Ayahuasca for Substance-Use Disorder Focus: polysubstance use disorder Author: Dr. Conor Watters ND MSAS PATP Healing Watters PLLC <u>drwatters@healh.watters.com</u> 11225 Roosevelt Way NE Seattle, WA 98125-6225 USA 425-380-3098

Funding Sources: Nothing to disclose. Author's contribution: Entirety. Conflicts of interest: None to disclose.

### Ayahuasca for Substance-Use Disorder

Background: Substance-use disorder is a complex chronic condition that is a global health concern. Ayahuasca has been an emerging alternative treatment option that has been the subject of increasing research in recent years. Aims: The aim of this review is to synthesize the new research in the last 5 years. Methods: A review of the significant research on Ayahuasca for substance use disorder from the past 5 years was performed using PubMed database. Results: The pre-clinical, observational, and parrative reviews located offered

supportive evidence for the utility of Ayahuasca in substance-use disorder treatment. Conclusions: Further research, in particular randomized-controlled trials, will help to document the efficacy and safety of Ayahuasca for substance-use disorder treatment, though it should be considered that randomized-controlled trials may not be the best evidence-model for the complicated totality which is Ayahuasca ceremonial healing.

### 1. INTRODUCTION

Substance Use Disorder (SUD) represents a complex chronic condition characterized by the compulsive use of substances despite harmful consequences [22]. This disorder encompasses a broad spectrum of psychological issues, including chemical dependency, trauma history, and mental health challenges such as anxiety, depression, and issues related to self-esteem, purpose, and social connections [5][21][22]. Particularly challenging is Polysubstance Use Disorder (PUD), where multiple substances are concurrently used, complicating both diagnosis and treatment [22][24]. In one study of PUD, it was found that 30-49.7% of opioid-use disorder (OUD) patients had polydrug use, and of note, it was found that there was a high rate of childhood mistreatment in OUD patients and a statistically significant association between PTSD, OUD, and PUD [40]. A study in China found that 40% of patients in compulsory treatment for heroin-dependence reported polysubstance use [41]. Given these complexities, innovative treatment approaches are of importance which can address the neurochemistry of addiction as well as the psychological wounds of addiction, and may have systemic benefits across multiple domains.

Ayahuasca, a traditional South American brew composed of the *Banisteriopsis caapi* vine (commonly referred to as "Ayahuasca") and a DMT-containing botanical, most often the *Psychotria viridis* leaf (commonly referred to as "Chakruna"), has emerged as a potential therapeutic tool in contemporary medical thought. Ayahuasca has gained attention in the scientific community for its potential to modulate key neurotransmitters including dopamine and serotonin, which are crucial in the pathology of SUD [24].

Commented [A1]: we certainly don't want the PRC using Ayahuasca on patients in compulsory treatment, i.e. set and setting and intention need to be protected for patient welfare

Commented [A2]: systemic or systematic?

Recent observational studies and limited clinical trials, including a randomized controlled trial [37] on treatment-resistant depression have highlighted its relevance and potential efficacy in treating SUD [1][2][3]. This paper focuses on polysubstance abuse and evaluation of Ayahuasca's therapeutic potential and the challenges it presents in application. To achieve that, this paper reviews portions of the literature from 2019 to 2024 on Ayahuasca's role in treating substance use disorder.

### Ayahuasca: An Overview

#### **Traditional Use**

Ayahuasca is deeply embedded within the Traditional Amazonian Plant Medicine (TAPM)[42] paradigm and has been utilized for centuries, if not millennia, in the Amazon basin. The exact time of the advent of the Ayahuasca ceremony is unclear and is subject to debate within academia, with estimates ranging from into antiquity, including ritual-associated vessels dating to 2400 BC [35] and DMT-containing snuffs dating back 1000 years [36], to as contemporary as during the tubber tapping boom of the 1800s as a socially reparative process [29][30]. Traditionally prepared and administered by an 'Ayahuasquero,' a healer trained through extensive apprenticeship with a master, Ayahuasca serves as a healing tool in various cultural practices. These range from the Ayahuasquero alone consuming the brew to diagnose and treat ailments to ceremonies where both the healer and the participants ingest Ayahuasca. Integral to these rituals are the 'icaros' or medicine songs, regarded by practitioners as directing Ayahuasca's healing power. The use of Ayahuasca has also given rise to syncretic religions such as Santo Daime and União do Vegetal (UDV), which blend indigenous traditions with

Commented [A3]: who coined the term "TAPM"?

Commented [A4]: Is there a consensus formed?

Christian theology, using the brew as a sacrament to promote spiritual awakening and healing. Ayahuasca is consumed in magico-religious ceremonies for purposes of divination, curing, hunting magic, social healing, among others in its original site of origin, the Amazon basin. Ayahuasca use has spread globally in the late 20th century and early 21st century.

### **Basic Pharmacology**

Banisteriopsis caapi is rich in beta-carbolines, including harmine, harmaline, and tetrahydroharmine, which act as monoamine oxidase inhibitors (MAOIs). MAOIs are crucial for the psychoactive effects of Ayahuasca by enabling the dimethyltryptamine (DMT) from *Psychotria viridis* to remain active in the central nervous system (CNS). DMT is a potent hallucinogenic tryptamine. In typical day to day circumstances, DMT is rapidly degraded by monoamine oxidase in the gut and the CNS. DMT escapes this fate in the presence of a MAOI and is able to travel to the CNS where it effects neurochemical action.

The pharmacokinetics of Ayahuasca include a rapid onset of effects, usually within 30 to 60 minutes of ingestion, with a duration of effects lasting approximately 4 to 6 hours [21].

. . .

Neurochemistry of Addiction

In regards to addiction, the prefrontal cortex, the basal ganglia, and the extended amygdala are considered to be especially significant areas of the brain [23]. The basal ganglia is involved in the formation of habits and the learning of routine behaviors. SubCommented [A5]: any facts or figures on this?

Commented [A6]: Can this be quantified, say in comparison to psilocybin?

Commented [A7]: do we have other data on the pharmacokinetics?

regions of the basal ganglia are of importance in the model of substance use disorders. The nucleus accumbens is associated with motivation and reward. The dorsal striatum is associated with the formation of habits and other routine behaviors. The extended amygdala regulates reactions to stress involving the sympathetic nervous system as well as negative emotions. The extended amygdala also communicates with the hypothalamus, thus impacting glandular responses to stressors. The prefrontal cortex is well involved in complex cognitive processes regarding organization, task-oriented behavior, time management, decision making, and impulse control [23]. In the addiction cycle, the basal ganglia is implicated in binge and intoxication behaviors, the extended amygdala is implicated in withdrawal and negative affect during withdrawal, and the prefrontal cortex is associated with preoccupation and anticipation of drug use [23]. The rewarding effects of dopamine-activating compounds, such as cocaine, amphetamine, and nicotine, act upon the nucleus accumbens. The rewarding effects of opioids and alcohol include effects upon the opioid system, which stimulates the nucleus accumbens both directly and indirectly through the dopaminergic systems [23]. Incentive salience, an association of a stimulus present during use with the reward of use, seems to be linked to the concept of conditioned-place preference, a rewarding effect of a stimulus measured by approaches and contact behaviors in animal studies [39].

#### Behavioral Health of Addiction

Correlation exists between SUD and depression in the literature. It has been found that 40% of patients with depression have a history of SUD or alcohol dependence in their

lifetime. [43] The causality between depression and SUD and/or alcohol dependence is not entirely settled in the literature at this time [44]. The association between substance use and depression is more specific for alcohol, cannabis, and opioids. Data is also available on stimulant agents and benzodiazepines. Oliva et al 2018 [45] ran a prospective study to estimate gender differences in anxiety, depression, and alcohol use among patients with alcohol-use disorder (AUD). Participants were assessed for AUD severity, state and trait anxiety, and depression in 187 patients entering inpatient alcohol detoxification and follow-up was performed at 6 and 12 months post-discharge. Assessment of the psychological dimension most worsened at 6-month follow-up found that the significant predictors of relapse at 12-month follow-up were depression in females and anxiety in males [45].

Why Ayahuasca Helps the Neurochemistry of Addiction Pharmacodynamically, Ayahuasca impacts several neurotransmitter systems, notably serotonin and dopamine, which are pivotal in its proposed therapeutic effects [5][21]. Studies have indicated that Ayahuasca may promote neuroplasticity, leading to longlasting changes in brain function, which could underpin its utility in treating addiction and other psychiatric disorders [29]. Research has found that emotional and cognitive processes were enhanced for 4 weeks after administration of Ayahuasca, an outcome thought to be due to neuroplastic changes that endure beyond the blood concentrations of the active constituents themselves and thought to mark adaptive changes in the neurological system [29]. The Sigma-1 receptor system is thought to play a role in chronic low-grade inflammation that is implicated in many chronic diseases [4] such as behavioral conditions like ADHD, depression, and schizophrenia as well as internal medicine conditions like cancer and cardiovascular disease. It is hypothesized that the sigma-1 receptor (Sig-1R) is associated with the psychopathology of addiction and fits well into a unifying concept of systemic and degenerative illnesses dependent upon chronic low-grade inflammation [4]. The serotonergic and dopaminergic neurons in the mesolimbic pathway have been implicated in the same [4]. Ayahuasca has been found to modulate sigma-1 receptors as well as has direct and indirect effects upon the serotonergic and dopaminergic neurons in the mesolimbic pathway [4]. Ayahuasca modulates y-aminobutyric acid (GABA) levels [4]. It is thought that the mediation of glutamate release by Ayahuasca increases blood flow in frontal and paralimbic regions and activates prefrontal and temporal regions of the brain [4]. The effects upon GABAergic and glutamatergic systems were proposed by Frecska et al 2016 [38] to affect brain-derived neurotrophic factor (BDNF) expression [4]. BDNF expression is thought to have impacts upon neuroplasticity, is hypothesized as implicated in remission from depressive and addictive symptoms, and was found by Almeida et al 2019 to be associated with antidepressant effects after Ayahuasca administration [4]. The therapeutic potential of Ayahuasca in addiction treatment is hypothesized [11][12] to stem from its modulation of neurotransmitter systems associated with reward and mood regulation and with conditioned-place preference (CPP), a marker of associated incentive salience.

2. METHODOLOGY

Commented [A8]: Can I remake this paper as a scoping review?

Literature Search Strategy: A literature search was conducted using the PubMed database, focusing on publications from 2019 to 2024. Key search terms included "substance use disorder", "Ayahuasca", "*Banisteriopsis caapi*", and "*Psychotria viridis*". The search aimed to capture a general array of studies examining the effects of Ayahuasca on SUD, with additional references sourced from the bibliographies of the primary articles selected [11][12]. This approach resulted in 30 papers being retrieved. **16** papers were ultimately utilized in this review article. Access (pay-wall) and language issues (author's lack of proficiency in non-English language) limited utilization of several papers.

Selection Criteria and Features of Selected Papers The selection criteria for the papers were that they were of the following designs: narrative reviews, preclinical trials, observational studies, randomized-controlled trials. The topic of the paper needed to be focused on substance use disorder and Ayahuasca. Papers were found to include populations studied varying from urban to rural dwellers, individuals actively struggling with SUDs and PSUDs, those in recovery, and members of Ayahuasca religious communities. Papers focusing on a wide range of substances were included. The subjects of those papers included alcohol, cannabis, cocaine, fentanyl, heroin, methamphetamine, methylphenidate, tobacco, and others. Papers that did not meet these criteria based on design or topic focus were excluded. Papers referencing related topics regarding Ayahuasca but not specific to substanceuse disorder, e.g. Palhano-Fontes et al. 2019 [37] paper on Ayahuasca for treatmentresistant depression, have been utilized as they are helpful to developing context. Commented [A9]: Is this accurate?

**Commented** [A10]: Did I articulate earlier that PSUDs = polysubstance use disorder?

### 3. AYAHUASCA AND SUBSTANCE USE DISORDER

#### **Clinical Evidence**

The therapeutic landscape for substance use disorders (SUDs) is evolving, with Ayahuasca emerging as a potential treatment agent due to its unique psychoactive properties and ritualistic application. A growing body of clinical evidence underscores its potential to address deep-rooted psychological and behavioral aspects of addiction across diverse cultural settings [1][2][3].

One of the pivotal clinical insights into Ayahuasca's efficacy comes from Apud et al. 2021 [1], who observed its effects among polydrug users in Catalonia, Spain. The study emphasized the impact of the ritualistic use of Ayahuasca, highlighting its role in transforming participants' personal narratives and enhancing social integration [1]. Argento et al. 2019 [2] conducted semi-structured interviews with 11 Indigenous participants engaged in Ayahuasca-assisted therapy at a ceremonial retreat and at 6month follow-up, finding significant benefits in reducing problematic substance use, including alcohol, tobacco, and cocaine, particularly applicable within the contemporary needs of a portion of the Coast Salish community [2]. 8 participants were found to report complete cessation of at least one substance at 6 month follow-up. Reduction in substance use and oravings was associated with reported increased connectedness with self, others, and nature or spirit. It should be noted that retreat that was the context of the Argento et al 2019 [2] paper was built as an observational study published by Thomas et al 2013 [46]. Thomas et al 2013 [46] found notable increases in mindfulness and reduction in substance use among the same population demographics.

Apud Peleaz et al 2020 [9] highlighted the benefits of ritual as a cultural device that enhances social commitment and cooperation, reduces anxiety, and assists in the production of new meanings and narratives. These effects occur at multiple levels including the physiological, the psychological, the social, and the cultural. These are referred to in medical anthropology as "symbolic healing" and in biomedical setting potentially as the "placebo response" [9]. Apud Peleaz et al 2020 [9] observed that narratives of healing were common in the testimony of Ayahuasca participants in Spanish psycho-spiritual networks, consisted of spiritual and/or existential experiences, and acted as pivotal moments in the participants' biographies.

Palhano-Fontes et al 2019 [37] found that Ayahuasca was helpful for treatment-resistant depression with significant antidepressant effects. A parallel-arm, double-blind randomized placebo-controlled trial was performed with 29 patients with treatment-resistant depression. Participants received one dose of Ayahuasca or placebo. Assessment of the Montgomery-Asberg Depression Rating Scale (MADRS) and Hamilton Depression Rating scale at baseline and at one, two, and seven days post-dosing was performed. Significant reduction in MADRS scores were observed in the Ayahuasca group compared to placebo at post-dosing days one, two, and seven. A near-significant remission rate was detected post-dosing at day seven. This suggests that Ayahuasca may be helpful for treatment-resistant depression [37].

Commented [A11]: I believe there should be a circle above the A in Asberg.

Hamill et al. 2019 [3] discussed Ayahuasca's behavioral impacts and potential clinical uses. It was suggested that relaxed regulations could facilitate more comprehensive research. The review highlighted that Ayahuasca does not impair neuropsychological functions and could be advantageous in reducing dependency on substances like alcohol and cocaine. This notion of Ayahuasca as a therapeutic option was reiterated by James et al. 2022 [4], who noted in their narrative review the ability to reduce behaviors linked to substance use initiation and progression as well as modification of pathologic traits such as neurotic and phobic qualities. Specifically, Ayahuasca was found to reduce behaviors associated with the initiation and development of alcohol use disorder and helped to reverse behaviors associated with chronic alcohol use. Ayahuasca was found to increase well-being in healthy individuals, reduce psychopathology traits, improve performance on neuropsychological tests with long-term use, and provide benefits in creativity, grief processing, and healthy body image [4].

From a treatment perspective, Berlowitz et al. 2020 [8] documented significant outcomes at the Takiwasi Center (Tarapoto, Peru), where a sample of 50 male participants showed marked improvements in drug use, psychiatric status, and social relationships post-treatment. Politi et al. 2021 [6] explored this finding with study of 390 patients to whom where administered a brew of exclusively *Banisteriopsis caapi* vine. Takiwasi Center calls this treatment "purgahuasca" and uses it to prepare participants for recovery work. Purgahuasca appeared helpful in fostering a reconnection with life's sacred dimensions, enhancing mental clarity, and preparing for work with Ayahuasca by providing physical and psychological cleansing [6]. The emetic effects of Ayahuasca are thought to cause vagus nerve activation with mesolimbic changes helpful for addiction treatment.

Adding to the clinical understanding, Giovannetti et al. 2020 [7] studied 31 male addiction treatment patients at Takiwasi Center and found that a combination of Ayahuasca and psychotherapy provided significant reductions in Beck Anxiety Inventory (BAI) and Beck Depression Inventory (BDI) scores. Participants reported higher quality of life and spirituality at the end of their treatment stay. These findings suggest that integrated approaches that combine traditional Amazonian medicine with psychological counseling can be quantifiably effective [7].

The safety and tolerability of Ayahuasca were focused upon by Hamill et al. 2019 [3]. Its side effect profile is described as relatively mild. They emphasize the need for further studies to fully understand the safety parameters. *Banisteriopsis caapi* infusions are known to cause emesis. Ayahuasca is no exception.

Observational and systematic reviews by O'Shaughnessy et al. 2021 [10] and Rodrigues et al. 2022 [11] have noted significant improvements in mental and emotional health, a reduction in cravings, and overall enhancements in life quality among participants, both in controlled settings and broader ritual use. These studies highlight Ayahuasca's capacity to effect positive changes early in the treatment process, which appear to be sustained over time. **Commented [A12]:** Can I elucidate the side effect profile? I know there is rapid heart rate, changes in blood pressure, psychomotor activation, limbic system changes (anxiousness, arousal, anger, myriad emotions released). The clinical evidence collectively demonstrates that Ayahuasca has promising therapeutic potential for treating SUDs, capable of facilitating profound psychological and behavioral changes with a good safety profile. However, the continued exploration through rigorous, placebo-controlled clinical trials remains a helpful option to confirm these findings and better integrate Ayahuasca into conventional treatment paradigms.

## 4. AYAHUASCA'S THERAPEUTIC POTENTIAL IN POLYSUBSTANCE ABUSE

Ayahuasca's potential as a treatment for polysubstance abuse represents a novel integration of traditional medicine into contemporary therapeutic practices that has potential benefits to compliment established pharmacological and psychological interventions for Substance Use Disorders (SUDs).

Comparative Analysis with Standard Treatments Conventional pharmacological treatments for SUDs, such as acamprosate and naltrexone, have demonstrated efficacy through extensive clinical trials. A systematic review by McPheeters et al. 2023 [15] found that these medications effectively reduce the likelihood of returning to drinking, with naltrexone particularly decreasing heavy drinking episodes. Despite these benefits, challenges remain, such as the variability in treatment outcomes and adherence rates. Minozzi et al. 2021 [16] highlighted the lack of superiority over placebo of oral naltrexone for opioid dependence and cited study results dependence on enforced adherence contexts (incarceration) for demonstration of effectiveness. The treatment for stimulant disorders, as reviewed by Vocci and Montoya 2009, leans heavily on behavioral therapies like Cognitive Behavioral Therapy (CBT) and contingency management, which have shown safety and efficacy but still require further research to address specific psychosocial needs. Similarly, Gates et al. 2016 [18] found that while psychosocial interventions can reduce the frequency of cannabis use and the dependency of its users, these interventions often result in low rates of long-term abstinence.

# 5. PATIENT EXPERIENCES AND QUALITATIVE STUDIES

The therapeutic potential of Ayahuasca in treating Substance Use Disorders (SUDs) extends beyond pharmacological effects, deeply influencing patients' psychological and emotional landscapes. Qualitative data from various studies illuminate the profound subjective experiences and psychological changes encountered by individuals undergoing Ayahuasca therapy.

# Subjective Experiences of Ayahuasca Therapy

Research into the subjective effects of Ayahuasca reveals significant introspective insights that contribute to its therapeutic potential. Apud [1] reports that participants experience vivid recollections of childhood and past traumas, allowing them to revisit and reinterpret memories linked to their addiction. These biographical revisitations often lead to profound psychological insights and a renewed recognition of personal strengths and resources, which are crucial for recovery. Similarly, Argento et al. 2019 [2] found

among 11 participants that Ayahuasca therapy helped reduce substance use and cravings and provided participants with a deeper introspective ability than traditional rehabilitation programs. Participants reported enhanced spiritual connections, a heightened sense of self, and improved interpersonal relationships, contributing to an overall positive reassessment of their lives.

### Phenomenology of Ayahuasca

The phenomenological aspects of Ayahuasca use, as described by James et al. 2022 [4], include experiencing complex visual imagery, geometric patterns, and synesthetic sensations, which are often accompanied by profound emotional openness and alterations in the perception of space and time. Such experiences frequently lead to ego dissolution or a sense of unity with the cosmos, fostering a transformative re-evaluation of personal identity and existential purpose. These experiences are not only therapeutically significant but often lead to encounters with what participants perceive as sentient entities, thus at times providing meaningful insights into personal and universal life themes via mystical experience. Similarly, mystical experience has been found in research by Griffiths et al 2009 [28] upon psilocybin to be one of the strongest predictors of therapeutic outcome.

Psychological and Social Impacts

The broader implications of Ayahuasca therapy are reflected in its significant impacts on mental health, social relationships, and overall quality of life. The narrative revision processes facilitated by Ayahuasca experiences can lead to long-lasting improvements

in anxiety and depression, as noted in multiple studies. Additionally, participants often report enhanced social connections and an increased ability to engage positively with their communities and families. Such improvements are helpful on an expanded level, as they contribute not only to individual healing but also to the reintegration of individuals into society, marking a significant step towards holistic recovery from substance dependence.

These qualitative insights suggest Ayahuasca's capacity to act as a powerful therapeutic agent. The facilitation of potent psychological transformations and the fostering of greater social integration makes Ayahuasca present a unique and multifaceted approach to the treatment of SUDs. The rich phenomenological experiences and the deep introspective journeys it provokes appear to catalyze an essential reconfiguration of personal identity and purpose, which is fundamental in overcoming the challenges of polysubstance abuse.

# 6. DISCUSSION

### Synthesis of Findings

The current body of research on Ayahuasca's therapeutic potential for treating polysubstance abuse underscores its efficacy primarily through observational and preclinical studies. These studies consistently report significant psychological benefits, including reductions in substance use and cravings, enhanced emotional and psychological well-being, and improved social relationships. The evidence base has several randomized clinical trials yet lacks sufficiently robust clinical trials needed to

systematically verify these outcomes. The observational studies existent at this time provide valuable insights into Ayahuasca's therapeutic effects. The variability in study designs and methodologies, alongside the reliance on self-reported data, suggests the need for more structured research to confirm these findings.

### Implications for Practice

The results indicate that Ayahuasca offers a helpful treatment approach for individuals dealing with substance dependencies due to its broad impact on mental and emotional well-being. Many participants in the studies experienced transformations, including addressing past traumas in a therapeutic setting and rediscovering their identity and purpose. These transformations are vital for sustaining recovery from substance abuse. The residential treatment approach adopted by Ayahuasca retreat centers, which includes both short-term and long-term care options creates an immersive environment that supports these positive changes. This approach could serve as an alternative to pharmacological treatments and residential care models by addressing some of the shortcomings of existing strategies for substance abuse treatment, such as high relapse rates and limited effectiveness of available interventions.

Integration into Treatment Programs Legal Considerations

Integrating Ayahuasca into existing treatment paradigms presents complex challenges, chiefly due to regulatory restrictions. The active ingredient in Ayahuasca, DMT, falls under stringent international regulations that severely restrict its use and research. The

Commented [A13]: Isn't it good to have a variety of study types?

decriminalization model brought to fruition in multiple states and municipalities in the USA for psilocybin (e.g., Prop 109 in Oregon) provides a potential state-level solution, though federal-level restrictions would still propose challenges.

# **Clinical Trial Approach**

Despite these barriers, there is a growing movement advocating for the incorporation of Ayahuasca into therapeutic settings [27][38], backed by emerging scientific literature and anecdotal evidence of its efficacy and transformative potential in treating SUDs. The U.S. FDA framework offers a pathway for clinical trials, which could pave the way for broader acceptance and integration of Ayahuasca as a treatment option. Proving the efficacy of a complicated admixture with accompanying healing modalities that are culturally unique such as the practices of the healer(s) may be difficult to replicate in RCTs due to issues of control.

### **Religious Freedom Approach**

The petitioning of the federal government of the United States for religious use has been successfully undertaken by the União do Vegetal, the Santo Daime, and the Church of the Eagle and Condor (2024) [25]. This route does not open up a wide path for research and science, nor for large-scale treatment, as the US government determines Religious Freedom Act approval on a case-by-case basis.

Standardization

The need for standardized Ayahuasca tea presents itself for both research and ceremonial purposes. AIMS Institute & Sacred Medicines Public Benefit Corporation (PBC) are developing a standardized product to be stewarded through the relevant processes needed for wider utilization [26]. This product could be beneficial for streamlining the research process by creating a standardized equivalent to the brew. The product should be sustainably and ethically harvested. Copyright practices that infringe upon the bio-legacy of this brew should be avoided.

## Ethics

Sensitivity should be applied with the use of South American cultural concepts that are inherent in the use of Ayahuasca. In 2024, several Shipibo groups wrote a joint letter condemning the Church of the Eagle and Condor before the US Government due to claims of misappropriation of Shipibo cultural heritage in the utilization of Ayahuasca in North America. The CEC took action to address these claims and to determine the intent of the signatories [47]. These complaints should be addressed, means of reciprocity should be devised, and best practices should be developed for Ayahuasca treatment to remain culturally sensitive to members of its communities of origin while also allowing it to be a useful tool for sincere use in the manner that the CEC demonstrates.

**Commented [A14]:** Explain further how the CEC responded and how CEC demonstrates cultural sensitivity.

Research Gaps and Future Directions

While the number of randomized-controlled trials on the topic of Ayahuasca is limited, we have one randomized-controlled clinical trial to highlight the topic of Ayahuasca as

relevant to substance use disorder treatment in the work by Palhano-Fontes et al. 2019 [37] on Ayahuasca for treatment-resistant depression which underwent secondary analysis for treatment of suicidality [24]. Many different directions of applicability are being explored in the field, such as potential benefits for the emotional dysregulation features of borderline personality disorder [31]. Future research should focus on conducting clinical trials in residential settings that evaluate the sustained impacts of Ayahuasca therapy over extended periods. These studies should aim to clarify the therapeutic mechanisms of Ayahuasca, its efficacy compared to traditional treatments, and its safety and tolerability across diverse populations. These further trials could be run at retreat centers with a cohort matched with a standard of care group in a different retreat location. It will be a difficult scientific undertaking to determine to what proportion the healing effects of Ayahuasca come from the chemistry, from the therapeutic effect of the healer, and to what amount. Ultimately, it may be wiser to avoid pulling apart a functional tool into its component pieces and to instead study the functional tool as a whole.

Ayahuasca appears to be most effective in a group setting where peer support is built into the therapeutic container. Cohort studies could be performed at the retreat centers to determine further the outcomes from the consumption of Ayahuasca tea and participation in Ayahuasca ceremony. Similar cohorts from conventional treatment centers could be compared to determine outcomes for specific substance-use disorder conditions. There seems to be much to learn when the legal obstacles to the study of Ayahuasca are be overcome. Great benefit could come to many patients who are suffering.

## 7. CONCLUSION

Through an array of study designs—from pre-clinical studies to observational trials to needed randomized-controlled trials—the review has highlighted Ayahuasca's complex pharmacodynamics, its historical and cultural usage, and its impact on both neurological and psychological pathways relevant to addiction [3][5].

The integration of Ayahuasca into Western medical practices as a supplementary treatment for polysubstance abuse within SUD frameworks presents both promising opportunities and formidable challenges. While the current evidence, primarily derived from observational studies and preclinical research, underscores Ayahuasca's potential efficacy, the conspicuous lack of extensive clinical trials represents a significant gap in the literature. This gap should be addressed to move beyond anecdotal and preliminary findings and to establish a robust basis for clinical application. At this time, the evidence in favor of Ayahuasca treatment of SUD suggests that utilization may already be possible in experimental settings and the clinical need may be justifiable for treatment to proceed within that framework. Legal considerations need be made and advocacy must be performed so that an expanding situation of state and federal laws can shift into a permissive and friendly landscape for the scientific study and the clinical utilization of Ayahuasca by qualified practitioners.

By integrating holistic and traditional healing practices into the fabric of contemporary medical treatments, Ayahuasca could potentially offer a novel and enriching approach to the complex challenges of addiction therapy, signaling a new horizon in the amalgamation of traditional knowledge with modern clinical practices.

### REFERENCES

 Apud I.Ayahuasca as an Addiction Treatment in Catalonia: Cognitive and Cultural Perspectives. In Ayahuasca Healing and Science; Springer International Publishing: Cham, 2021; Vol. 7, https://doi.org/10.1007/978-3-030-55688-4\_9. pp 153–170.
 Argento, E., Capler, R., Thomas, G., Lucas, R., & Tupper, K. W. (2019). Exploring ayahuasca-assisted therapy for addiction: A qualitative analysis of preliminary findings among an Indigenous community in Canada. Drug and alcohol review, 38(7), 781–789. https://doi.org/10.1111/dar.12985

 Hamill, J., Hallak, J., Dursun, S. M., & Baker, G. (2019). Ayahuasca:
 Psychological and Physiologic Effects, Pharmacology and Potential Uses in Addiction and Mental Illness. Current neuropharmacology, 17(2), 108–128.
 https://doi.org/10.2174/1570159X16666180125095902

(4) James, E., Keppler, J., L Robertshaw, T., & Sessa, B. (2022). N,N-dimethyltryptamine and Amazonian ayahuasca plant medicine. Human psychopharmacology, 37(3), e2835. https://doi.org/10.1002/hup.2835
(5) Maia, L. O., Daldegan-Bueno, D., Wießner, I., Araujo, D. B., & Tófoli, L. F. (2023).

Ayahuasca's therapeutic potential: What we know - and what not. European

neuropsychopharmacology : the journal of the European College of

Neuropsychopharmacology, 66, 45–61. https://doi.org/10.1016/j.euroneuro.2022.10.008

(6) Politi, M., Friso, F., Saucedo, G., & Torres, J. (2021). Traditional Use of

Banisteriopsis caapi Alone and Its Application in a Context of Drug Addiction Therapy.

Journal of psychoactive drugs, 53(1), 76–84.

https://doi.org/10.1080/02791072.2020.1820641

(7) Giovannetti, C., Garcia Arce, S., Rush, B., & Mendive, F. (2020). Pilot Evaluation of a Residential Drug Addiction Treatment Combining Traditional Amazonian Medicine, Ayahuasca and Psychotherapy on Depression and Anxiety. Journal of psychoactive drugs, 52(5), 472–481. https://doi.org/10.1080/02791072.2020.1789247
(8) Berlowitz, I., Walt, H., Ghasarian, C., O'Shaughnessy, D. M., Mabit, J., Rush, B., & Martin-Soelch, C. (2020). Who Turns to Amazonian Medicine for Treatment of

Substance Use Disorder? Patient Characteristics at the Takiwasi Addiction Treatment Center. Journal of studies on alcohol and drugs, 81(4), 416–425.

(9) Apud Peláez I. E. (2020). Personality Traits in Former Spanish Substance Users Recovered with Ayahuasca. Journal of psychoactive drugs, 52(3), 264–272.

https://doi.org/10.1080/02791072.2020.1752960

(10) O'Shaughnessy, D. M., Berlowitz, I., Rodd, R., Sarnyai, Z., & Quirk, F. (2021).
Within-treatment changes in a novel addiction treatment program using traditional Amazonian medicine. Therapeutic advances in psychopharmacology, 11, 2045125320986634. https://doi.org/10.1177/2045125320986634

(11) Rodrigues, L. S., Rossi, G. N., Rocha, J. M., L Osório, F., Bouso, J. C., Hallak, J.

E. C., & Dos Santos, R. G. (2022). Effects of ayahuasca and its alkaloids on substance

use disorders: an updated (2016-2020) systematic review of preclinical and human studies. European archives of psychiatry and clinical neuroscience, 272(4), 541–556. https://doi.org/10.1007/s00406-021-01267-7

(12) Mendive, F., Giovannetti, C., & García Arce, S. (2023). Ancient medicine for a modern disease: traditional Amazonian medicine to treat substance use disorders. The American journal of drug and alcohol abuse, 49(6), 691–704. https://doi.org/10.1080/00952990.2023.2264466

(13) Ismael Apud, Juan Scuro, Ignacio Carrera & Andrés Oliveri (2023) Ayahuasca
Ritual, Personality and Sociality: Observational Research Conducted in a Substance
Use Disorder Rehabilitation Center in Uruguay, Journal of Psychoactive Drugs, 55:2,
141-150, DOI: 10.1080/02791072.2022.2053004

(14) Agin-Liebes, G., Zeifman, R., Luoma, J. B., Garland, E. L., Campbell, W. K., & Weiss, B. (2022). Prospective examination of the therapeutic role of psychological flexibility and cognitive reappraisal in the ceremonial use of ayahuasca. Journal of psychopharmacology (Oxford, England), 36(3), 295–308.

https://doi.org/10.1177/02698811221080165

(15) McPheeters, M., O'Connor, E. A., Riley, S., Kennedy, S. M., Voisin, C., Kuznacic,
K., Coffey, C. P., Edlund, M. D., Bobashev, G., & Jonas, D. E. (2023). Pharmacotherapy
for Alcohol Use Disorder: A Systematic Review and Meta-Analysis. JAMA, 330(17),
1653–1665. https://doi.org/10.1001/jama.2023.19761

(16) Minozzi, S., Amato, L., Vecchi, S., Davoli, M., Kirchmayer, U., & Verster, A. (2011).Oral naltrexone maintenance treatment for opioid dependence. The Cochrane database

### of systematic reviews, 2011(4), CD001333.

### https://doi.org/10.1002/14651858.CD001333.pub4

(17) Vocci, F. J., & Montoya, I. D. (2009). Psychological treatments for stimulant misuse, comparing and contrasting those for amphetamine dependence and those for cocaine dependence. Current opinion in psychiatry, 22(3), 263-268. https://doi.org/10.1097/YCO.0b013e32832a3b44 (18) Gates, P. J., Sabioni, P., Copeland, J., Le Foll, B., & Gowing, L. (2016). Psychosocial interventions for cannabis use disorder. The Cochrane database of systematic reviews, 2016(5), CD005336. https://doi.org/10.1002/14651858.CD005336.pub4 (19) United Nations, Office on Drugs and Crime, Single Convention on Narcotic Drugs, 1961: https://www.unodc.org/unodc/en/treaties/single-convention.html. (20) United Nations, Convention on Psychotropic Substances, 1971: https://www.unodc.org/pdf/convention\_1971\_en.pdf. (21) Ruffell SGD, Crosland-Wood M, Palmer R, Netzband N, Tsang W, Weiss B, et al. Ayahuasca: a review of historical, pharmacological, and therapeutic aspects. Psychiatry Clin Neurosci Rep. 2023; 2:e146. https://doi.org/10.1002/pcn5.146 (22) Bhalla, I.P., Stefanovics, E. A., & Rosenheck, R. A. (2017). Clinical Epidemiology of Single Versus Multiple Substance Use Disorders: Polysubstance Use Disorder. Medical care, 55 Suppl 9 Suppl 2, S24-S32. https://doi.org/10.1097/MLR.0000000000000731

(23) Substance Abuse and Mental Health Services Administration (US); Office of the

Surgeon General (US). Facing Addiction in America: The Surgeon General's Report on

Alcohol, Drugs, and Health [Internet]. Washington (DC): US Department of Health and Human Services; 2016 Nov. CHAPTER 2, THE NEUROBIOLOGY OF SUBSTANCE USE, MISUSE, AND ADDICTION. Available from:

https://www.ncbi.nlm.nih.gov/books/NBK424849/

[24] Zeifman, R. J., Palhano-Fontes, F., Hallak, J., Arcoverde, E., Maia-Oliveira, J. P., & Araujo, D. B. (2019). The Impact of Ayahuasca on Suicidality: Results From a Randomized Controlled Trial. Frontiers in pharmacology, 10, 1325.
<u>https://doi.org/10.3389/fphar.2019.01325</u>
[25] Church of Eagle and Condor. (n.d.). CEC Final Agreement. Retrieved from

https://www.churchofeagleandconder.org/uploads/1/4/4/2/144296459/final\_cec\_agreem ent\_\_signed\_.pdf

[26] Standish, L. (2019). World AYA Conference 2019 Presentation. AIMS Institute. Retrieved from https://www.aimsinstitute.net/wp-content/uploads/2020/06/standish-2019-world-aya-conference.pdf

[27] Lau, R. (2016, September 12). The Ayahuasca Boom in the U.S. The New Yorker. Retrieved from https://www.newyorker.com/magazine/2016/09/12/the-ayahuasca-boomin-the-u-s

[28] Griffiths, R., Richards, W., Johnson, M., McCann, U., & Jesse, R. (2008). Mystical-type experiences occasioned by psilocybin mediate the attribution of personal meaning and spiritual significance 14 months later. *Journal of psychopharmacology (Oxford, England), 22*(6), 621–632. https://doi.org/10.1177/0269881108094300 [29] de Vos, C. M. H., Mason, N. L., & Kuypers, K. P. C. (2021). Psychedelics and Neuroplasticity: A Systematic Review Unraveling the Biological Underpinnings of Psychedelics. Frontiers in psychiatry, 12, 724606.

https://doi.org/10.3389/fpsyt.2021.724606

[30] de Mori, B. B. (2011). Tracing hallucinations: Contributing to a critical ethnohistory of ayahuasca usage in the Peruvian Amazon. The internationalization of ayahuasca, 23-47.
[31] Domínguez-Clavé, E., Soler, J., Pascual, J.C. et al. Ayahuasca improves emotion dysregulation in a community sample and in individuals with borderline-like traits. Psychopharmacology 236, 573–580 (2019). https://doi.org/10.1007/s00213-018-5085-3
[32] Nardou, R., Sawyer, E., Song, Y.J. et al. Psychedelics reopen the social reward learning critical period. Nature 618, 790–798 (2023).

https://doi.org/10.1038/s41586-023-06204-3

[33] Substance Abuse and Mental Health Services Administration (SAMHSA). (2023, November 13). HHS, SAMHSA Release 2022 NSDUH Data. Retrieved from https://www.samhsa.gov/newsroom/press-announcements/20231113/hhssamhsa-release-2022-nsduh-data

[34] Inserra A. (2018). Hypothesis: The Psychedelic Ayahuasca Heals Traumatic
 Memories via a Sigma 1 Receptor-Mediated Epigenetic-Mnemonic Process.
 Frontiers in pharmacology, 9, 330. <u>https://doi.org/10.3389/fphar.2018.00330</u>

[35] Naranjo P. El ayahuasca en la arqueología ecuatoriana. América indígena.1986; 46(1): 117–127.

[36] Miller MJ, Albarracin-Jordan J, Moore C, Capriles JM. Chemical evidence for the use of multiple psychotropic plants in a 1,000-year-old ritual bundle from South America. Proc Natl Acad Sci USA. 2019; 116(23): 11207-11212. [37] Palhano-Fontes, F., Barreto, D., Onias, H., Andrade, K. C., Novaes, M. M., Pessoa, J. A., Mota-Rolim, S. A., Osório, F. L., Sanches, R., Dos Santos, R. G., Tófoli, L. F., de Oliveira Silveira, G., Yonamine, M., Riba, J., Santos, F. R., Silva-Junior, A. A., Alchieri, J. C., Galvão-Coelho, N. L., Lobão-Soares, B., Hallak, J. E. C., ... Araújo, D. B. (2019). Rapid antidepressant effects of the psychedelic ayahuasca in treatment-resistant depression: a randomized placebo-controlled trial. Psychological medicine, 49(4), 655-663. https://doi.org/10.1017/S0033291718001356 [38] Frecska, E., Bokor, P., & Winkelman, M. (2016). The Therapeutic Potentials of Ayahuasca: Possible Effects against Various Diseases of Civilization. Frontiers in pharmacology, 7, 35. https://doi.org/10.3389/fphar.2016.00035 [39] Davis, C. M. (2017). Animal Models for Studying Substance Use Disorder: Place and Taste Conditioning. Animal Models for the Study of Human Disease (Second Edition), 556-584. https://doi.org/10.1016/B978-0-12-809468-6.00022-X [40] Hassan, A. N., & Le Foll, B. (2019). Polydrug use disorders in individuals with opioid use disorder. Drug and alcohol dependence, 198, 28–33.

https://doi.org/10.1016/j.drugalcdep.2019.01.031

[41] Yang, M., Huang, S. C., Liao, Y. H., Deng, Y. M., Run, H. Y., Liu, P. L., Liu, X. W., Liu, T. B., Xiao, S. Y., & Hao, W. (2018). Clinical characteristics of poly-drug abuse among heroin dependents and association with other psychopathology in compulsory isolation treatment settings in China. International journal of psychiatry in clinical practice, 22(2), 129–135.

https://doi.org/10.1080/13651501.2017.1383439.

[42] Tafur, J (2017) The Fellowship of the River: A Medical Doctor's Exploration into Traditional Amazonian Plant Medicine. Espiritu, Phoenix.<u>Google Scholar</u>
[43] Danzo S, Connell AM, Stormshak EA: Associations between alcohol-use and depression symptoms in adolescence: examining gender differences and pathways over time. J Adolesc. 2017, 56:64-74.

10.1016/j.adolescence.2017.01.007

[44] Porter B, Hoge CW, Tobin LE, Donoho CJ, Castro CA, Luxton DD, Faix D:
Measuring aggregated and specific combat exposures: associations between combat exposure measures and posttraumatic stress disorder, depression, and alcohol-related problems. J Trauma Stress. 2018, 31:296-306. 10.1002/jts.22273
[45] Oliva F, Nibbio G, Vizzuso P, Jaretti Sodano A, Ostacoli L, Carletto S, Picci RL:
Gender differences in anxiety and depression before and after alcohol

detoxification: anxiety and depression as gender-related predictors of relapse.

Eur Addict Res. 2018, 24:163-172. 10.1159/000490046

[46] Thomas, G., Lucas, P., Capler, N. R., Tupper, K. W., and Martin, G. (2013).

Ayahuasca-assisted therapy for addiction: results from a preliminary

observational study in Canada. Curr. Drug Abuse Rev. 6, 30–42. doi:

10.2174/15733998113099990003

[47] Authors personal communication with Dr. Joe Tafur MD 06-05-2024.