the lungs and then distributed throughout the body and into the brain (Brito-Da-Costa, Da Silva, Gomes, Dinis-Oliveira, & Madureira-Carvalho, 2021).

Salvinorin A acts as a potent, selective agonist at the kappa-opioid receptor, producing dissociative and hallucinogenic effects. The kappa-opioid receptor is widely distributed throughout the brain and is involved in various processes, such as pain perception, mood regulation, and cognition (Brito-Da-Costa et al., 2021).

The onset of the effects of *Salvia divinorum* occurs within minutes. The duration of the effects varies depending on the dose and method of administration, with effects typically lasting about 30 to 60 minutes after smoking and up to 2 hours after oral consumption. The half-life of *Salvia divinorum* is not well documented in humans, but studies in rats suggest a half-life of approximately 10 minutes (Cunningham, Rothman, & Prisinzano, 2011).

The liver plays a minor role in *Salvia divinorum* metabolism, and the compound is primarily eliminated unchanged in the urine. The clearance pathways for *Salvia divinorum*'s metabolites remain unclear, but it is posited that a small portion of the compound is excreted in the bile and feces (Brito-Da-Costa et al., 2021).

Medical research on *Salvia divinorum* is limited. Subsequently, no standard administration method has been established for research purposes. *Salvia divinorum* is typically smoked or vaporized by study participants. The dose and method of administration in research studies vary widely, with some studies using standardized doses of *Salvia divinorum* preparations, while others rely on self-administration by participants (Brito-Da-Costa et al., 2021; Cunningham et al., 2011).

Table 2 summarizes the administration routes, medical administration routes, target organs or systems, target receptors, onset of effects, duration of effects, and type of effects for each entheogen.

Table 2. Administration Methods, Targets in the Human Body, and Effects

Substance	Administration Routes	Medical Administration Routes	Target Organs/Systems	Target Receptors	Onset of Effects	Duration of Effects	Type of Effects
Psilocybin	Oral (ingestion, brewing in tea)	Oral (capsules, tablets)	Central Nervous System (CNS), Peripheral Nervous System (PNS)	Serotonin (primarily)	20-40 minutes	4-6 hours	Perceptual, cognitive, emotional alterations
DMT	Inhalation, Injection, Oral, Sublingual	IV, IP (Intravenous, Intraperitoneal)	Central Nervous System (CNS)	5-HT_{2A}, sigma-1, trace amine-associated receptors	Seconds to minutes	Less than 1 hour	Perceptual, cognitive, emotional changes
Mescaline	Oral (ingestion, brewing in tea)	Oral	Central Nervous System (CNS)	Serotonin 5-HT_{2A}, 5-HT_{2C}	30 minutes	Up to 12 hours	Cognitive, sensory, affective alterations
LSD	Oral (tablet, capsule, blotter paper)	Oral, IV, IM (Intravenous, Intramuscular)	Central Nervous System (CNS), Peripheral Nervous System (PNS)	Serotonin 5-HT_{2A}	30-45 minutes	Up to 12 hours	Altered sensory, emotional, cognitive experiences
Ayahuasca	Oral (ingestion)	Oral	Central Nervous System (CNS), Peripheral Organs	Serotonin 5-HT_{2A}, sigma-1	30-60 minutes	4-6 hours	Changes in mood, perception, ego-death experiences
Ibogaine	Oral (capsules, tablets, crude extract)	Oral, IM, IV (Intramuscular, Intravenous)	Central Nervous System (CNS), Peripheral Organs	NMDA, mu-opioid, kappa-opioid	1-3 hours	24-72 hours	Altered mood, perception, cognitive processes
Salvia divinorum	Smoking, Vaporization, Chewing	Not established	Central Nervous System (CNS)	Kappa-opioid	Within minutes	Up to 2 hours	Dissociative, hallucinogenic effects

Potential Therapeutic Benefits and Notable Medical Applications

Entheogenic substances have shown potential therapeutic benefits for several psychiatric disorders, including addiction, anxiety, depression, and post-traumatic stress disorder (PTSD), as well as pain management and cluster headaches (Table 3).

Table 3. Overview of the Clinical Applications of Each Entheogen

Entheogen	Addiction	Anxiety	Depression	PTSD	Pain Management	Cluster Headaches
Psilocybin		✓	✓	✓		✓
DMT	✓		✓			
Mescaline	✓	✓	✓			
LSD		✓				
Ayahuasca	✓	✓	✓			
Ibogaine	✓					
Salvia divinorum	✓				✓	

Note: The data in the above table are derived the following sources: Bouso et al. (2020), Brito-Da-Costa et al. (2021), Cunningham et al. (2011), Dinis-Oliveira (2017), Dornbierer et al. (2023,) Holze et al. (2022), Krediet et al. (2020,) Liechti (2017), MacCallum et al. (2022), Nichols (2016), and Thomann et al. (2022).

Adverse Effects of Entheogens

There are several potential adverse effects associated with the use of entheogenic substances. Short-term effects can include nausea, vomiting, anxiety, panic attacks, and psychotic symptoms such as paranoid ideation, hallucinations, and thought disturbances. Long-term effects may include changes in mood, perception, and cognition, as well as the development of persistent psychotic symptoms such as delusions and mood disorders. (Refer to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition [DSM-5], Section II "Bipolar and Related Disorders" and "Depressive Disorders" for a review of specific mood disorders).

Psilocybin exhibits a low potential for abuse and toxicity. Nonetheless, it can induce adverse reactions, including nausea, vomiting, panic attacks, and mydriasis. Recent trials have demonstrated its efficacy in reducing depressive symptoms, but some studies indicate potential long-term mood and behavioral changes (Lowe et al., 2021).

DMT, while having low toxicity and abuse potential, may lead to persistent psychotic symptoms with prolonged use. Adverse effects such as panic attacks, seizures, and psychotic symptoms have been reported (Frecska et al., 2016; White et al., 2024).

Mescaline shares similar low toxicity and abuse potential traits. While it shows promise in anxiety and depression treatment, there's a risk of persistent psychotic symptoms (Dinis-Oliveira et al., 2019).

LSD presents potential addiction risks, with higher doses increasing the likelihood of a "bad trip" or flashbacks post-discontinuation (Fuentes et al., 2020; Liechti, 2017).

Ayahuasca can elevate heart rate and blood pressure, posing risks for individuals with heart conditions and potentially leading to complications such as heart failure or stroke. Additionally, it carries a potential risk of developing psychotic symptoms (Brito-Da-Costa et al., 2020; Dornbierer et al., 2023).

Ibogaine, effective in addiction treatment, may cause vomiting, nausea, and bradycardia. Higher doses can induce pharmacologic psychosis, necessitating specialized medical supervision (Mash et al., 2018).

Salvia divinorum's adverse effects are not fully elucidated due to limited research, but studies suggest potential adverse reactions, including nausea, vomiting, and persistent mood and behavioral changes (Brito-Da-Costa et al., 2021; Zawilska & Wojcieszak, 2013).

The potential negative effects of entheogens may depend on several factors, including the method of administration, dose, and individual factors (e.g., age, medical history, and co-occurring psychiatric conditions). Adverse effects can be reduced through proper medical supervision and the use of appropriate dosage.

Safety Considerations

The safety and efficacy of entheogenic substances depend on several factors, including the set and setting of use, dose, individual mental and physical health, and the quality of the substance administered.

The term "set" refers to an individual's mindset, prior experience with drugs, and overall personality, while "setting" refers to the physical and social environment in which the drug is consumed (Hartogsohn, 2017).

Some studies have suggested that the set and setting of entheogen use can significantly influence the nature of the experience and associated psychological outcomes. Using entheogens with supportive personnel and integrated practices in a therapeutic setting can lead to positive and lasting outcomes. However, adverse outcomes can occur if the setting is unsupportive or non-therapeutic (Dos Santos, Bouso, Rocha, Rossi, & Hallak, 2021; Hartogsohn, 2017).

The dose of entheogenic substances is another crucial factor, as many adverse effects can be the result of taking excessively high doses. Studies have suggested that appropriate dosing regimens with entheogens, administered under proper medical supervision, can lead to positive therapeutic outcomes with a low likelihood of abuse or clinically significant adverse effects (Dos Santos et al., 2021; Elsey, 2017).

The mental and physical health of individuals should be assessed before the administration of entheogenic substances to ensure their safety. Certain health conditions, such as heart or lung disease or a history of psychiatric disorders, may make individuals more vulnerable to developing adverse reactions. Medical supervision of entheogen use minimizes negative outcomes (Marrocu et al., 2024; Schlag, Aday, Salam, Neill, & Nutt, 2022).

The quality of the substance being ingested is also critical, as some entheogenic compounds adulterated with other substances can lead to severe consequences. Toxic substances can cause liver damage, while impure substances can cause gastrointestinal distress, muscle tremors, and other negative symptoms (Baumeister, Tojo, & Tracy, 2015; Jo, Hossain, & Park, 2014). Obtaining these compounds from a reliable source and testing them for purity can minimize the risk of unwanted effects.

The safety of entheogenic substances requires proper dosing, individual risk assessment, mental support, and medical supervision, as well as set and setting considerations.

Limitations of Research

The scientific exploration of entheogenic compounds is nascent, accompanied by various challenges and constraints. These include issues such as the breaking blind problem, placebo effects, and the absence of a well-defined mechanism of action for many of these agents.

Entheogenic substances often induce profound perceptual alterations, complicating clinical trials to demonstrate therapeutic efficacy. Moreover, limited participant numbers in such trials hinder conclusive safety and efficacy determinations (Barker, 2018; Vogt et al., 2023).

Regulatory skepticism and funding hurdles further impede entheogenic research progress. Ethical complexities demand meticulous participant safeguarding (Pilecki, Luoma, Bathje, Rhea, & Narloch, 2021).

Despite obstacles, continued investigation is imperative to unravel entheogens' therapeutic potential. Key research avenues include elucidating their mechanisms of action, devising standardized administration protocols, and determining optimal therapeutic dosages (Madrid-Gambin et al., 2023). Long-term effects and associated risks also warrant investigation.

Adherence to rigorous clinical trial standards and transparent methodologies is crucial. Enthusiasm for entheogenic applications in psychiatry underscores the need for rigorous research to develop safe, effective mental health treatments (Aday et al., 2022).

Conclusion

Entheogens, encompassing substances such as psilocybin, N,N-dimethyltryptamine (DMT), mescaline, lysergic acid diethylamide (LSD), ayahuasca, ibogaine, and *Salvia divinorum*, represent a burgeoning area of interest in medical research due to their potential therapeutic applications in various psychiatric disorders and pain management. These substances exert their effects primarily through interactions with serotonin receptors and other neurotransmitter systems in the brain, leading to profound alterations in perception, mood, and cognition.

Clinical studies have demonstrated promising results in the treatment of addiction, anxiety, depression, post-traumatic stress disorder (PTSD), and cluster headaches. However, safety considerations are paramount, with adverse effects including nausea, vomiting, anxiety, panic attacks, and potential long-term mood and behavioral changes. Proper medical supervision, dosage regulation, and consideration of individual health factors are essential to mitigate these risks.

Challenges in entheogenic research include regulatory obstacles, funding constraints, ethical complexities, and methodological limitations. Despite these challenges, continued investigation is imperative to unlock the therapeutic potential of entheogens. Future research should focus on elucidating mechanisms of action, standardizing administration protocols, determining optimal dosages, and assessing long-term effects and associated risks.

Conflict of Interest Statement

The authors declare that this paper was written without any commercial or financial relationship that could be construed as a potential conflict of interest.

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