A Review of the Psychotherapeutic Effects of Ayahuasca

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Objective: This paper aims to outline the background, pharmacology, subjective effects, and tolerability of the South American hallucinogenic tea, ayahuasca.
Methods: Literature Review
Discussion: Ayahuasca is a South American hallucinogenic tea that has been used in shamanistic practices for centuries and has become popularized globally through use by Brazilian churches and has potential implications for the treatment of psychiatric conditions due to its serotonergic activity. It relies on monoamine oxidase inhibition to prevent degradation of its psychoactive ingredient, DMT, allowing it to be absorbed into the systemic circulation and act centrally. Subjective effects acutely include perceptual, cognitive, affective, and somatic changes and is generally well tolerated with mild increased in cardiovascular parameters, possible gastrointestinal symptoms such as vomiting, and rarely prolonged psychosis

Introduction

The Amazonian tea, ayahuasca, prepared from a combination of botanical ingredients, has been used in religious ceremonies and for medicinal treatment in South America for centuries. Its use has also spread to the United States and Europe through religious groups, including Santo Daime and the União do Vegetal [2]. It is prepared from the vine *Banisteriopsis caapi* in combination with other Amazonian plant species which contain psychoactive molecules, thus leading to its classification as a hallucinogen [5]. Generally, hallucinogens fall into three different structural groups; tryptamines (including psilocybin and DMT), lysergamides (including LSD), and phenethylamines (including mescaline) [3]. Ayahuasca exerts its hallucinogenic effects through monoamine oxidase inhibition (MAOI) properties caused by *B. caapi* in combination with effects derived from plants containing N, N-dimethyltryptamine (DMT).[1] *Psychotria viridis* and *Diplopterys cabrerana* (used in Ecuador and Columbia) are plant species commonly responsible for providing the hallucinogen, DMT, found in Ayahuasca [2]. Historically in the United States, the recreational use of hallucinogens was met with backlash, which led to stigmatization and legislative restrictions stifling research into other potential treatments [4]. However, the church, União do Vegetal, victoriously asserted at the Supreme Court of the United States that their religious use of ayahuasca is protected under the First Amendment's free exercise of religion clause. This ruling may open the door for potential research into other psychiatric uses of ayahuasca [4].

Hallucinogens such as DMT exert their effect through the serotonergic system, and as a result, have implications for the treatment of psychiatric disorders. Ayahuasca may offer an alternative effect on the serotonin system through an entirely separate neurotransmitter pathway, which may be beneficial to individuals afflicted by psychopathology who have not responded to conventional therapies [1,3]. There may be a potential benefit in the treatment of substance use, anxiety, and depressive disorders [1]. In a recent longitudinal and cross-sectional study on participants naïve to ayahuasca use, there was a significant reduction in participants meeting diagnostic criteria for psychiatric illness at both 1 and 6 months following ayahuasca use. They used a battery of questionnaires at baseline and found that 45% of participants in the study met the criteria for psychiatric illness prior to ayahuasca administration. Of the 45% that had met criteria, 61% no longer met criteria for psychiatric illness at follow-up, and 22.2% had a reduction in the number of current psychiatric conditions. The psychiatric conditions of the participants at baseline were primarily anxiety, substance use, and mood disorders [11]. In a separate study on six volunteers with varying severity of major depressive disorder, there was a statistically significant reduction in MADRS and HAM-D scores following ayahuasca use on

days 1, 7, and 21 after administration [12]. Panic-like symptoms and hopelessness were found to be reduced in a study of Santo Daime members after the acute ingestion of ayahuasca as well.[14] In another study of 12 subjects participating in 4 days of counseling in addition to two ayahuasca ceremonies, there was a statistically significant reduction in cocaine use in the participants following the intervention [13].

The increasing use of ayahuasca world-wide, as well as being a potential therapy for psychiatric pathology, warrants a further investigation into its pharmacology as well as effects on users. This paper will discuss the historical use of ayahuasca, the absorption of DMT, pharmacology, subjective effects, and tolerability of ayahuasca.

Background

Ayahuasca use is common in several South American countries, including Peru, Columbia, Brazil, and Ecuador. According to the book, "Sacred Vine of Spirits: Ayahuasca," the name ayahuasca is derived from the language, Quecha. "Huasca" meaning "vine" in Quecha and "aya," meaning "souls," "dead people," or "spirit." The ceremonial brew is believed to have up to 70 different names [2] including caapi, natema, mihi, and yage [7]. One of the botanical components is the vine of the plant, *Banisteriopsis caapi,* which has MAO-inhibitor properties. It is used in combination with a plant species containing N,N-dimethyltryptamine (DMT), commonly *Psychotria viridis*. However, other plant species containing DMT may be used, such as *Diplopterys cabrerana,* which is frequently found in brews in Ecuador and Columbia. There are complex variations of ayahuasca containing up to 90 different plants [2]. The brew is often used in shamanistic societies. Shamanism, which is any practice of healing and divination that involves the purposive induction of an altered state of consciousness according to "Sacred Vine of Spirits: Ayahuasca." In shamanistic ceremonies, fast-paced, rhythmic drumming is utilized to keep visions moving, which prevents stagnation on potentially terrifying images. Brazilian churches such as Santo Daime or União do Vegetal use priests or officiants (rather than shamans or healers) to administer ayahuasca as a sacrament in group worship and celebration. Generally, the ceremonies take place in dim light or darkness to be more conducive to visions derived from the experience. Guided tours to areas of South America involving Ayahuasca sessions performed by a shaman have increased as interest and awareness has grown. Ayahuasca administrators have made trips to the United States and Europe to perform ceremonies [7].

In addition to the previously mentioned Brazilian churches use of ayahuasca, other groups such as The North American Peyote church using peyote and the African bwiti cult using iboga also use "entheogens" in their rituals. The term "entheogen" has been used to describe substances such as LSD, DMT, mescaline, and psilocybin that promote an altered sense of consciousness for religious or spiritual reasons [7].

DMT Absorption

The effects of ayahuasca rely on the interplay between compounds derived from multiple plant species that allow for N,N-dimethyltryptamine (DMT) to be absorbed into the systemic circulation [3]. The vines from *B. caapi* are ground up and provide compounds such as harmine, harmaline, and tetrahydroharmine (THH). These are alkaloids with beta-carboline structure and have monoamine oxidase inhibitor properties, which prevent degradation of DMT in the gastrointestinal tract [2]. As mentioned previously, DMT is derived from other plant species such as *P. viridi* [5]. After degradation of DMT is prevented by beta-carbolines (harmine, harmaline, and THH), DMT is able to enter the systemic circulation. DMT is structurally similar to serotonin and is, therefore, able to bind to serotonin receptors centrally [2].

In a double-blind, placebo-controlled, crossover trial measuring ayahuasca's pharmacokinetic properties following consumption, blood levels of DMT, harmine, harmaline, and THH were obtained. Harmine levels were undetectable during the study, but its degradation product, harmol, was

present, suggesting that it is rapidly degraded after consumption. In this study, urinary metabolites from MAOI activity were also measured. With extensive MAOI activity, a reduction in metabolites of serotonin, norepinephrine, and dopamine would be expected, but this was not found in this study. The lack of a reduction in these metabolites suggest that the MAOI activity of ayahuasca is in the periphery, enough to prevent metabolism of DMT, but not enough activity to have significant effects on these other neurotransmitters centrally [2].

Pharmacology

Ayahuasca's subjective effects generally begin 30 minutes after its consumption,[1, 6] with peak effects occurring at ~1.5-2 hours[2] and ending 4-6 hours after ingestion[1, 6]. The peak effects from ayahuasca are similar to DMT's [1]. Maximum visual analog scale scores following consumption of ayahuasca were achieved around 1.5-2 hours in one study, with initial scores at 30 minutes and a significant increase at around 60 minutes. Return to baseline occurs within 6 hours [2]. This is compared to psilocybin which is active for 4-6 hours and LSD which can be active for 12 hours [3]. When the DMT levels are measured in plasma following the consumption of ayahuasca, they correlate with the subjective reports of its effects [2]. Measurable levels of harmaline and THH seem to peak after the psychedelic effects of ayahuasca have resolved [1]. Subjective effects from Ayahuasca seem to occur in the absence of measurable plasma levels of harmine after administration [2].

Mechanism of Action

Hallucinogens exert their effects primarily through agonism on the serotonergic receptor 5-HT2A. This hypothesis finds support in research demonstrating that partial agonists and antagonists at the 5-HT2A receptor block the effects of the hallucinogen psilocybin. Other serotonergic receptors are likely implicated in the psychedelic effects of hallucinogens as well. The agonist lisuride, having a high affinity for the 5-HT2A site, produces no hallucinogenic effect, while LSD being a comparatively weak partial agonist at the 5-HT2A site has significantly more hallucinogenic effects than lisuride, supporting the theory of other receptor sites contributing to the effects seen with psychedelic substances. Additionally, hallucinogens have potent effects at other serotonergic receptors, such as 5-HT2C and 5-HT1A. These receptors have been implicated in psychiatric disorders [3].

As mentioned previously, N, N-dimethyltryptamine (DMT) is present in the plant species *P. viridis* and other plant species found in ayahuasca brews. DMT is made available for absorption due to MAOI effects from compounds found in *B. caapi* that prevent the first-pass metabolism in the liver and GI tract. Similar to LSD and mescaline, DMT binds as an agonist at the 5-HT2A receptor in the central nervous system.[2] Its structural similarity to serotonin allows it to have an affinity for the 5-HT2A receptor, making it a possible therapeutic modality with potential benefits for the treatment of depression and anxiety disorders among other psychiatric conditions [1].

Subjective Effects

Ayahuasca has been found to produce perceptual, affective, cognitive, and somatic changes in users [6]. Perceptual changes from DMT include changes in visual imagery, such as visualizing geometric patterns, brighter or more intense colors, and auditory effects such as high-pitched noises or hyper-awareness of room sounds. Somaesthesia effects include sensations of hot and cold temperatures with alterations between the two. Some patients experience a detachment or dissociation from their body, described as a lack of awareness of their physical body. Changes in affect include anxiety at the start that evolves into a feeling of euphoria. Some users also note alterations in emotion from euphoria to anxiety to a sense of calm. Cognitive changes involve speeding up thought processes, having a new perspective on their life, or describing the experience of being in a dream-state. Alterations in volition are also noted with DMT use. Users of DMT note a loss of control and have a feeling of helplessness [8].

In a study of 12 volunteers receiving IV DMT at various doses, the Hallucinogen Rating Scale was used to measure the subjective effects of DMT with subscales to measure effects on somaesthesia, affect, volition, cognition, perception, and intensity. Subjective effects correlated with blood levels of DMT. At the lowest dose of 0.05 mg/kg of IV DMT, some physical effects were elicited but difficult to differentiate from placebo at times. At the 0.1 mg/kg dose, somaesthetic properties were predominant. Increasing to the 0.2 mg/kg dose and above, hallucinogenic effects became present, and all subjects reported visual perceptual disturbances such as brightly colored, shifting visual images. At the 0.4 mg/kg dose, subjects of the study were overwhelmed with the intensity and rapid onset of effects [8].

In a study of 6 volunteers that consumed freeze-dried ayahuasca tea, changes in perceptual, cognitive, affective, and somatic domains were found. Compared to IV DMT, ayahuasca's effects were of longer duration and less intense overall, which is thought to be due to the oral route of administration as opposed to IV DMT. A significant effect was found in all subscales of the Hallucinogen Rating Scale previously discussed, except for volition. Like IV DMT, lower doses of ayahuasca produced somatic effects rather than significant perceptual effects. The highest dose of ayahuasca resembles a moderate dose of IV DMT for all of the statistically significant subscales except for cognition. This indicates possible milder effects of ayahuasca when compared to IV DMT. Other scales were also used to measure subjective effects during ayahuasca use, such as the Visual Analog Scale and the Addiction Research Center Inventory. Significant increases were also found in all Visual Analog Scale items, which include "any effect," "good effects," "liking," "drunken," "stimulated," and "high" categories. Within the Addiction Research Center Inventory, the Amphetamine, LSD, and Morphine-Benzedrine groups were significantly elevated, which indicates a degree of activation, somatic-dysphoric effects, and euphoria or feeling of well-being, respectively [6].

Tolerability

Hallucinogens generally appear to be well tolerated [3]. Risks of hallucinogen use generally appear to be psychological rather than physiologic in nature, and without significant risk for organ damage or neurotoxicity. Classic hallucinogens increase heart rate and blood pressure, however, as well as a rare risk of prolonged psychosis or persistent perceptual disturbances following use [4].

Studies of effects from ayahuasca ingestion have suggested an increase in both blood pressure and heart rate as well [6]. In a study of subjective effects and tolerability of ayahuasca, systolic blood pressure and diastolic blood pressure trended upward without meeting statistical significance. The peak difference in systolic blood pressure between placebo and high dose ayahuasca (1mg DMT/kg) was 13.8 mmHg. The peak difference was 8.8 mmHg between placebo and low dose ayahuasca (0.5mg DMT/kg). There was a trend of an increase in diastolic blood pressure as well, with a peak difference of 10.4 mmHg between high dose and placebo. The peak difference was 8.6 mmHg between low dose and placebo. Heart rate was modestly affected as well, with an increase of 9.2 beats per minute between the high dose and placebo, and 6.2 bpm for low dose vs. placebo [6]. In a study conducted with 17 participants administered ayahuasca in two consecutive doses given 4 hours apart, tolerance in regard to increases in systolic blood pressure and heart rate following the second dose was noted. Overall, the second dose of ayahuasca was not tolerated as well due to gastrointestinal side effects, which correlated with increases in DMT plasma concentrations [5].

It was hypothesized that nausea associated with Ayahuasca was possibly due to beta-carbolines present in the tea, that would not be present with IV DMT [6]. Serotonin is present in the gastrointestinal tract, and the MAOI activity of these beta-carbolines may be responsible for the gastrointestinal symptoms following ingestion. Mestizo healers, despite being unaware of the specific pharmacologic properties of the plants, understood that the vine with harmine compound was responsible for the gastrointestinal symptoms. They even referred to the

reaction from these plants as "la purge." They adjusted the proportions of each plant in the brew according to the reaction they wanted. For example, they would increase the number of vines containing harmine in the brew if they wanted to purge toxins from their system [7].

The potential risk of a prolonged psychotic episode following acute hallucinogen use has been reported. However, these cases have considered being rare [4]. A 1960 study on LSD; a questionnaire was sent out to LSD and mescaline investigators to determine the subjective effects of these substances. It was found that the rate of prolonged psychosis (psychosis lasting >48 hours after use) was 0.8 per 1000 in experimental participants and 1.8 per 1000 in patients undergoing psychotherapy [10]. In a relatively recent systematic review of ayahuasca and DMT risk of psychotic episodes, it was found that prolonged psychosis is relatively rare across multiple settings. Cases of psychosis following DMT and ayahuasca use was often in subjects that had other factors possibly contributing to their psychosis, such as history of psychosis, family history of psychosis, or concurrent drug use. Therefore, it was suggested that the rare cases of psychosis following DMT or ayahuasca could be reduced by adequate screening of personal history of psychotic disorder, bipolar disorder, or substance use prior to administration [9].

Conclusion

Ayahuasca has been used historically for spiritual and religious reasons for centuries in South America [5]. Use of ayahuasca has become more common in the United States and Europe in part by the use of religious groups, including Santo Daime and Uniao do Vegetal as well [2]. Its effect on the serotonin system may make it a research candidate for the treatment of psychiatric conditions in the future [1,3]. Subjective effects and potential benefits rely on DMT that is provided by various plant species, and *B. caapi* that has monoamine oxidase inhibitor activity, which prevents degradation of DMT in the periphery leading to successful absorption [2,3]. Once consumed, the tea produces subjective effects including, perceptual, somatic, affective, and cognitive changes[6]. At lower doses, the effects of DMT are more somaesthetic and physical, and perceptual disturbances predominated at higher doses [6,8]. Compared to IV DMT, actions of ayahuasca are slower in onset, milder, and longer lasting Generally, hallucinogens appear to be fairly well tolerated. Ayahuasca, like other hallucinogens, has the potential to increase blood pressure and heart rate [6]. In addition to increases in these cardiovascular parameters, ayahuasca has the potential for unpleasant gastrointestinal symptoms believed to be from MAOI activity in the gastrointestinal tract [7]. In conclusion, ayahuasca is a psychoactive, South American tea with potential therapeutic benefit in psychiatric illness. It has acute somatic, affective, perceptual, cognitive, and volitional effects and is generally adequately tolerated with acute gastrointestinal side effects, modest increase in cardiovascular parameters, and rare complication of prolonged psychosis.

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