Natural Psychedelics

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Faculty

Chelsey McIntyre, PharmD, is a clinical editor for Natural Medicines, a clinical reference database focused on natural products and alternative therapies. She earned her Bachelor of Science degree in Genetics from the University of California, Davis. She then went on to complete her PharmD at Creighton University, followed by a clinical residency at the Children's Hospital of Philadelphia (CHOP). Dr. McIntyre held the position of Clinical Drug Information and Policy Development Pharmacist at CHOP until her move to Washington state in 2017. Since that time, she has worked with the Natural Medicines database at TRC Healthcare. Her professional interests include provider and patient education, as well as the application of evidence-based research to patient care, particularly in patients with chronic conditions.

Faculty Disclosure

Contributing faculty, Chelsey McIntyre, PharmD, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Division Planner

Margaret Donohue, PhD

Senior Director of Development and Academic Affairs

Sarah Campbell

Division Planner/Director Disclosure

The division planner and director have disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Audience

This introductory course is designed for healthcare professionals whose patients are taking or have questions about natural psychedelic products.

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Course Objective

The purpose of this course is to provide psychologists with an increased understanding of natural psychedelics and the considerations associated with the safety, effectiveness, and legal use of these substances.

Learning Objectives

Upon completion of this course, you should be able to:

1. Define the terminology associated with psychedelic substances.
2. Review the regulatory and practical limitations to conducting research on natural psychedelics.
3. Identify the most commonly used natural psychedelics and their active constituents.
4. Discuss the evidence for the use of natural psychedelics for therapeutic purposes.

EVIDENCE-BASED PRACTICE RECOMMENDATION

Sections marked with this symbol include evidence-based practice recommendations. The level of evidence and/or strength of recommendation, as provided by the evidence-based source, are also included so you may determine the validity or relevance of the information. These sections may be used in conjunction with the course material for better application to your daily practice.

INTRODUCTION

Natural psychedelics have a long history of use in various cultures. This history covers a wide range of uses, including within sacred rituals and as therapeutic remedies. Over the past several decades, many of these substances have also become known for their use as recreational drugs. However, there has also been growing interest in the mainstream use of psychedelics as medical treatments, particularly for mental health disorders.

Some of this interest focuses on synthetic chemicals that have other accepted medical uses, such as ketamine. However, there is also a growing interest and body of research on the use of natural psychedelics, which are derived from plants. This course will focus on the natural psychedelics.

DEFINITIONS

Hallucinogens are a class of psychoactive drugs that can produce altered states of consciousness characterized by major alterations in thought, mood, and perception, among other changes. Hallucinogens can be split into three sub-categories: psychedelics, dissociatives, and deliriants [1; 2].

Psychedelics are substances causing unusually strong experiences of color, sound, smell, taste, and touch, and other mental effects, such as feelings of deep understanding or hallucination. Examples of chemicals in this class include dimethyltryptamine (DMT), ibogaine, lysergic acid diethylamide (LSD), and psilocybin. Although a psychedelic is considered a hallucinogen, not all hallucinogens are considered psychedelics.

Dissociatives are substances that cause feelings of separation and detachment from the body or physical environment. At high doses, these substances can cause analgesia, amnesia, and cataplexy. They can also cause hallucinations and other changes in thoughts, emotions, and consciousness. Examples of drugs in this class include ketamine, phencyclidine (PCP), and nitrous oxide.

Deliriants are substances that cause a state of delirium, often characterized by confusion and a lack of control of one's actions. Angel's trumpet (*Brugmansia suaveolens*), western jimsonweed (*Datura wrightii*), jimsonweed (*Datura stramonium*), and henbane (*Hyoscyamus niger*) are all considered deliriants.

Many plants that are classified as deliriants exert their effects via anticholinergic activity. These effects are often caused by tropane alkaloids, many of which (e.g., scopolamine, atropine) have known therapeutic uses when purified and administered in small doses. Because the quantity of these constituents can vary based on growing conditions, time of year, and method of preparation, many of these plants are considered toxic. In fact, deaths have been reported with even small doses of many popular deliriants, including jimsonweed and angel's trumpet [3; 4].

This course will focus on plants and plant-derived chemicals that have been traditionally classified as psychedelics.

PSYCHEDELICS AS THERAPY

Although psychedelics are considered to be a promising option for the treatment of mental health disorders, understanding of their effects is limited. Much of the original interest in this use grew out of anecdotal reports of promising improvements after recreational use. Since that time, some exploratory research has further encouraged interest in this area.

Most psychedelics exert their effects via the serotonin (5-HT) system. This system is involved in the pathology and treatment of psychiatric disorders, including depression, anxiety, and cognitive deficits. Although many psychedelic chemicals are thought to exert effects via a number of other pathways as well, the known activity within the serotonin system has been considered supportive of the potential use of psychedelics for mental health care [5].

Exploratory research in humans has also confirmed that psychedelic substances can alter the function of the brain. For example, LSD and psilocybin have been shown to increase connectivity between some regions of the brain and decrease connectivity between others. These chemicals have also been shown to alter the level of blood flow to different regions of the brain. Other research has indicated that various psychedelic chemicals might alter the processing of sensory information, including emotions and facial expressions, which may have a measurable improvement in certain mental health conditions [5].

UNIQUE CONSIDERATIONS

Natural psychedelics present a unique set of considerations that should be kept in mind with any type of use, from recreational to therapeutic.

LEGAL CONCERNS

Since the 1970s, most psychedelic substances have been classified as Schedule I controlled substances by the U.S. Drug Enforcement Agency (DEA). This classification indicates that these substances have "no currently accepted medical use and a high potential for abuse." Although many countries have imposed similar restrictions on these substances, a small number of countries, such as Portugal and the Netherlands, have not criminalized their use [1].

The use, possession, sale, and manufacture of Schedule I substances is considered federally illegal. As such, the heavy restrictions placed on these chemicals can make it very difficult to conduct both preclinical and clinical research. In the late 1990s, the DEA began to permit limited research on certain psychedelics; however, there are still many barriers to conducting research on these substances [1].

Although the federal regulatory status of psychedelics in the United States has remained the same since the 1970s, other changes are occurring. For example, the U.S. Food and Drug Administration (FDA) has designated some psilocybin-based therapies as breakthrough therapies for treatment-resistant depression [6]. This status is intended to expedite the development and review of drugs that may treat a serious condition. Also, some municipalities and states have moved toward decriminalizing certain psychedelic substances, typically psilocybin, and developing laws that allow for the supervised use of these substances [7].

Over the past two decades, research has begun to suggest that certain psychedelic substances may carry a low potential for dependence and provide possible therapeutic benefits. If these findings are replicated in high-quality research, this may prompt a review of the Schedule I classification for certain chemicals [1].

RESEARCH LIMITATIONS

Although higher-quality research on some psychedelic chemicals has recently become available, much of the older research in this area is limited to anecdotal reporting. This introduces a risk for reporting bias, a situation in which there may have been a tendency to report on positive, but not negative, outcomes. Additionally, even though many of the studies being conducted today are utilizing a randomized, controlled design, even these studies are subject to inherent weaknesses that occur with the use of psychedelic chemicals [8].

Appropriate Placebo Selection

There is still significant controversy on the selection of an appropriate placebo for psychedelic research. Examples of placebos used in recent clinical trials include very low, nontherapeutic doses of the same psychedelic substance being evaluated, as well as treatment doses of drugs with known neurologic effects, such as diphenhydramine. However, the majority of patients in these studies have been able to accurately guess the treatment group to which

they were assigned. Inadequate blinding and masking prevent studies from appropriately controlling for a placebo effect, which may skew study results.

Subject Expectations

Many patients enrolled in studies of psychedelic products have preconceived expectations related to the upcoming experience, referred to as response expectancy. This confounder is a known issue in the field of psychiatry and has been discussed in relation to the study of antidepressants. For psychedelics, response expectancy can further undermine attempts to control for the placebo effect. This can result in subjective reports that indicate a greater positive effect with the psychedelic chemical and general absence of effect with the placebo.

Controlled Environment

Research on the use of psychedelics to date has typically provided the study subjects with a highly controlled, positive environment in which to experience the effects of the substance. For example, many studies allow or require the subject to remain in a clinic environment, with access to a therapist, for eight hours after dosing. If the intent is for patients to take the substance outside of a clinic, this experience is dissimilar from the intended use of psychedelic chemicals. However, to date, therapeutic use of psychedelics has been limited to controlled clinical settings.

When these individual limitations are considered together, their potential to result in an overestimation of the treatment effect becomes even greater. Experts in the field have recommended standard assessments of blinding/masking and response expectancy to provide a clearer picture of the risk of bias in any given study. These limitations should be kept in mind when interpreting the literature in this area.

OTHER SPECIAL CONSIDERATIONS

Whole Plant versus Isolated Chemical

Some people may choose to consume a fresh or dried plant for psychedelic effects. Others may choose to consume psychedelic chemicals that have been purified from these plants. These differing sources are often discussed interchangeably by the media and consumers. However, it is important to recognize that these two different sources may provide very different effects.

For example, consuming psilocybin mushrooms can produce a psychedelic effect. However, the concentration of psilocybin (the chemical responsible for this effect) present varies from 0.37% to 1.3% depending on the exact species of mushroom consumed. Further, samples of psilocybin mushrooms obtained from various sources have yielded psilocybin concentrations that vary by a factor of four to ten [9; 10; 11]. For most plants, the time of year that harvesting occurs, as well as the methods used to harvest and process the plant, can also significantly alter chemical composition.

Purified psilocybin, however, can be given in very exact doses, similar to a prescription drug. When psilocybin is evaluated in clinical research, it is provided and dosed in the purified form, ensuring consistent potency and reproducible effects. The use of psilocybin mushrooms, on the other hand, would be expected to provide less consistent effects and potency.

This consideration is important for all natural psychedelics, as the psychedelic effects of any given plant are mostly obtained from one or two constituents found in that plant. Some examples include:

- Ayahuasca: This concoction is made from whole plants and contains DMT.
- Iboga: This plant contains the psychedelic alkaloids ibogaine, ibogaline, and ibogamine
- Peyote: This cactus contains the psychedelic chemical mescaline.
- *Salvia divinorum*: The leaf of this herb contains salvinorin A, a psychedelic chemical.

When potency concerns are raised, many people immediately consider the impact on therapeutic and psychedelic effects. However, variable potency can also lead to the development of significant and unexpected adverse effects that do not occur consistently with each use. There are many case reports of whole psychedelic plants causing serious adverse effects and even death in people with a history of use [119].

Therapeutic Dosing versus Microdosing

As might be expected, psychedelic substances have traditionally been used in doses that are intended to exert a hallucinogenic effect. Most often, psychedelics are taken in single doses or isolated doses taken weeks or months apart from each other. Similar doses are also used in clinical research and tend to be considered "therapeutic" doses for these chemicals.

However, there has been interest in the use of very small doses that are not expected to exert a hallucinogenic effect. These small doses, referred to as microdoses, are not strictly defined, but are often about 10% of the amount that would be expected for a "medium to high" single therapeutic dose, taken either every three days or two to four times per week [9; 12].

The theory behind this dosing strategy is that regular use of nonpsychedelic doses will boost mood and energy and reduce anxiety without causing a hallucinogenic high. Unfortunately, any research on this theory is very limited and most publications provide only anecdotal reports. Currently, people who utilize this dosing strategy have self-selected for this use and have determined their own dosing regimen. Thus, this form of treatment is thought to be particularly prone to response expectancy and a placebo effect [9; 13].

Microdosing with psilocybin mushrooms may be particularly difficult, as concentrations of the psychedelic substance can vary widely between mushrooms. These concentrations can also change depending on whether the mushroom has been processed in any way.

Many people aiming to microdose have ended up taking much larger doses than intended, leading to hallucinations, paranoia, and increased blood pressure and heart rate. Even when doses are correctly measured, there is limited information on the short- and long-term safety of this practice [9; 12].

NATURAL PSYCHEDELICS

AYAHUASCA (DMT)

Ayahuasca is a psychotropic drink that is used for therapeutic and religious rituals in several Amazonian countries, including Brazil, Peru, Colombia, and Ecuador. The word ayahuasca is based on the Quechua language and comes from *aya*, meaning spirit or soul, and *huasca*, meaning rope or vine [14; 15; 16; 17; 18; 19; 20].

Ayahuasca is most commonly brewed by boiling the vine of *Banisteriopsis caapi* with the leaves of *Psychotria viridis*. In some cases, other plants, such as *Diplopterys cabrerana* and other *Psychotria* species, may be used as the source of leaves, or the leaves may be excluded entirely.

Regardless of the specific ingredients used, ayahuasca brews contain DMT, a known psychedelic chemical. Some other constituents, including harmine and tetrahydroharmine, may act to enhance the psychedelic effects of DMT [19; 21; 22; 23; 24]. DMT is classified as a Schedule I controlled substance by the DEA [121].

In addition to ayahuasca's historical use in rituals, there has also been growing interest in its use as a therapeutic agent for various mental health disorders. In fact, some resorts and clinics in Mexico, where ayahuasca is legal, now offer ayahuasca-based retreats.

The exact contents of ayahuasca change with each brew, and the concentration of its therapeutic constituents can vary significantly. Most tested preparations of ayahuasca have been found to contain DMT in quantities ranging from 0.088 mg/mL to 2.687 mg/mL and harmine in quantities ranging

from 0.14 mg/mL to 4.44 mg/mL [24]. This wide variability from batch to batch would be expected to significantly alter any therapeutic or adverse effects that occur with use.

Mechanism of Action

DMT is a serotonin (5-HT) 2A, 2C, and 1A receptor agonist in the central nervous system (CNS). Harmine is a reversible inhibitor of monoamine oxidase (MAO)-A. This is thought to enhance the effect of DMT by inhibiting its metabolism in the gastrointestinal tract and allowing larger quantities to reach the CNS. Another constituent, tetrahydroharmine, has demonstrated activity as a selective inhibitor of serotonin reuptake, which may also produce neurologic effects [25].

However, there is limited reliable research on the actual effects of ayahuasca in humans. The available literature suggests that any effects may be dose- and patient-dependent. Some animal research suggests that low doses may produce stimulant effects, whereas high doses may reduce CNS activity. A small study in humans suggests that baseline mental health diagnoses may alter the outcomes of ayahuasca use [120].

Clinical Effects

Depression

To date, evidence on the use of ayahuasca for depression is limited to very small, low-quality trials, most of which were conducted in Mexico. In one trial of 29 patients with moderate-to-severe treatment-resistant depression, taking a single dose of ayahuasca 1 mL/kg moderately improved symptoms of depression after seven days when compared with placebo. The response rate with ayahuasca was two- to three-fold greater than that seen with placebo [23]. Two small, open-label trials in patients with recurrent major depressive disorder show that taking a single dose of ayahuasca 2.2 mL/kg improved symptoms of depression when compared with baseline [26; 27].

The U.S. Department of Veterans Affairs asserts that ayahuasca use may be associated with a short-term reduction in depression symptoms and suicidality. (https://www.hsrd.research.va.gov/publications/esp/psychedelics-mh-brief.pdf. Last accessed June 16, 2023.)

Level of Evidence: Low

Prolonged Grief Disorder

One observational study in patients with prolonged grief disorder found that taking part in a retreat including four to nine ceremonial ayahuasca experiences was associated with moderately reduced grief severity when compared with baseline. About 50% of the patients at the retreat attributed a sense of healing to the ayahuasca [19]. There is no prospective clinical research evaluating ayahuasca for this purpose.

Substance Use Disorder

There is interest in the use of ayahuasca for multiple forms of substance use disorder, including alcohol, opioids, cannabis, and mixed substances. However, no prospective clinical research has evaluated its use for this indication.

Observational research in patients with multiple self-reported addictions has found that taking ayahuasca twice during a four-day group-counseling retreat is associated with improved feelings of hopefulness, empowerment, mindfulness, and quality of life for up to six months after the retreat. Use of alcohol, tobacco, and cocaine, but not cannabis or opioids, may also decrease [28].

Safety

Ayahuasca has been associated with a number of adverse effects, ranging from mild to severe. The most common adverse effects reported with use include gastrointestinal upset, mydriasis, slurred speech, tingling, trembling, and sweating [21; 23; 26; 27; 30; 31]. It can also cause transient elevations in blood pressure and heart rate that typically return to normal after 30 minutes [16; 21; 32].

The hallucinations that occur with ayahuasca can last for several hours and may cause disorientation, delusion, agitation, and dissociation [16; 21; 110].

Some of the more serious adverse effects reported with use have included convulsions, coma, and psychosis. However, due to the anecdotal nature of many of these reports, it is unclear if ayahuasca was the cause or if there were other precipitating factors [25; 33; 34; 35].

Interactions

Some of the alkaloids in ayahuasca, such as harmine and harmaline, have been shown to inhibit cytochrome P450 (CYP) 2D6 and 3A4 in laboratory research. Although this effect has not been confirmed in humans, ayahuasca should be used with caution in patients taking drugs that are substrates of these enzymes [36].

Because DMT, harmaline, and harmine all have serotonergic effects, or the ability to enhance the serotonergic effects of other substances, ayahuasca should be used with caution in patients taking serotonergic drugs. In fact, there has been at least one case report of serotonin syndrome in a patient who was stabilized on fluoxetine 20 mg daily and consumed ayahuasca 100 mL [25; 37].

Serotonin syndrome occurs when high levels of serotonin build up in the body, typically due to the use of multiple drugs that increase serotonin levels. Although this is a rare occurrence, serotonin syndrome can be life-threatening. Symptoms include shivering, diarrhea, muscle rigidity, tremors, fever, severe headache, altered mental status, and seizures.

Although many drugs may have minor serotonergic activity, the drug classes most commonly associated with serotonin syndrome include:

- Monoamine oxidase inhibitors (MAOIs)
- Selective serotonin reuptake inhibitors (SSRIs)
- Selective serotonin-norepinephrine reuptake inhibitors (SNRIs)
- Tricyclic antidepressants (TCAs)
- Atypical antipsychotics

The risk for serotonin syndrome increases with the addition of each serotonergic drug to any drug regimen. However, the risk is highest when MAOIs are used in combination with other serotonergic drugs. This is because MAOIs inhibit the breakdown of serotonin, perpetuating the effects of other serotonergic agents.

Many herbs and supplements can also increase the risk for serotonin syndrome and should be included in patient risk evaluations.

Summary

Although there have been many promising anecdotal reports suggesting that ayahuasca may be beneficial in patients with treatment-resistant mental health disorders, there is not enough clinical research to support its use for any purpose. Additionally, ayahuasca should be used with caution in patients with certain underlying conditions and medication regimens.

HAWAIIAN BABY WOODROSE (LYSERGIC ACID AMIDE)

Hawaiian baby woodrose (*Argyreia nervosa*), also referred to as elephant creeper, is a flowering vine that grows in Florida, California, and Hawaii. The seeds of this plant are sometimes touted online as "natural LSD" due to the presence of a chemical called lysergic acid amide (LSA), which is structurally similar to LSD. This plant and others containing LSA have been used in shamanistic rituals in South America [111].

The seeds of the plant have been shown to contain LSA in concentrations up to 83%. However, the alkaloid content of the seeds varies significantly from batch to batch. When used recreationally, the seeds may be eaten whole, crushed, or soaked in water [38; 112]. Despite the presence of a known psychoactive chemical, this plant and its seed remain legal for sale in the United States.

Mechanism of Action

LSA has effects at the dopamine D2 receptor. It also seems to be a partial agonist or antagonist at adrenergic and serotonergic receptors, including serotonin 2A. The hallucinogenic effects that occur with LSA are thought to be similar to those seen with LSD [39; 40]. However, LSD is a synthetic chemical that does not occur in nature.

LSA in doses of 2–5 mg is considered enough to cause hallucinations. In pharmacokinetic studies, LSA has become detectable in the blood within 30 to 40 minutes of ingestion and levels continue to increase for approximately 90 minutes. Psychedelic effects are reported to last approximately four to eight hours [41; 42; 43].

Clinical Effects

Hawaiian baby woodrose continues to be used primarily as a recreational drug and has not garnered attention as a potential therapeutic agent. There is currently no clinical research evaluating its use for any medical purpose.

Safety

Hawaiian baby woodrose has been associated with many side effects, including nausea and vomiting, fatigue, dizziness, mydriasis, and sweating, as well as elevations in blood pressure and heart rate. In addition to hallucinations, it has also been reported to cause blurred vision and altered visual perception. Multiple reports also suggest that consuming the seeds of this plant can cause suicidal ideations, paranoia, weakness, and vertigo [38; 41; 42; 43].

Interactions

Hawaiian baby woodrose has serotonergic effects and should be used with caution in patients taking other serotonergic agents. It may increase the risk of serotonin syndrome.

Summary

There is no known medical use for Hawaiian baby woodrose; its primary use has been for recreational purposes, as a "natural" source of an LSD-like chemical. Because its use is associated with many adverse effects, some serious in nature, it should not be recommended for any purpose.

IBOGA (IBOGAINE)

Iboga (*Tabernanthe iboga*) is a shrub that grows wild in certain parts of Africa. Its root bark is used in some ceremonial practices for its hallucinogenic and stimulant properties. The root bark contains the psychoactive chemical ibogaine. It also contains a number of other constituents that are thought to contribute to hallucinogenic effects, including ibogaline, ibogamine, and tabernanthine [44; 45; 46; 47].

Although iboga has a long history of traditional use, any modern research for therapeutic purposes has used purified ibogaine only. It is not clear how much ibogaine is naturally found in iboga, or how the processing of iboga may alter the total ibogaine content. Ibogaine is classified as a Schedule I controlled substance by the DEA [121].

Mechanism of Action

Pure ibogaine has been shown to exert serotonergic effects, act as an agonist at kappa-opioid receptors, and act as an antagonist at *N*-methyl-D-aspartate (NMDA) receptors. Noribogaine, a metabolite of ibogaine, seems to have overlapping, and possibly stronger, affinities for these same receptors. Noribogaine has also demonstrated activity at the mu-opioid receptor [48; 49].

Clinical Effects

There is interest in the use of iboga for various purposes, including depression, fatigue, and sexual arousal. However, all available clinical reports are specific to ibogaine, are anecdotal or observational in nature, and evaluate patients with substance use disorders.

Multiple case series in patients with opioid use disorder suggest that ibogaine may offer some benefit for the acute relief of opioid withdrawal symptoms. These reports also suggest that some patients may experience long-term relief of withdrawal symptoms for up to 14 weeks. The doses used in these studies ranged from a single dose of 12–25 mg/kg to 25–55 mg/kg provided over multiple doses within 24 to 96 hours [49; 50; 51; 52].

One observational study in patients in withdrawal due to opioid dependence has found that taking ibogaine 25–55 mg/kg, given in multiple doses over 24 to 96 hours, is associated with a reduction in addiction severity, drug use, and feelings of depression for 12 months after treatment [52]. An additional observational study has found that providing ibogaine as part of a one-week detoxification protocol for opioid use is associated with the elimination or significant reduction of withdrawal symptoms in 80% of patients. Additionally, cravings and opioid use were modestly reduced [53].

One observational report evaluated the effects of ibogaine in patients with mixed substance use disorder—these patients primarily had cocaine use disorder, but some also used alcohol, tobacco, and cannabis. A single dose of ibogaine was associated with 5.5 months of self-reported abstinence; multiple doses of ibogaine were associated with 8.4 months of self-reported abstinence. It is important to note, however, that these patients had already been required to maintain abstinence for 30 days prior to treatment, which may have increased the success rate [113].

There are no prospective clinical studies that have evaluated the use of ibogaine for any purpose. The reports discussed here represent anecdotal evidence and should be interpreted with caution.

Safety

All known safety information is specific to ibogaine, as opposed to the whole plant. In general, ibogaine is known to cause multiple adverse effects, which may range from mild to very severe. The most common adverse effects reported with pure ibogaine are ataxia, confusion, diarrhea, headache, nausea, and vomiting. Multiple case reports have also associated the use of ibogaine with ventricular arrhythmias, cardiac arrest, and QT interval prolongation. QT interval prolongation progressed to torsades de pointes in some cases. In many of these reports, the patients had no prior history of heart disease [46; 47; 48; 54; 55; 56; 57; 58; 59; 60; 114].

There have also been multiple reports of death after ibogaine use. Although the exact cause of death is unclear in these cases, most reports provide objective data, such as serum ibogaine levels, that suggest ibogaine may have been a contributing factor [50; 52; 61; 62; 115].

There are also at least two reports of death occurring after the use of the iboga plant. In one case, the patient reported taking one teaspoon of iboga root in addition to methadone and diazepam and died 12 hours after ingestion [44]. In the other case, the patient consumed an unknown quantity of a powder that was labelled as iboga [63]. In both cases, ibogaine was detected in postmortem serum.

Interactions

Ibogaine can cause serotonergic effects and should be used with caution in patients taking other serotonergic agents [48]. Additionally, ibogaine is a substrate of CYP2D6, suggesting that its metabolism may be altered by drugs that inhibit or induce this enzyme [45; 59].

In fact, one clinical study found that paroxetine, a CYP2D6 inhibitor, can delay the metabolism of ibogaine [65]. Taking paroxetine 20 mg daily increased exposure to ibogaine and its metabolite, noribogaine, by twofold [65]. Considering that paroxetine is also a serotonergic drug, it is important that patients avoid the use of these chemicals in combination.

Because ibogaine has been reported to cause QT interval prolongation, it should be used with caution in patients taking drugs that are known to prolong the QT interval.

Summary

Although there is growing interest in the use of ibogaine for substance use disorder, there is no prospective clinical research supporting its use for any medical purpose. As its use has also been associated with serious adverse effects, it should not be recommended as a treatment option.

The whole iboga plant should be avoided, as there is no research on its safety or effectiveness and its use has been associated with reports of death.

PSILOCYBIN MUSHROOMS

The term "magic mushrooms" refers to various mushrooms that contain a psychedelic chemical called psilocybin. Most of these mushrooms are in the genus *Psilocybe*. However, there are also other mushrooms that contain psilocybin, including certain species in the genera *Conocybe*, *Galerina*, *Gymnopilus*, *Inocybe*, *Panaeolus*, *Pholiotina*, and *Pluteus*. These mushrooms have a history of traditional use for religious and spiritual rituals. However, they are also well known for their popular use as recreational drugs [10; 11; 66].

As mentioned, psilocybin can comprise 0.37% to 1.3% of the dry mushroom and there is high variability in the total psilocybin content for psilocybin mushrooms sold in various venues [9; 10; 11]. Psilocybin is classified as a Schedule I controlled substance by the DEA, though its use has been decriminalized in some states/cities [121].

Mechanism of Action

Purified psilocybin has recently been the focus of an extensive amount of laboratory and clinical research. Although there is limited information available on the use of psilocybin mushrooms, information on the safety and effectiveness of psilocybin is increasing rapidly.

Psilocybin is a prodrug that metabolizes to psilocin, a hallucinogenic tryptamine that acts at serotonin 2A receptors [67; 68; 69; 70]. Although this seems to be the primary site of action, it is thought that psilocybin may also act on other pathways in humans. Some brain imaging suggests that it may have activity at serotonin 1A receptors as well. It seems to have little affinity for dopamine receptors [10; 69; 116].

The hallucinogenic effects of psilocybin involve visual, auditory, tactile, and other illusions, as well as changes in time and space perception. Some patients have reported recurrent drug-like experiences, mostly visual in nature, that occurred more than 24 hours after the last dose of psilocybin. These flashbacks lasted for seconds to minutes and were considered mild in nature [66; 71; 72; 73; 74; 75; 76; 77; 78].

Clinical Effects

Psilocybin has been evaluated in a number of small prospective studies. The evidence to date suggests that it may be beneficial for some people, although the benefits vary and it is unclear how these benefits compare to standard therapies.

Anxiety

Small studies on the use of psilocybin for anxiety suggest that, when used in combination with psychotherapy, it may reduce symptoms of anxiety in some patients for up to six months when compared with either a niacin placebo or low-dose psilocybin. However, most of this research was not conducted in patients with a specific diagnosis of anxiety at baseline. Rather, patients had anxiety, depression, and/or existential distress related to cancer. These studies used psilocybin 0.2–0.43 mg/kg, provided either as one or two doses [71; 73; 79; 80; 117].

Depression

The largest study conducted to date enrolled 59 patients and compared psilocybin 25 mg, taken as two separate doses three weeks apart, to escitalopram 20 mg daily for six weeks. The patients in this study were also receiving psychological support. The study found that psilocybin and escitalopram were equally effective for reducing symptoms of depression. Additionally, 57% of patients taking psilocybin achieved remission, compared with 28% of those taking escitalopram. However, it is unclear if these effects persisted beyond the six-week time period [81].

Small clinical studies also indicate that taking psilocybin as an adjunct to psychotherapy reduces symptoms of depression in some patients for up to 12 months when compared to baseline, delayed treatment, niacin placebo, or low-dose psilocybin. However, most of this research was not conducted in patients with a specific diagnosis of depression. Rather, patients had anxiety, depression, and/or existential distress related to cancer. Psilocybin was given as a single dose of 0.2–0.43 mg/kg or 10 mg and 25 mg given seven days apart [71; 73; 79; 80; 82; 83; 84; 85; 117; 118].

EVIDENCE-BASED PRACTICE RECOMMENDATION

According to the U.S. Department of Veterans Affairs, psilocybin-assisted psychotherapy may reduce depression severity and lead to sustained remission for some participants at 12 months compared to wait list controls, but these benefits were not observed when psilocybin-assisted psychotherapy was compared to intensive psychotherapy and daily escitalopram.

(https://www.hsrd.research.va.gov/publications/esp/psychedelics-mh-brief.pdf. Last accessed June 16, 2023.)

Level of Evidence: Low

Substance Use Disorder

There is significant interest in the use of psilocybin as a treatment for various forms of addiction and substance use disorder, including alcohol, tobacco, and opioids. Clinical research in this area is very limited and has mostly involved small, uncontrolled exploratory studies.

The highest quality study to date was conducted in patients with alcohol dependence. This study, which enrolled 93 patients, suggests that psilocybin may be modestly beneficial for further reducing alcohol intake when compared with diphenhydramine. However, it did not increase rates of total abstinence, and it is unclear if it would be beneficial in patients with more severe alcohol use disorder. In this study, psilocybin was provided as a single dose of 25 mg per 70 kg in the fourth week and a single dose of 25–40 mg per 70 kg in the eighth week [86].

Other Uses

There has also been some early research on the use of psilocybin for a variety of other mental health conditions, including demoralization and obsessive-compulsive disorder, as well as for the general improvement of psychological well-being. However, the available research is limited and inconclusive.

Safety

The use of nonstandardized psilocybin mushrooms has been associated with multiple cases of toxicity. For example, seizures, myocardial infarction, and acute kidney failure have been reported in some patients [11; 87; 88].

There is also a growing body of literature on the adverse effects of purified psilocybin. Most clinical research agrees that the most common side effects noted at therapeutic doses are headache, nausea, anxiety, and transient elevations in blood pressure and heart rate. The increases in heart rate and blood pressure seem to peak at about two hours and last for approximately six hours after use [73; 86]. Unlike iboga, psilocybin has not been associated with QT interval prolongation [73; 89].

Headaches associated with psilocybin are typically mild to moderate in nature. They have most often been reported to start about seven hours after psilocybin use and last for one to two days [71; 72; 79; 83; 84; 118].

The experience with psilocybin may be patient-dependent and may also be strongly influenced by environment. Some patients in clinical trials have reported experiencing fear, paranoia, anxiety, emotional disorder, and affect lability [76; 78; 88; 90]. These symptoms are generally mild to moderate. However, some patients have also reported experiencing severe anxiety that lasted days to weeks [78; 91].

Similarly, some patients responding to surveys have noted a reduction in feelings of well-being, and while some people have had a remission of suicidal ideation, some have experienced a worsening of suicidality [92]. It should be noted that many patients in these trials had underlying depression or anxiety, potentially confounding these findings.

There is very limited information available on the safety of microdosing, an increasingly popular method of administration for psilocybin. A survey of 278 individuals who reported microdosing found that physiological discomfort, including visions, numbness, temperature dysregulation, insomnia, headaches, and gastrointestinal issues, were reported by 18% of people. Impaired focus and cognition, excessive or inadequate energy, increased anxiety, and worsening mood were reported in 2.3% to 8.8% of respondents. However, these were all subjective, anecdotal reports, and some patients were also microdosing with LSD [12].

Interactions

Psilocybin should be used with caution in patients taking serotonergic drugs. Psilocybin has known serotonergic activity and may increase the risk for serotonin syndrome. Additionally, psilocybin has demonstrated stimulant activity in the CNS and should be used with caution in patients taking CNS stimulants.

Summary

Growing research on the use of psilocybin for various mental disorders is encouraging, although findings suggest a more modest benefit than what is often touted in mainstream news. It is important to remember that studies on psilocybin are at risk for response expectancy and that, to date, no studies have identified a method for adequate blinding.

Additionally, psilocybin has consistently been studied in conjunction with psychotherapy and provided to patients in a controlled, pleasant environment. Administering psilocybin in this environment allows the patient to be monitored for serious adverse effects and elevations in blood pressure and heart rate. It also provides a positive environment that can influence the psychedelic experience. This context should be kept in mind when interpreting the research.

PEYOTE (MESCALINE)

Peyote (*Lophophora williamsii*) is a type of cactus that grows in dry, desert regions of Mexico and Texas. Certain parts of the cactus have been used traditionally in rituals and recreationally as a hallucinogen [64; 93; 94; 95].

Most often, the disc-shaped buttons found on the cactus crown are sliced and dried. The dried buttons can either be chewed or soaked in water to make a tea. The psychoactive effects of peyote are attributed to the chemical mescaline [93]. The entire plant is considered a Schedule I controlled substance by the DEA, although this designation does not apply to the use of this plant in religious ceremonies conducted by the Native American Church [64; 121].

Mechanism of Action

Mescaline has known sympathomimetic and hallucinogenic activity that is similar in nature to LSD. However, mescaline is known to be much less potent than LSD. Its effects typically occur within 1 hour of ingestion, peak within about 4 to 6 hours, and seem to last for approximately 12 hours [93].

Clinical Effects

Unlike many other psychedelic plants with a long history of ritualistic use, peyote has not gained much traction as a potential therapeutic agent. To date, there is no clinical research evaluating its use for any medical purpose.

Safety

The most commonly reported adverse effects with peyote are nausea, vomiting, and diarrhea. These effects typically occur within 30 to 60 minutes of ingestion. It has also been reported to cause mydriasis, sweating, tremor, and elevations in blood pressure and heart rate within one hour after ingestion [95; 96].

The hallucinations that occur with peyote have also been associated with anxiety, paranoia, fear, and emotional instability that has the potential to lead to self-inflicted or accidental injury [95; 97; 98].

Mescaline, the major active constituent of peyote, has been reported to cause respiratory depression when used in large doses (20 mg/kg or more) and, rarely, death. Most symptoms seen with mescaline subside within 24 hours of use [95; 96].

Summary

There is no known medical use for peyote. Its recreational use can be associated with unpleasant experiences and serious adverse effects. It should not be recommended for any medical purpose.

SALVIA DIVINORUM (SALVINORIN A)

Salvia divinorum, which is sometimes referred to as diviner's mint or diviner's sage, is a plant native to central Mexico. It has traditionally been used in rituals by the Mazatec people in Oaxaca, Mexico. However, it is also popular as a recreational psychedelic [29; 99; 100; 101].

The leaves are the part of the plant used for hallucinogenic purposes. They are chewed and swallowed, chewed and sucked on, brewed into a tea, or smoked. The chemical thought to be responsible for its psychedelic effects is salvinorin A, which is also called divinorin A. Ingestion of this plant is reported to cause auditory, visual, tactile, and kinesthetic hallucinations [29; 99; 100; 101]. Although the growth and use of this plant is prohibited in some countries, it can be grown legally in some parts of the United States. As of 2023, it is considered a drug of concern by the DEA and in Canada.

Mechanism of Action

Salvinorin A is thought to cause hallucinations through activity at the kappa-opioid receptor. In contrast to many other natural psychedelic chemicals, salvinorin A does not seem to have activity at mu- or delta-opioid receptors, nor have any effect on serotonin, dopamine, or monoamine oxidase [101; 102; 103; 104; 105].

The onset of hallucinogenic effects occurs within 5 to 10 minutes of chewing on the leaves or within 10 seconds of inhaling the leaves. The effects seem to last for about one hour after chewing or about 20 to 45 minutes after inhalation. However, the duration of effect may be dose-dependent [29; 100; 106].

Clinical Effects

Despite some interest in the use of salvinorin A for the treatment of depression and substance use disorders, there is no clinical research evaluating either the whole plant or the chemical for this purpose.

One small, exploratory study in adults with a history of hallucinogen use shows that inhaling salvinorin A can affect the brain default mode network. This refers to the parts of the brain that are more active during passive tasks, as opposed to tasks that require direct attention. However, research in animals undergoing alcohol withdrawal found no benefit with salvinorin A [106; 107]. To date, it is unclear whether *Salvia divinorum* or salvinorin A may be beneficial for any therapeutic purposes.

Safety

Ingestion of *Salvia divinorum* has been reported to cause headache, restlessness, hyperactivity, disorientation, loss of coordination, dizziness, slurred speech, and fatigue [99; 100; 101; 103; 108]. Some people also report feelings of severe anxiety, fear, and panic with the use of this plant, and it has been associated with reports of both acute and chronic psychotic episodes [101; 108; 109].

Summary

Although there is interest in the use of *Salvia divinorum* for medical purposes, there is no clinical research to support its use for any indication. It should not be recommended for any medical use.

CONCLUSION

Although a number of psychedelic plants have a long history of use for various purposes, only some of these substances have been pursued as potential therapeutic agents. Regardless of whether a specific substance has been evaluated for therapeutic use, recreational use persists, and healthcare professionals should have a general understanding for potential risks and benefits.

Due to natural variation in chemical concentrations within a given plant, which often depend on time of year, growing conditions, and processing methods, the form of the natural psychedelic will impact its safety and efficacy. When natural psychedelics are studied as therapeutic agents, researchers utilize the purified chemical responsible for the psychedelic effect. The use of whole plants will not necessarily mirror the outcomes reported with purified chemicals in clinical research.

In general, natural psychedelics are associated with self-limiting adverse effects, including transient increases in blood pressure and heart rate, headache, mydriasis, sweating, and tremors. Although specific effects vary by chemical and plant, most adverse and hallucinogenic effects resolve within 6 to 12 hours of use. Although most patients report a positive experience, some patients (particularly those with pre-existing psychosis or a risk for psychotic episodes) do report a worsening of mental state and mental health issues after use; patients should be made aware of this risk.

Some natural psychedelics can also cause very severe adverse effects. In some cases, they have been associated with reports of death. However, just as anecdotal reports of benefit should be interpreted with caution, case reports connecting serious adverse effects and death to a specific substance must also be interpreted with caution.

The true benefits of some of these chemicals remain unclear, even those that have been the subject of higher-quality research, such as psilocybin. Methodological limitations, including inadequate blinding and controlling for response expectancy, continue to hamper the production of high-quality, reproducible research. Additionally, the legal status of many of these substances limits the widespread evaluation of their clinical use.

As additional research is published, the place in therapy, if any, for these substances will become clearer. As this research receives attention from media and patients, healthcare professionals should critically evaluate any claims and consider the unique research limitations with these substances.

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