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Review Article

The Application of Psychoactive Substances in Psychiatric Research

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Abstract

Psychedelics are regarded as mind-revealing drugs. They are considered a group of substances that act on serotonergic receptors (serotonin5-HT) and, thus, are also known as serotonergic hallucinogens. The origin of these drugs or substances dates back to various ritual beliefs and cultural practices. Current research has explored and highlighted their therapeutic applications in specific psychiatric disorders, such as anxiety and depression. This review shares insights regarding the history, research, and applications of various better-known psychoactive substances (LSD, ecstasy, psilocybin, cannabis, and more)—as well as the more familiar herbal stimulants caffeine and nicotine. The article also sheds light on the ethical and legal framework in the current era of medical research regarding such substances.

Keywords: *Ayahuasca; Betel Nut; Cannabis; Chamomile; Ecstasy; Jimsonweed; Ginseng; Hallucinogen; LSD; Opium; Peyote; Psilocybin; Tobacco*

Abbreviations

CBD: Cannabinoids; EWA: Early Warning Advisory; LSD: Lysergic Diethylamide; MDMA: 3,4 Methylenedioxymethamphetamine; NMDA: N-methyl D-aspartate; OCD: Obsessive-compulsive Disorder; PTSD: Post-traumatic Stress Disorder; THC: Tetrahydrocannabinol; UNODC: United Nations Office on Drugs and Crime

Introduction

Psychoactive substances influence and alter mental processes, such as perception and cognition. They target specific neural receptors upon administration, leading to a state of confusion during the acute period. Psychedelics are principally a group of substances that act on serotonergic receptors (serotonin5-HT).

Psychedelics were once a highly stignatized topic in medical research. However, currently, such research is becoming more accepted and applicable. Humphry Osmond coined the term "psychoactive". This term was initially shunned by the medical community. Still, the medical field and government agencies have not accepted psychedelics as having beneficial properties or therapeutic applications [1–3].

Known history of psychoactive substances

Since ancient times, psychoactive substances have been held sacred, being used in various settings and ceremonies. It is held that research by Albert Hofmann in 1938—which created lysergic diethylamide (LSD) while trying to synthesize a stimulant—begat modern psychedelic research. LSD experimentation commenced with cutting-edge investigations in the following years [4]. LSD's research popularity continued into the 1970s albeit unpredictable outcomes and interactions [5].

The human use of herbal or medicinal plants for physical healing and spiritual awakening is as old as humankind. The search for and awareness such substances to cure or treat specific illnesses, disorders, or diseases date to humanity's distant past [6]. The Vedas, the holy Indian books, mentioned treatment with spices, such as pepper, clove, and turmeric [7]. Dioscorides is considered the father of pharmacognosy and one of the most prominent authors on herbal drugs. He wrote the classic work *De Materia Medica*, which offers a wealth of healing knowledge. A contemporary of Dioscorides, Pliny, traveled the globe, noting about 1,000 medicinal plants [6,8].

Discussion

Psychedelic research in the past century focused mainly on LSD, psilocybin, and mescaline. After extensive research and trials in the human population, scientists learned their pharmacology and potential therapeutic benefits. These observations helped establish a research framework for other psychedelpic and mind-althering substances [9].

Classification of hallucinogens

Hallucinogens are classified according to their pharmacological mechanisms of action and chemical structures. The various types include psychedelics, entactogens, dissociatives, and other types considered in an atypical class. The classes listed below do not share a mechanism of action; however, they exhibit a similar effect to a person's mental abilities with an altered consciousness [9].

- Psychedelics are a class of serotonergic 5-HT agonists (examples are LSD, psilocybin, peyote, ayahuasca, and many more). These are classified as Schedule I substances, according to legal regulations. However, proponents have cited religious use and the treatment of certain mood and anxiety disorders [9].

- Entactogens are also classified as Schedule I substances; however, they differ in their chemical class. These are monoamine release and reuptake inhibitors, having therapeutic benefits in post-traumatic stress disorder (PTSD). A typical example of this class is 3,4 methylenedioxymethamphetamine (MDMA) or ecstasy [9].

- Dissociatives are restricted or unscheduled substances—a class of glutamatergic agonists: N-methyl D-aspartate receptors (NMDA) and ketamine, currently being investigated for applications in anesthetics and depression [9].

- The atypical class is distinct—miscellaneous—with unrelated pharmacological properties. This class includes a diverse list of substances, including: and ibogaine that acts as a serotonin 2A agonist and NMDA antagonist—showing potential medicinal use for addiction; cannabinoids (CBDs); and terpenes [9].

Types of psychoactive substances

Psychoactive substances also have a new tag name, *herbal highs*. The list includes amphetamines, LSD, cannabis, alkaloids, and other drugs or substances. Fresh or dried substances from these plants (mainly seeds or fruit berries) are typically chewed, smoked, or drank [10]. These substances are divided into four types, depending on the effects in the body and brain [11] (Table 1).

Type/Category	Effect	Examples
Stimulants	Improvement in mood leads to excitement and a feeling of euphoria and alertness [12]	Nicotine, caffeine, cocaine, amphetamine
Depressants	Causing muscle relaxation and stress relief [13]	Alcohol, sleeping pills, tranquilizers, such as benzodiazepines
Opioids	Relief from pain symptoms, causing drowsiness and euphoria [14]	Pain medications, such as opioids (morphine, oxycodone) and heroin—also, also called street drugs
Hallucinogens	Rapid mood swings; experiences of altered reality (hallucination); and possible paranoia [15]	LSD, dextromethorphan, ketamine

Table 1: *Classification of psychoactive substances.*

Papaver somniferum—commonly known as opium

Poppy seeds have been used in beverages for centuries and are considered an effective natural remedy for pain. Opium is extracted from the dried exudate of the unripe poppies seedpods, *Papaver somniferum.* The components include a variety of substances, such as plant wax, fats, proteins, latex, morphine, and codeine [16].

Opioids are alkaloids that bind to specific protein opiate receptors—widely distributed in the central and peripheral nervous systems—easing pain. Thus, opioid therapy became the primary approach to mitigate severe pain experienced by cancer patients and those with severe medical conditions [16,17].

Numerous healthcare professionals endorsed the practice. Nevertheless, by the mid-20th century, they observed the risk of addiction, dependence, and increased tolerance with the long-term use of opioids in managing chronic pain, ultimately forming a controversial image.

Specific health care professionals legally prescribe opioids to treat pain; whereas, illicit opioids are shared or sold "on the street". The National Survey on Drug Use and Health recorded a substantial increase—of 42% between 2000 and 2002 and 186% between 1997 and 2002—for non-medical users or opioid abusers [17].

Lophophora williamsii—commonly known as peyote

Peyote is a spineless cactus that grows in the deserts of the United States, Mexico, and Peru. This succulent came under scrutiny in the late 1800s when mescaline was isolated, and its psychedelic effects were observed [18]. It contains the alkaloid mescaline (3,4,5-trimethoxyphenethylamine)—the oldest known hallucinogen—affecting perception and behavior.

Several clinical trials have reported the propitious use of mescaline to treat obsessive-compulsive disorder (OCD), depression, and anxiety. Also, peyote has been found to have various other alkaloids of different classes, resulting in a combination that may enhance the effects of mescaline. The interaction of mescaline and its related compounds with serotonin receptors leads to euphoria, hallucination, and possible psychosis.

Seizures, hyperthermia, agitation, tachycardia, and muscle stiffness are some specific adverse symptoms of mescaline poisoning and overdose. The complete toxicological profile of mescaline is unknown; however, the metabolites are excreted primarily in the urine. Currently, there is medical interest in exploring the potential therapeutic use of peyote [18,19].

Cannabis (*Cannabis sativa*)—commonly known as marijuana

Cannabis is a complex dioicous, widely distributed throughout the world. It is complex due to its numerous reactions, and each individual tends to respond differently. Tetrahydrocannabinol (THC) is the psychoactive metabolite in the cannabis strain of *Sativa*, whereas the non-psychoactive metabolite is CBD. Medical applications include treatment of spasms, pain, insomnia, and depression [20]. The plant is referred to by many names, such as marijuana or pot. The medical and political landscape regarding medical marijuana has shifted toward legalization in various countries. Legalization has made people aware of beneficial and adverse effects in both short- and long-term use.

However, few studies have demonstrated harmful effects. However, poor judgment, paranoia, and impaired motor coordination are observed in excessive consumption. In specific cases, addiction or long-term or heavy use of the drug can lead to cognitive impairment, altered brain functioning, and an increased risk of chronic disorders, such as schizophrenia.

The National Survey on Drug Use and Health reported in 2012 that 2.7 million people aged 12 years and older have varying degrees of dependence on marijuana [20].

3,4-methylenedioxymethamphetamine (MDMA)—commonly known as "ecstasy"

MDMA is an amphetamine derivative with hallucinogenic properties. The street name of this drug is ecstasy or molly. It is known to produce *energic effects* when consumed. This drug gained popularity in the 1980s as a trend in rave and club parties. Some immediately reported adverse effects are anxiety, panic attacks, irritability, and impulsive behavior [21].

The drug's functional effects are extreme in both positive and negative aspects. It causes intense euphoria by increasing body temperature and cortisol levels. However, adverse effects are observed, leading to a deficit in problem-solving, sleep disturbances, and memory loss. Some studies have reported damage to serotonin neurons by MDMA, adversely affecting cognitive function. The neuropsychological effects of the drug are still being investigated and will need to be better understood before it can be applied safely [21,22].

Banisteriopsis caapi and *Psychotria viridis*—traditionally known as ayahuasca

Ayahuasca originates in the Amazon and derives its psychoactive properties from two distinct plants, e.g., the bark of *Banisteriopsis caapi*, which produces alkaloids, and the leaves of *Psychotria viridis*, which produces the hallucinogen N, N-dimethyltryptamine. The combined action of the two different plants has been challenging to understand. Nevertheless, it seems that the indigenous population was well aware of it for millennia. It has been used in religious rituals and as a cure for depression and anxiety in various South American countries.

Recently, ayahuasca has crossed borders, entering North America and Europe primarily for recreational purposes. Also, it is gaining recognition among individuals seeking spiritual support and hallucinogenic experiences. Thus, understanding ayahuasca's effects is relevant [23].

Shanon (2007) observed an enhanced level of improvisation in playing musical instruments. Kavenska and Simonova (2015) reported a sense of self-confidence and a new perspective that can be helpful in psychotherapy. Morgenstern (1994) noted that none of the addictive users experienced any difficulties weaning off the drug or using it in a controlled manner. These results infer that any negative aspects of ayahuasca are comparatively lower than other hallucinogens and do not appear to produce any significant adverse psychological effects [23].

Areca catechu—commonly known as betel nut

Betel nut is the seed of a palm tree, *Areca catechu,* and is consumed sliced or wrapped in betel vine leaves, also known as betel quid. It is chewed by millions of people worldwide; however, the percentage of consumption is somewhat higher in Asia and the Pacific. The psychoactive ingredient in betel nut is arecoline, an alkaloid, characteristic of a muscarinic acetylcholine receptor agonist. Betel nut is also consumed in a mixture prepared with tobacco, which increases the nicotinic activity. The observed effects are euphoria, drowsiness, sedation, and arousal [24].

There have been ancient reports of the use of betel nut as an aphrodisiac. These effects were noted with short-term use, resulting in its social acceptance. Nevertheless, betel nuts can adversely affect oral health, leading to oral cancer and gum disease [24].

Nicotiana tabacum—commonly known as tobacco

Tobacco originated in America and quickly reached the continent of Europe by the 1500s due to its prominent nicotine ingredient—an addictive alkaloid. By the 1800s, tobacco was used as a style icon in commercial cigarettes, and became a cash crop. Revenue and sales of tobacco cigarettes significantly increased at the beginning of the 1900s [25]. Individuals who experience PTSD, depression, and other anxiety-related problems tend to smoke, as nicotine reduces anxiety by increasing beta-endorphin levels—thus framing the network of nicotine addiction in the brain-stress cycle [25].

Habitual, long-term use of tobacco products leads to severe addiction and dependence [26,27]. Also, continuous use of tobacco by smoking can have adverse effects, such as mental illness, irritability after withdrawal or gradual reduction, cardiovascular disease, indigestion, and detrimental effects on insulin levels, increasing the risk of diabetes [26].

Benowitz and Henningfield (2013) reported low levels of addiction when reducing the nicotine content in cigarettes. The initial proposal to reduce nicotine levels in cigarettes was put forth in 1994. However, it took a decade to conduct research studies and observe the effect of smoking cessation with low nicotine levels [28].

Datura stramonium L.—commonly known as Jimsonweed (or Jimson weed)

Datura stramonium L., also known as Jimsonweed (or Jimson weed), is a globally cultivated plant with hallucinogenic properties due to the alkaloids atropine, scopolamine, and hyoscyamine. Roots, seeds, and the entire plant are edible, producing euphoria and hallucinations, acting as an acetylcholine receptor antagonist [29]. In early times, it was used in witchcraft and wizardry. According to the Indian Vedas, Lord Shiva was known to consume and smoke cannabis and Datura—to this day, being offered in temples [30].

Jimsonweed elicits positive effects in muscle spasms, epilepsy, burns, and depression. There have been reports of the continuous use of the seeds and other Jimsonweed plant sources as an anti-inflammatory, analgesic, and antihistaminic, either individually or in combination with different parts of the plant, such as seeds and flower petals.

Medical researchers began examining for adverse effects from continuous and long-term use. They observed blurred vision, mydriasis, increased heart rate, delirium, loss of motor coordination, and, in severe cases, respiratory failure leading to death. Jimsonweed has complex ingredients that require further analysis to consider all the ingredients present in roots, seeds, and other edible parts— and their combined interactions [30].

Psilocybin

Psilocybin, similar to other psychedelics, is centuries old and has been used for sacred purposes. Psilocybin has been reported in approximately one hundred species of mushrooms in the genus *Psilocybe.* The prodrug psilocybin is dephosphorylated to psilocin, which is an active agent in the central nervous system. It produces behavioral features through a 5-hydroxytryptamine serotonin receptor agonist and is used therapeutically to treat depression and other mental disorders [31]. Several studies have shown promising effects in reducing depression and anxiety in patients with life-threatening cancers compared to screening, baseline, and follow-up monitoring events [31,32].

Psilocybin research has suggested a low risk of addiction and low toxicity levels with increasing interest in treatment-related depression. However, user-reported outcomes and experiences include mental confusion, agitation, paranoia, panic attacks, and bizarre psychotic episodes. A study by Bienemann., *et al*. (2020) analyzed publicly available data by cluster formation, finding that adverse effects were caused by high doses of psilocybin or its concurrent use with other substances [33].

Lysergic acid diethylamide (LSD)

LSD was the accidental discovery of Albert Hofmann in 1938. LSD gained popularity in the 1970s, being used to observe and evaluate behavioral and personality changes with unpredictable results and interactions between brain cells and serotonin. The synthetic compound LSD is prepared from lysergic acid found in ergot fungus, which grows on grains, such as rye. LSD was considered a classic hallucinogen, used to treat depression, anxiety, and addiction. In addition, treatment of mood disorders in patients with terminal cancer has shown a positive response when LSD is co-administered with cancer therapies [4,5].

Each person's response to LSD differs as responses depend on a set of variables and criteria, such as the level of emotional and cognitive sense: the dosage requirement, and the follow-up needed for proper monitoring. Denson (1970) found that neurotic symptoms, such as anxiety, hysteria, depression, and OCD, improved significantly in the LSD treatment group. Torrens 2020) conducted systematic reviews and developed a search strategy to improve access to of LSD research in the public domain [34].

Schmid and Liechti (2017) observed significant positive experiences with long-lasting effects in otherwise healthy participants, such as mood, social, and behavioral changes [35]. According to Nichols and Grob (2018), LSD is considered medically safe if consumed in therapeutic dosages.However, toxicity and overdose can have fatal effects, such as cardiovascular incidents and hyperthermia leading to death [36].

Other known herbal substances

Specific herbal substances with psychedelic properties are widely available. A few examples are coffee, ephedra, ginseng, and chamomile. Caffeine, found in coffee, chocolate, and cocoa foods (*Theobroma cacao*), helps with specific disorders and acts as a stimulant, pain reliever, and weight-loss product.

Studies have reported that participants who consume a large amount of caffeine tend to sleep for a shorter period and take comparatively longer to fall asleep. Ephedra contains ephedrine, which is prescribed as a stimulant and sometimes for weight loss, along with caffeine.

Ginseng has Asian and Korean origins, containing ginsenosides, which are traditionally prescribed for fatigue. Chamomile is of German (*Matricaria recutita*) and Roman (*Anthemis nobilis*) origins and is used as a mild sedative—due to the flavonoid apigenin, which acts by binding to benzodiazepine receptors. Clinical studies have shown a positive effect on sleep deprivation; however, some mild allergic reactions were observed in some participants [37].

Gyllenhaal., *et al*. (2000) opined that many other herbal substances produce psychedelic effects by creating positive "vibes" and a sense of well-being when consumed within the therapeutic dose. However, they highlighted that each substance should be studied in more detail to explore the possible side effects of long-term, excessive, and unmonitored consumption [37].

Ethical and legal considerations of psychedelics

In the United States, psychedelic substances are listed in Schedule I of the Controlled Substance Act of 1970, which mainly lists drugs with high abuse potential, a lack of evidence on approved medical use, and serious adverse events related to safety. Schedule I is the most restrictive class of drugs, prohibiting any significant research that could encourage a broader understanding of psychedelics [11].

Pilecki., *et al*. (2021) reported that possession of these substances is considered illegal—although numerous individuals covertly seek these substances for therapy or other uses. Psychiatrists have an ethical responsibility to provide psychotherapeutic support to individuals undergoing psychedelic treatments. Access to legally approved psychoactive substances has improved psychedelic-assisted therapies. Any practice in which psychedelics are banned should not be included in treatment to reduce any possible risk. A general approach of "know the law and know thyself" should be followed [38].

Federal laws and regulatory agencies purport that psychoactive substances pose numerous health hazards to humans. However, old and new substances should be included in the research list related to proper monitoring and quality analysis before a substance is banned. This reporting will ensure the correct administration of the dose, which can be beneficial in treating various psychological disorders. Furthermore, the impact of monitoring and evaluating any of these substances and drugs globally may provide much-needed clarity on any potential benefical application [39].

The United Nations Office on Drugs and Crime (UNODC) has explained NPS as a "new psychoactive substance"—according to global data collected in 2020. UNODC has defined NPS as "substances of abuse, either in a pure form or a preparation, that are not controlled by the 1961 Single Convention on Narcotic Drugs or the 1971 Convention on Psychotropic Substances, but that may pose a public health threat". Some examples include bath salts, legal highs, and research chemicals.

The term "new" does not refer to new interventions or substance discovery; instead, it means increased market availability of such substances that have caught the attention of government agencies. UNODC has also published Early Warning Advisory (EWA) guidelines, including information on specific substances and their pharmacological effects for consumer awareness. Comprehensive information on distribution, harmful effects, and any need of professional or technical assistance have also been provided to anyone in dire need of professional assistance after ingesting any of these substance [40].

Conclusion

Specific plants have been used historically in the treatment of illnesses, disorders, and diseases. However, there remains a demand for more research on banned and widely consumed substances. There may be a fine line between understanding pharmacological proper-

ties excess-dose amounts within the therapeutic paradigm. Specific mechanisms of action of substance combinations need to be explored further to comprehend any beneficial or adverse interactions.

Psychedelics are widely used by drug abusers and religious groups due to their hallucinogenic characteristics, which led to an interest in expanding the knowledge of these substances' poorly understood cognitive and psychological effects. Thus, serious and sincere dialogue is warranted among scientists, policymakers, federal agents, health care professionals, spiritual leaders, activists, and other key opinion leaders, regarding how psychedelics can aid human welfare and in supporting research investigating possible and potent novel substances.

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 osf interest.

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Volume 11 Issue 2 February 2022