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Psychedelics as Medicines for Substance Abuse Rehabilitation: Evaluating Treatments with LSD, Peyote, Ibogaine and Ayahuasca

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Abstract: Substances known as psychedelics, hallucinogens and entheogens have been employed in ethnomedical traditions for thousands of years, but after promising uses in the 1950's and 1960's they were largely prohibited in medical treatment and human research starting in the 1970's as part of the fallout from the war on drugs. Nonetheless, there are a number of studies which suggest that these substances have potential applications in the treatment of addictions. While these substances are generally classified as Schedule I, alleging no established medical uses and a high drug abuse potential, there is nonetheless evidence indicating they might be safe and effective tools for short term interventions in addictions treatment. Evidence suggests that the psychedelics have a much greater safety profile than the major addictive drugs, having extremely low levels of mortality, and producing little if any physical dependence. This paper reviews studies evaluating the use of LSD, peyote, ibogaine and ayahuasca in the treatment of dependencies and the possible mechanisms underlying the indications of effectiveness. Evidence suggests that these substances help assist recovery from drug dependency through a variety of therapeutic mechanisms, including a notable "after-glow" effect that in part reflects their action on the serotonin neurotransmitter system. Serotonin has been long recognized as central to the psychedelics' well-known phenomenological, physical, emotional and cognitive dynamics. These serotonin-based dynamics are directly relevant to treatment of addiction because of depressed serotonin levels found in addict populations, as well as the role of serotonin as a neuromodulators affecting many other neurotransmitter systems.

Keywords: Ayahuasca, entheogens, hallucinogens, ibogaine, LSD, peyote, psychedelics, psychointegrator.

INTRODUCTION

The substances known as psychedelics, hallucinogens, entheogens, psychointegrators and sacred medicines have been employed in ethnopharmacologies for thousands of years [1, 2]. While there was a brief renaissance of their use in psychiatry in the 1950's and 1960's, these substances have been largely excluded from human research and treatment since their broad international prohibition in the 1970's. Nonetheless, there has emerged significant evidence that a number of these substances have important applications in the treatment of a variety of conditions, including addictions (see [3], Vol. 2 for review articles).

While it might seem somewhat incongruous to treat addicts with substances which are generally classified as Schedule I substances (alleging no medical uses and a high drug abuse potential), there are nonetheless many forms of evidence that suggest they are both reasonable and effective treatment for many conditions. First, the psychedelics have a much greater safety profile than the other major drugs, legal and illegal [4]. Even if we include the vast range of illicit use there is very little mortality associated with their use. Perhaps the greatest risk from the use of the psychedelics is from people thinking they can fly from the upper stories of buildings while under the influence [5]. Furthermore, the psychedelics produce little if any physical dependence [6]. And in contrast to the idea that these drugs might provoke additional addictive behaviors among susceptible populations, there is evidence that they reduce substance abuse, an "after-glow" effect that often appears to allow addicts to easily remain drug free for a period of several weeks to months after administration of psychedelics.

This afterglow effect appears to reflect action on the serotonin neurotransmitter system, which constitutes another significant reason for their use in addictions treatment. Since the 1960s the principal effects of the psychedelics have been recognized as derived from their effects on the serotonergic neurotransmitter system (see 7-10 for reviews). While psychedelics activate other neurotransmitter systems, it is the effects on serotonin neurotransmission that underlie psychedelics' well-known phenomenological, physical, emotional and cognitive dynamics. These serotonin-based dynamics are directly relevant to treatment of addiction because of depressed serotonin levels found in addict populations, as well as the role of serotonin as a neuromodulators affecting many other neurotransmitter systems.

A variety of forms of evidence indicate the possible effectiveness of psychedelics such as LSD, peyote, ibogaine and ayahuasca in the treatment of substance abuse. These four substances appear to constitute the bulk of the research on the use of psychedelics in addictions treatment, although there are some indications that psilocybin and ketamine also have useful applications[1]. This paper first reviews the evidence regarding their effects when used as drug abuse

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[1]There is also some evidence which suggests that psilocybin [77], MDMA [78] and ketamine [73, 74, 79] might also have effectiveness in treating addictions.

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treatment strategies, followed by consideration of the possible mechanisms through which therapeutic effects might be achieved. This is followed by an assessment of the support for their use as treatments according to the phases of evaluation typically used by the Food and Drug Administration (FDA) of the United States government to evaluate novel remedies.

LYSERGIC ACID DIETHYLAMIDE (LSD) IN THE TREATMENT OF ALCOHOLISM

While LSD is considered to be a synthetic chemical, it has its natural analogues in the ergot alkaloids found in a number of plants [1]. The use of LSD in the treatment of alcoholism is the most widely investigated clinical application of the psychedelics in the treatment of addictions [see 11-15 for meta-analysis). The early (*i.e.*, 1950's and 1960's) applications of LSD to the treatment of alcoholism suggested their potential to curtail use and reduce recidivism. Some studies indicated that those who received the greatest effects in achieving sobriety were those who experienced a profound spiritual or transcendent experience from LSD. LSD sessions could produce a vivid awareness of one's personal problems, presenting graphic images of the immediate and long-term deleterious effects of the alcohol. The recovering alcoholics often credited these realizations as providing the motivation to change their behavior. Spiritual realizations which provided motivation for recovery was often attested to by the former alcoholics, echoing the main theme of Alcoholics Anonymous[2]: alcoholism is a disease characterized by a deep spiritual craving that can be overcome only by a spiritual awakening and change of consciousness produced through an awareness of a power greater than one's self.

The limited methodological designs (*i.e.*, lacking double-blinds and placebo controls) typical of many early studies, as well as the limited follow-up periods of better designed studies, made it easy for many to dismiss the findings. Halpern [13, 14], however, has shown that there are some valuable findings and applications to be culled from this early research. Halpern's assessment of the literature suggests that the anti-addictive effects of a single dose may last only 1-2 months. They nonetheless appear to provide a time-limited "afterglow" where the addict experiences a reduction in craving for drugs and an increased openness to communication about personal problems that can contribute to their therapeutic resolution.

Meta-analyses have also shown the extended effects found as consequences of LSD treatments. Abuzzahab and Anderson [11] performed a meta-analysis of 31 early (1953-1969) studies using LSD with alcoholics, illustrating the positive effects of LSD in addictions treatment. Single dose studies showed an improvement of greater than 50% in treatment over control groups. Krebs and Johansen [15] provide a meta-analysis of early LSD treatments for alcoholism, using only those studies that were based on randomized controlled clinical trials. They selected studies from the PubMed and PsycINFO databases (1943–2010), supplemented by contacting the researchers involved. In the six eligible randomized controlled trials that they identified, all participants in the study were being treated for alcoholism, generally within in-patient treatment programs; excluded were patients with significant psychiatric complications. Because several of the studies had substantial loss to follow-up, the bias was accounted for by assigning the dropout study participants to a "no improvement" condition, reflecting their likely relapsed to problematic alcohol use, and producing a bias against a significant treatment effect. While many of the individual randomized controlled trials were underpowered (few participants), and consequently did not report statistically significant differences when analyzed individually, the pooled effects were found to have significant treatment effects. The analyses revealed that LSD provided a significant beneficial effect in the treatment of alcoholism in the short-term (3 month) and medium-term (6 month), as well as differences at long-term follow-up which were not statistically significant. While there were a few adverse reactions noted during LSD sessions, none of the studies reported any persistent detrimental effects on psychosocial functioning attributed to LSD treatments.

Krebs and Johansen [15] concluded that the pooled analysis of data from six randomized controlled clinical trials showed that a single dose of LSD can produce significant reductions in alcohol abuse, with the significant beneficial effects found at both the first follow-up assessment and 6 months, but that these treatment effects had declined by the 12 month follow-up. This is similar to the findings of many other non-randomized studies or studies with weak controls that have also reported a lack of significant differences at follow-ups done at 1 year or more, pointing to the limitations of a single dose of LSD in treatment of alcoholism.

In general these studies indicate that a more effective treatment of alcoholism derives from a psychedelic model (using large doses to produce spiritual experiences), rather than a psycholytic model (using small repeated doses to facilitate insight) (see [16]). Large psychedelic doses that produce life-transforming cosmic experiences appear to be a critical factor in changing one's self-concept and lifestyle in ways that contribute to a resolution of alcoholism. Yensen and Dryer [17] place the therapeutic effects of LSD in the context of the relationship between addiction and peak experience and the reactions of hopelessness and despair to emotional (and physical) pain that leads to addiction as a substitute solution. Peak experiences provide a fundamental shift in consciousness that lead one from the anger, despair and false gratification to a shift in consciousness that provides a profound motivation for positive change. They attribute the therapeutic outcomes to the drug's ability to contribute to the complex re-living of memories in a safe and supportive context which facilitates psychotherapeutic transformation.

Mechanisms of Therapeutic Effects

Bogenschutz and Pommy [18] note that the persistent therapeutic effects of psychedelics on addictions remission must be a result of some persisting brain changes. Nonetheless, the mechanisms by which LSD has physiological effects on the human brain are based on

[2]One of the founders of Alcoholics Anonymous, Bill Watson, advocated for the use of LSD in the AA but was voted down by the Board (see [80] pp. 370-71; thanks to Tom Roberts for the reference).

inference from laboratory studies on rodents. The mechanisms through which the psychedelics act on neurotransmission include not only the widely recognized agonist effects on serotonin, as well as antagonism of other receptor classes (NMDA, kappa opioid, and muscarinic acetylcholine) [18]). In addition to the classic psychoactive effects of psychedelics on serotonin receptors, which results in activation of areas of the cerebral cortex through stimulation of pyramidal cells, there are also secondary effects on the glutamatergic system that also increase cortical activity through inducing the release of glutamate from pyramidal cells [18].

Serotonergic Effects

A principal physiological aspect of the therapeutic mechanisms underlying the psychedelic treatment of addiction in general comes from effects on the serotonergic neurotransmitter systems. Both the tryptamines (*e.g.*, DMT, LSD, psilocin, and psilocybin) and phenylethylamines such as mescaline, MDMA ('ecstacy') and 2C-B have similar end effects on the serotonergic neurons [see 7-10 for reviews]. These effects enhance the levels of serotonin, addressing the low serotonin levels depleted by long-term drug use. The effects of the LSD-like psychointegrators on serotonin is presumably responsible for the widely-noted mood enhancing effects, as well as the reported reduction of anxiety, depression, aggression and compulsions. Serotonin's role as a neuromodulator, with direct effects upon other neurotransmitter systems, enables serotonin enhancement effects to cascade into other neurotransmitter systems affected by addictions.

Bogenschutz and Pommy [18] propose that three well-established mechanisms that mediate recovery from addiction—reduction in craving, enhancement of self-efficacy, and increased motivation - can be affected through the therapeutic use of psychedelics through several of the mechanisms they activate. The phenomenon of craving involves neuronal pathways of the brain's reward system (dopaminergic, glutamatergic and opioidergic) as well as the serotonergic system, which is involved in the modulation of craving and the regulation of motivational, appetitive and reward related behaviors. They note that augmentation of serotonergic activity should result in reduced craving, normalization of stress, improvement of mood and anxiety, and consequently reduced risk of relapse. They propose that the psychedelic mediated treatment of addictions has therapeutic effects through mechanisms that produce persisting improvements in mood, a reduction in anxiety, personality changes and changes in beliefs and value.

Since self-efficacy, the person's belief in their own ability to quit, is significant associated with maintenance of sobriety, there are several ways in which the effects of psychedelics can contribute to drug use cessation. These include the induction of mystical experiences and personality changes that increase self-efficacy. Mystical experiences also can produce persistent changes in personality, mood and affect that contribute to changes in addictive behavior; these psychological effects, which prompted by physiological effects of the drug, may be much more dependent on reinforcing effects of set and setting. There are also spiritual effects produced by psychedelics, such as found in the study by Griffiths *et al*. [19] that shows that psilocybin objectively produces mystical experiences, that is to say under double blind control conditions. Psychedelics could also affect motivation to change through processes found to be elicited by the psychedelics, including: consciousness raising, changes in personality and self-evaluation, a heightened awareness of negative consequences of drug use, a sense of self-liberation and relief, and a reevaluation of one's environment [18].

Alteration of Consciousness

Another general therapeutic effect of the psychedelics in the treatment of addictions involves the alteration of consciousness and the myriad of healing effects produced [20-22]. They also can induce spiritual experiences, particularly with large doses that produce life-changes that help in ending addictive behaviors. This paradigm of LSD use known as the psychedelic paradigm suggests that the changes in world view and perceptions produced by these dramatic experiences are key to the treatment effects. While psycholytic therapy with small doses may have a role in addictions treatment, the general consensus is that the best results come from the large psychedelic doses that produce profound effects [16]. These changes in world view include a sense of connection with nature and others, providing a sense of wholeness and connection often lacking in the addict.

The alteration of consciousness is often expressed in spiritual terms, or directly as in Alcoholics Anonymous as a change of consciousness. A wide variety of means of altering consciousness, including drug and non-drug procedures, have basic similarities [23-25]. This high voltage slow wave EEG activity (alpha, theta, and delta, especially 3-6 cps) provokes slow wave hypersynchronous discharges across the hippocampal-septal-reticular-raphe circuit which spreads to the frontal lobes, producing pleasurable sensations and feelings of well-being [23]. General physiological aspects of this alteration of consciousness--parasympathetic dominance, interhemispheric synchronization, and limbic-frontal integration--are an inherent aspect of human consciousness, the integrative mode of consciousness [25]. These manifestations of consciousness have inherent therapeutic effects related to addiction involving stress reduction and activation of aspects of the brain related to mental and emotional integration.

Psychointegration

Winkelman [24, 25] characterizes the effects of the alteration of consciousness in general, and the effects of psychedelics in particular, as psychointegration. The common effects of LSD on serotonergic neurotransmission and the roles of serotonin on the brain reflect processes of psychological and systemic integration. A synthesis of laboratory, clinical and ethnographic findings on the sacred medicines also illustrates why the term "psychointegrator" is a more appropriate characterization of the similar effects of these diverse substances [24, 26]. The root "psyche" - referring to the soul-- also reflects the conceptualization of the basic effects of these sacred medicines as seen from the perspective of the many cultures.

This concept of psychointegration reflects similar effects revealed by neurophysiologic, clinical and cross-cultural

studies, reflecting their action within the serotonin system, which has multiple roles reflected in its characterization as "neuromodulator" that regulates the balance among many neurotransmitter systems. Psychointegrative effects are epitomized in: the functions of serotonin in modulating the activities of dozens of bodily and brain processes and neurotransmitter systems; and by psychointegrators' systemic effects on the serotonergic neurotransmitter system that enhances the integration of information across levels of the brain. This enhanced integrative function is epitomized in the systemic effects at the level of the raphe and reticular formation, where there is an enhancement of excitatory effects; and the limbic brain, where emotions and memories are formed.

The effects of psychointegrators are reflected in synchronized alpha and theta brain wave hyperactivity across the neuraxis, the nerve bundle linking the structural levels of the brain from the brain stem to the frontal cortex. In the process of inducing synchronous discharges across this nerve bundle, psychointegrators elicit processes central to awareness and fundamental aspects of self, emotions and attachments. These processes of psychointegration are manifested physiologically in the typical coherent theta wave discharges that produce a synchronization of brain waves across the neuraxis and lobes of the brain. Psychointegration is reflected in highly synchronized and coherent brain wave patterns that propagate from the brain stem through the emotional (limbic) brain and into the frontal cortex [23]. These brain wave patterns integrate information from physiological, behavioral, and emotional levels of the brain into the frontal cortex. These synchronized theta waves also produce a relaxation response and physiological integration of behavioral, emotional, and cognitive processes.

Psychointegration is also manifested in psychological experiences, particularly those related to emotional healing and the sense of interconnectedness (*e.g.,* cosmic consciousness and other transpersonal experiences). Psychointegrators' effects on neural, sensory, emotional, and cognitive processes enhance consciousness through integrating normally unconscious emotional and self information into the frontal cortex and consciousness. This integration of the unconscious into consciousness underlies the general potentials of psychedelics as an addiction treatment and harm reduction approach.

PEYOTE AND THE NATIVE AMERICAN CHURCH AS ADDICTIONS TREATMENT

There is a long history of the use of peyote (*Lophophora williamsii*), a sacrament within the Native American Church (NAC, the "Peyote Religion" or "Peyote Way"), in the treatment of Native American alcoholism [27]. The principal active ingredient of peyote is mescaline, which has stimulant properties similar to ephedrine and amphetamines; while different from indole alkaloids typical of LSD, its transformation in the body produces similar pharmacological outcomes that are mediated through the serotonergic system [6]. The physiological effects of peyote in healing addictions is characterized by Jilek [28] as involving alterations of consciousness that he points out can be induced through non-drug means (*i.e.*, drums, chanting, prolonged sleeplessness; also see [24]).

NAC members consume peyote in an all-night meeting during which all the community may participate in the singing, prayers, chanting, and drumming. The amount of peyote ingested may be quite small, often less than the minimal dose required for notable visual psychoactive effects. The pharmacological effects are not the only mechanism of treatment. The effectiveness of the NAC as a health care delivery system is also dependent on a variety of supportive psychotherapeutic modalities: a master guide, marathon group sessions, ego reduction techniques, social networks, and self-actualization [29-32]. Many addictions professionals consider the NAC the only effective treatment of alcoholism among Native Americans, and the U.S. Indian Health Service provides reimbursement for the treatment of Native American alcoholics by "road men," the peyote ritual leaders [31]. The Peyote Religion rejects the use of alcohol, making it a natural support group for recovering alcoholics.

The overnight nature of the activity also contributes to the typical visionary experiences predicting one's future ruin as an addict. This awareness contributes to a sense of "hitting bottom" and a heightened consciousness of the need to change lifestyle. The NAC also addresses addiction through social psychological mechanisms, forming a sense of community that promotes a new identity and a social support group that does not use nor tolerate alcohol use. The NAC brings hope to Native American communities, instilling a moral code of devotion to family and obligation to the community, and producing feelings of spirituality and unity [33]. Peyotism provides Native Americans with religious healing, transcendence, release from guilt, and guidance and a sense of purpose. A significant aspect of the effects of peyote is inducing a sense of control in meeting challenges and initiating change, and managing cultural alienation experienced by Native Americans, providing a context for construction of a positive identity with one's culture. The Peyote Religion contributes to the development of a new sense of identity through grounding and connection with community that gives a sense of belonging. Jilek [28] conveys the peyotists' perspective that the Peyote ritual combats alcoholism through reducing physical and mental stress and enhancing mental and physical strength through contact with the supernatural.

Calabrese [30, 31] describes the Peyote Way as a cultural psychiatry involving "meaning-manipulative" therapies engaging social and intrapsychic processes. He characterizes peyote as a "desematicizing agent" that facilitates a reinterpretation of self. Calabrese [30, pp. 238-239] assesses the effects in terms of a "social manipulation of consciousness states and symbols to support socially-valued patterns of ritual experience, self awareness and emotional control ... [rendering] adults more suggestible and thus more open to education and mental health interventions." In this sense peyote rituals heal by shaping consciousness in ways that facilitate symbolic healing processes. Calabrese [30] also notes that unlike many traditional etiologies that attribute personal misfortune to supernatural causes (*e.g.*, witches, taboo violations), the Peyote Way instead places the causal factors in a lack of personal responsibility for one's own behavior.

The NAC has many effects on social, psychological and emotional well-being. Specific pharmacological actions of

peyote in the treatment of addictions may be best characterized in terms of the general effects of inducing an alteration of consciousness and the associated transcendental spiritual experiences. Aberle [33] points to the ability of peyote to induce a sense of connection with the spiritual world that was lost by many Native American individuals and groups in their forcible assimilation to American culture. The significance of spiritual experiences for rehabilitation of the addicted self has been noted in many therapeutic traditions, and may be particularly relevant for Native American groups deprived of their own spiritual traditions.

Mechanisms of Therapeutic Effects

While the ritual processes and the associated psychosocial effects are clearly a significant factor in the effectiveness of the NAC, the physiological effects of peyote in addressing the dynamics of addiction should not, however, be completely discounted. This physiological effect is noted in the "after-glow" (see [13] for review) that has been considered as conducive to therapeutic interventions. This after-effect lasts up to 6 weeks, and includes not only enhanced affect but an increased openness to communication regarding one's problems, making them more accessible to therapeutic intervention. The mechanisms by which peyote achieves its effects, apart from the ritual context provided by the Native American Church, likely include the general effects of LSD reviewed above. The phenylethylamines such as mescaline, MDMA ('ecstacy') and 2C-B) have effects on the serotonergic neurons that are similar to the influence the tryptamines (*e.g.*, LSD, DMT, psilocin, and psilocybin; see [7-10] for review). These biochemical effects are primarily based in serotonin disinhibition and the consequent loss of its inhibitory effects on dopamine and the mesolimbic structures. The indoleamines' (tryptamines and phenylethylamines) effects on serotonin have end-effects that alter consciousness through a common mechanism--production of high-voltage slow-wave (theta) brain wave activity [23, 24] that may provide a variety of therapeutic effects.

IBOGAINE USE IN WITHDRAWAL CESSATION

Ibogaine is an extract from the root of iboga plant (*Tabernanthe iboga*). It is characterized as both a stimulant and hallucinogen, with dosage and other factors (additives, diet, activity) determining whether it induces dreamy visions, and possibly stupor and unconsciousness, or acts as a powerful stimulant [34]. The traditional uses of iboga in West Central Africa were primarily ritual, but it was also employed for relief of fatigue, to enhance hunting skills, and for divinatory purposes. Iboga was also imbibed in large quantities to produce stupor by the Bwiti secret societies of Gabon and Congo and in all-night village or inter-village initiation ceremonies [35]. The Bwiti cult combined Christian and traditional symbols in a revitalization movement that addressed community dislocation caused by colonialism. Communicating with and affirming relationships with the ancestors reintegrated individuals into traditional kinship ties and systems of social control that helped re-establish social stability and well-being [34]. Iboga was interpreted as provoking experiences of contact with the ancestors, a sense of the relationship of the individual to group spirit.

Ibogaine also has a history of informal treatment of addiction in addict communities, functioning largely within the context of both addict and medical subcultures in the public sector rather than in conventional medical settings (but see [36-42]). Discovery of the effects of ibogaine in the treatment of drug addiction occurred in informal experiments carried out by Howard Lotsof in New York City in the early 1960s. Users who sought self-exploration through drug use discovered spontaneously that the administration of ibogaine lead within a few hours' time to a notable reduction in drug cravings and withdrawal symptoms associated with their heroin use, with persistent reductions in withdrawal syndromes lasting for at least several days and for up to two months. This discovery eventually led to use in self-help groups of heroin addicts, who employed the iboga root and ibogaine extracts in treatment for narcotic addiction, particularly to terminate withdrawal from amphetamines, opiates and cocaine. Informal research began within the U.S. in the 1960's, and while placed on Schedule I in 1967, has remained unscheduled in other countries where various forms of research have continued [39]. Ibogaine has consequently remained available in alternative non-medical treatment settings around the world, and through more conventional medical approaches in countries where permitted by law. Ibogaine became an important element in heroin self-help groups in the Netherlands, where it became a central feature of the harm reduction movement there.

This persistent use is based not only on the wide-spread success encountered among the addict and medical subcultures involved [40], but also because of the findings of a wide range of studies which illustrate that ibogaine is effective in addressing addictions. The U.S. National Institute of Drug Abuse (NIDA) funded Phase I studies of toxicity in the early 1990's [36], but in spite of promising results failed to continue funding the study for Phase II evaluations. The FDA withheld funding for the planned and approved Phase I and II studies because of concerns about safety (see below). The continuing use of ibogaine for addictions treatment around the world has been characterized as a largely uncontrolled experiment, but systematic human and animal research [39] establishes that ibogaine has physiological effects in reducing withdrawal cravings and addictions. In reviewing non-medical clinical studies in the US and the Netherlands, Alper & Lotsof point to the "attenuation of opioid withdrawal symptoms within several hours of ingestion, and lasting resolution of the acute opioid withdrawal syndrome within 12 to 18 hours" [39, p. 49]. These limited studies also suggest a short term effect in reducing cocaine addictions that lasts several weeks to months. Physiological effects (rather than placebo effects) are illustrated in animal studies that show ibogaine may reduce the reinforcing effects of opiates and decrease the experience of withdrawal (see [39] for review and original sources).

The typical use of ibogaine in addict communities and medical subcultures is without the ritual and ceremonial aspects associated with the indigenous traditions, but there are also other models, including spiritual ones (see [43], *Manual for Ibogaine Therapy*). Ibogaine is typically used

with the patient located in a dark room and with a bed for reclining during the majority of the session. Administration (also see [39] for details) is with large doses that provoke visions causing incorporation of repressed memories. While often characterized as a hallucinogen, the effects may be better conceptualized as "oneiric", referring to the dream-like experiences evoked in the internal mental space experienced with eyes closed. The visual effects are characterized as high density images generally of autobiographical nature and central to life narrative, although archetypal and cartoon-like imagery is also reported. Notable effects reported by addicts include the loss of craving and the lack of withdrawal symptoms and an aversion to the drug, generally eliminating the addict's desire to further use drugs. The patient's experience under ibogaine typically includes visions that provide psychological insight into their drug use, particularly understandings that help overcome psychological blocks [39]. Iboga's ability to induce a "cosmic consciousness" experience may also underlie iboga's effectiveness in treatment of drug addiction. Iboga's effectiveness in facilitating psychotherapy is attributed to its ability to evoke repressed memories, clarify thoughts, promote introspection, and facilitate manipulation and re-enactment of images and scenes.

Brown [44] provides a review of the substantial evidence regarding the effectiveness of ibogaine, pointing out the wealth of data in particular from preclinical and non-blinded (open-label) clinical studies (also see [45]). These studies, combined with data from animal studies support the long history of anecdotal reports regarding the ability of ibogaine to interrupt addiction and reduce or even eliminate withdrawal symptoms from a variety of drugs, especially the opiates and cocaine. A wide range of animal studies show the ability of ibogaine to reduce self-administration of morphine, heroin, cocaine and alcohol for at least several days. However, as seems to be the case with humans as well, persistent reductions in drug self-administration are more likely achieved with the administration of several doses over time.

Mechanisms of Therapeutic Effects

Some of the general mechanisms of the therapeutic effects of ibogaine are likely similar to those of other psychedelics that have effects of serotonin transmission. One of the similarities of ibogaine influences with that of other psychedelics is noted in the frequent comments made by the clients that they were given insights into their past and forced to accept the impact that their addictive behaviors had on their families and friends. Bogenschutz & Pommy [18] review research that shows that while ibogaine is not a typical serotonin-based psychedelic, it does act as an agonist at the 5HT2 and 5HT3 receptors and displays agonism of serotonin transport, but primarily exhibits activity at a variety of other neuroreceptor sites (NMDA; mu, kappa and sigma opioid; and muscarinic and nicotinic cholinergic receptors). Brown [44] reviews the primary literature which established that ibogaine causes the presynaptic release of serotonin, increases brain serotonin levels, acts on the 5HT2a and 5HT3 receptors, inhibits serotonin reuptake, and acts as an agonist at NMDA and muscarinic receptors.

Alper & Lotsof [39] propose, however, that the primary mechanisms of action of ibogaine are not derived from effects on opiate or serotonin receptors but rather "results in the 'resetting' or 'normalization' of neuroadaptations thought to underlie the development of dependence" ([39], p.44). They point to evidence indicating that ibogaine has a selective effect on the learning related to the encoding of a drug's salience, providing a selective interference with learning related to prior drug exposures. Other mechanisms of ibogaine action include effects on the inferior olive of the brain stem and the Purkinje cells, where it induces prolonged tremors caused by the release of glutamate [42]. Studies in animals suggest that effects on these centers controlling behavioral routines could produce cessation of addiction due to the destruction or exhaustion of these cells, eliminating previous behavioral patterns. In humans, this brain stem excitation is hypothesized to ascend into the brain circuitry underlying REM sleep (dreams) and the thalamus and locus coeruleus. These natural mechanisms involved in forgetting may produce similar destruction of previous behavior patterns reinforcing addiction.

AYAHUASCA IN ADDICTIONS TREATMENT

Ayahuasca typically refers to a combination of two plants, *Banisteriopsis caapi* and *Psychotria viridis*. The *Banisteriopsis* vine (also called ayahuasca) contains several monoamine oxidase (MAO) inhibitors that render the N,N-Dimethyltryptamine (DMT) of *Psychotria* orally active [46]. Scientific characterizations of the active ingredient from ayahuasca brews principally implicate the DMT from the *Psychotria*, but the *Banisteriopsis* is generally considered to be the source of the more important psychoactive ingredients among many cultures which use it ritually. Research on the likely mechanisms of ayahuasca's action in ameliorating addiction implicates the chemical ingredients of both plants.

In pre-modern, modern and post-modern contexts ayahuasca was used for a wide range of purposes [47]. Primary pre-modern uses focused on shamanic development, community-wide rituals, and contacting spirits of the dead; telepathy, clairvoyance, diagnosis, prophecy and healing; and adult transition rites. Ayahuasca traditions have also diffused to urban areas, where broad segments of the population employ them for healing psychosomatic and ethnomedical conditions, particularly those associated with anxiety and stress [34]. Among these urban traditions are the Brazilian "ayahuasca churches" (see [48]) that have incorporated ayahuasca as a sacrament in syncretic religions that combine indigenous, mestizo, spiritualist and Christian traditions such as União do Vegetal and the Santo Daime churches.

However, in spite of a variety of treatment centers there are as of yet no formal clinical evaluations of outcomes using double-blind clinical studies. In spite of the lack of controlled studies, there is a range of evidence that establishes that ayahuasca rituals can positively affect addiction outcomes, especially for those who have a long history of relapse and treatment failure (see [49] a collection which has the majority of the articles illustrating the evidence that ayahuasca has therapeutic success in the area of addictions treatment). Substantial evidence of positive effects and safe use is found from material reviewed below:

1) the long term treatment centers such as Takiwasi in Peru and studies of toxicology and safety implied in the long term healthy use by religious groups; 2) clinical and ethnographic evidence regarding the psychophysiological effects of ayauasca such as purging, visions and the release of a variety of pychodynamic processes; 3) formal quantitative studies using standardized instruments to evaluate changes in the psychological status of addicts participating in rituals using ayahuasca; and 4) a number of recognized pharmacological mechanisms by which the constituents of ayahuasca provide a variety of effects for treating the dynamics of addiction.

Treatment Programs and Processes

Today treatment centers in a number of different countries offer ayahuasca-based therapies for the treatment of addictions [49, 50].

The Takiwasi Program

The fame of ayahuasca as an anti-addiction treatment began with self-reports of former drug users who experienced recovery from experiences in ayahuasca retreats and participation in ayahuasca religions. For more than 20 years, Jacques Mabit and the Takiwasi center in Peru has been a pioneer in the use of ayahuasca treatments for addiction [51, 52]. The Takiwasi program incorporates ayahuasca in ritual treatments for addicts in remote settings in the Peruvian Amazon. The Takiwasi program is known for its work with cocaine and cocaine paste addicts, as well as a variety of polysubstance users. The program claims widespread evidence of clinical success, although formal clinical studies are lacking. The success is attributed not to the ayahuasca alone, but the ritual setting and interactions with therapists. The program integrates traditional ayahuasca rituals and physical, psychological and spiritual activities into treatments that address a range of factors contributory to addiction. Therapeutic success is attributed to the interplay of ayahuasca's effects with other aspects of traditional medicine such as emetics, special diets, spiritual interventions, ritual activities, as well as interactions with therapists and therapeutic community The traditional medicines and rituals are combined within the Takiwasi program with modern transpersonal psychology and social techniques to guide the personal transformation of addicts, using the ayahuasca ritual to produce profound alterations of consciousness that change addicts' outlook on life and their spiritual strength and faith.

The Takiwasi program takes the ritual approach to treatment seriously, incorporating traditional medicine approaches at organic, psychological and spiritual levels. These three levels of treatment are synchronized with the induction of ASC to enhance access to unconscious levels of the individual. This shamanic approach takes the addicts desire to engage in an alteration of consciousness and initiates them into a kind of "vision quest" to accesses deep levels of meaning and a sacred dimension of experience that produces personal reorganization.

The Takiwasi treatment program begins with a focus on the organic level of the body, providing a physical detoxification to eliminate toxins acquired through drug use. The consequences of withdrawal and dependency are also addressed. Treatments at the psychological level address the emotional dynamics that contributed to drug addiction. Ayahuasca alters consciousness in ways that bypass rational functions to provide access to deep levels of the personal unconsciousness, particularly repressed memories. The patient is empowered through the ayahuasca to become their own healer, discovering the cause of their problems in their visions and taking personal responsibility for the healing processes that they must engage. The verbalization of these realizations with their therapist allows patients to reflect on their personal conditions and receive feedback regarding their self-perceptions, attitudes and emotions. These ayahuasca induced experiences also provide access to spiritual and transpersonal levels that takes the patient beyond themselves, instilling a value orientation that provides new meaning to life. This spiritual restructuring is an essential aspect of the healing process. It requires a deflation of the ego that produces reconciliation with self, others, Nature, and the universe at large.

The first phase of the Takiwasi program begins with ten day isolation, followed with up to two months of detoxification to deal with the long-term consequences of cocaine paste addiction and withdrawal symptoms. This includes the use of purgatives, rituals, chants, massages, and tobacco smoke to address tension and anxiety and balance the patient's energy level. Meditation, music therapy, saunas and relaxing teas are the focus after the isolation period. Following a two month isolation from family, visits from family members are allowed. This third month also begins a period of retreats into the isolation of the jungle to take additional plants specific for the personality of the individual and their therapeutic needs. A folk healer administers the plants and a carefully controlled diet and observes the patient for energetic disturbances. This experience, similar to an initiation, helps reinforce the will to heal and overcome addiction. The treatment program continues up to 7 or more months, using ayahuasca and other ASC induction techniques (*e.g.*, meditation, holotropic breath work) to reveal unconscious material for therapeutic work. Dream material is also the focus of therapeutic processes, integrating the unconscious dynamics into a fuller understanding of self. This enhanced self-knowledge contributes to an increasing sense of serenity and a focus on transcendent concerns that reflect a spiritual deepening in their lives.

The positive treatments effects of ayahuasca ritual treatments are considered the consequence of many factors--the physiological properties of the ayahuasca, their interaction with the patients' psychological condition, the environment, and the social relations with therapists and other participants in the treatment center. The physiological action of ayahuasca has been characterized as a disinhibitor that promotes the manifestation of the most basic perceptual capacities of the organism. This is manifested in the visions and other experiences loosely characterized as "hallucinations," but reflecting symbolically important information for the person. The patient's psychological condition, particularly attitudes of openness, trust and surrender, accompanied by commitment to the process, evoke the healing power of ayahuasca. Inappropriate diet, drug use, and sex before or after sessions are considered to undermine the therapeutic process or even cause deleterious

effects. The therapists consider a central aspect of the treatment effects to be produced through the tobacco smoke blown on the patient and the songs sung throughout the sessions.

Institute of Applied Amazonian Ethnopsychology

Another group which has applied shamanistic perspectives in the treatment of addictions with ayahuasca is the Institute of Applied Amazonian Ethnopsychology (IDEAA) (see [53]). Unlike many ayahuasca rituals however, the approach is based on a minimalist model, without extensive focus on ritual processes. The approach nonetheless integrates a variety of sources of ritual knowledge and practice, including the Brazilian Santo Daime religion, shamanism, Eastern meditative disciplines and transpersonal psychology to engage healing process. True to the biopsychosocial features of shamanistic healing, the IDEAA approach also includes other healing techniques outside of the ayahuasca sessions such as: "individual psychotherapy; workshops on emotions, breathing techniques, psychodrama, and bibliotherapy; and family constellation therapy [and] ... other practices such as massage, colonic irrigation, shiatsu, and naturopathy" ([53], p. 166).

Fernández and Fábregas [53] characterized six basic themes that emerged from these ayahuasca-ritual practices: a: review of one's past, insights into patterns of behavior, powerful emotional experiences, death experiences, experiences of contact with nature, and transpersonal or transcendental experiences. While the community context was an important factor in counteracting the extreme individualism and self-centeredness of the addict, the treatment also involved solitary periods during ayahuasca sessions when the participants would retreat to their own cabins for periods of introspection and reflection during the sessions. This gave the participants the supportive conditions necessary for engaging their own healing processes based on self-regeneration that created healing from within the person.

Religious Participation as Ayahuasca Therapy for Addictions

Studies of the adherents to the Brazilian ayahuasca church União do Vegetal (UDV) revealed that people with a history of alcoholism underwent profound life changes leading to sobriety shortly after joining the church [54, 55]. The effects were seen as derived from the changes in their world view and development of a generous attitude towards others. There was also an effect upon social relations, restoring stability to personal and familial relationships. Case study approaches [56] have also implicated ayahuasca in recovery mechanisms. Case-control studies showed that long-term regular religious ayahuasca users were healthier than non-ayahuasca users in terms of drug abuse and psychiatric symptomatology [57-60] and were similar on neuropsychological assessments, suggesting no negative effects from ayahuasca use. This evidence shows that participation in the UDV ayahuasca churches reduces the risk of adolescent alcohol use, as well as anxiety, depression and psychiatric symptomology [59, 60].

Psychophysiological Effects of Ayahuasca: Purging, Visions and Psychodynamic Processes

Physiolological factors are clearly at the core of a variety of physical effects of ayahuasca, such as the purgative and emetic effects, the visions and the recall of significant past memories. But how these are interpreted within the ritual and personal circumstances are important to the recovery processes. Within the shamanistic traditions, the vomiting, referred to as a purge (purge), is seen as a part of the process of detoxification of the body, not only the elimination of toxins, but also the expulsion of morbid emotional and mental conditions. Loizaga-Velder and Loizaga Pazzi [61] note that this emetic effect experienced through vomiting is seen as provoking an emotional release or unloading of psychological burdens, as well as provoking diverse emotional dynamics that trigger psychological and spiritual reactions.

The ayahuasca visions are also consequences of biological effects that contribute important therapeutic dynamics through connecting the patient with significant aspects of their personal past, elevating repressed memories into consciousness where they can play a role in psychological healing through restructuring. Loizaga-Velder and Loizaga Pazzi [61] report that a frequent theme of recovered addicts was that the ayahuasca-induced visions helped them to recover repressed memories of traumatic events that they were then able to work through, providing a basis for restructuring their personal life. Ayahuasca-induced awareness often leads to insights that facilitated self-reflection, producing changes in perspectives and perceptions of self that can trigger psychodynamics insights that provide creative solutions to personal problems and maladaptive psychological patterns that support addictive lifestyles. Ayahuasca can help to clarify personal conflicts by providing conscious insights into patterns of psychological functioning related to patterns of abuse and dependence. Insights from ayahuasca experiences often provided insights that enabled acceptance of previously denied problems and dysfunctional patterns. These visionary conditions of consciousness produced by ayahuasca can also provoke reflections on personal relationships that often resulted in increased understanding of and empathy for significant others which provided the motivation for making the changes necessary to resolve interpersonal problems. Another important effect of ayahuasca was the engagement with a positive experience of self that contributed to a sense of self-efficacy and positive self-image.

The subjective reports of ayahuasca's effects suggest underlying psychodynamic mechanisms that provide benefits in addictions treatment. The psycholytic effects typical of psychedelics can augment access to pre-conscious and unconscious memories, providing release of repressed emotions that can catalyze healing processes through facilitating the resolution of traumas. Access to those memories can contribute to freeing the person from dysfunctional habits that underlie the dynamics of addiction. Psycholytic processes engendered by ayahuasca also promote an awareness of not just past patterns of behavior

but also their future outcomes and personal consequences of addictive behaviors, providing an understanding of the likely futures if they do not change their addictive behaviors.

Fernández and Fábregas [53] suggest that ayahuasca impacts psychological process by provoking a confronting or facing of oneself, forcing a greater personal awareness, achieving a reconstruction and restructuring of awareness of the nature of oneself by returning to the past. This reassessment of the past provides an experience of cleansing from the unfolding of past events that provides new perspectives and insight through revealing patterns of behavior. Ayahuasca also produces transcendent and mystical experiences, the "peak experiences" that led to the "psychedelic" paradigm of LSD treatment that was based in recognition that these substances provide an effective treatment for alcoholism by changing the individuals personal awareness, self-perceptions and worldview. A significant dimension of the spiritual experience was a transformation of personal consciousness in ways that eliminated the craving for drugs.

Bouso and Riba [50] propose that a range of ayahuasca's effects may be mediated through evoked increases in activity in various areas of the right hemisphere (anterior insula, anterior cingulate/frontomedial cortex) that have been implicated in somatic awareness, emotional arousal, feelings and processing of emotional information, as well as increased activity in the left hemisphere's amygdala/parahippocampal gyrus structures that have been shown to play a role in emotional arousal and memory. They speculated that these effects enable ayahuasca to make repressed memories consciousness and to re-experience emotions associated with them, enabling them to be reprocess in more constructive ways. Ayahuasca's ability to activate brain networks involved in vision, memory, and intention gives these problematic issues a greater intensity of recall and therefore potential for processing in novel ways.

Loizaga-Velder and Loizaga Pazzi [61] provide insight into the bases of ayahuasca therapies from an empirical study of therapists who used ayahuasca professionally in addictions treatment and addicts who participated in ayahuasca treatment programs based on indigenous shamanistic approaches. "[A]yahuasca-induced subjective experiences ... that they considered significant in relation to their recovery ... can be categorized in four interrelated, psychotherapeutically relevant aspects that include body-oriented, emotional/social, insight oriented/cognitive, and transpersonal." [61, p. 136]. Loizaga-Velder and Loizaga Pazzi [61] note that most patients interviewed reported that they perceived therapeutic effects involving: "augmenting body awareness, reducing drug-craving, triggering different types of emotional processes (catharsis, perception of previously suppressed emotions, generating inner resources for coping with emotions or urges to use), supporting introspection (self-analysis, eliciting consciousness of addiction and its adverse effects on oneself and others), and enhancing self-efficacy (becoming aware of positive aspects of oneself, thus improving self-esteem and confidence to stay sober)" [61, p. 136-137.] Ayahuasca activates body-oriented dynamics that provide relief of stress and an experience of detoxification associated with the emetic effects that produce an attenuation of craving. Personal accounts of addicts reveal that many believe that the ayahuasca experiences led them to perceive that their drug use was leading them down a path of self-destruction that would lead to their ruin and even death, a realization that helped them to realize a radical change in their behavior and personal orientation. Ayahuasca often produced a variety of death experiences, sometime a sense that one was dying, or a vision of oneself as dead as a consequence of drug use, providing additional motivation to make necessary changes in personal behavior and lifestyle. The prolonged social contact among participants that is typical of ayahuasca based treatments provides the opportunity for developing of social support that is crucial to recovery. The ceremonial context enhances bonding among participants that can facilitate therapeutic processes, especially through the provision of social support and the enforcement of social norms that encourage an abstinent lifestyle. The participants in ayahuasca ceremonies of the churches provide social support for managing stress and give a sense of belonging that motivates lasting behavioral changes among members of the group.

Mate [62] proposes that ayahuasca is capable of successfully treating a wide range of conditions because physical as well as psychological conditions are based in complex unconscious psychological conditions and the stress they produce. Psychedelics can assist in the treatment of many conditions by helping to bring these dynamics into consciousness and begining the process of liberating the person from these influences. Mate proposes that the ability of psychedelics to resolve addiction dynamics may lie in part in a causal relationship between trauma during childhood and the development substance dependency during adulthood. Mate proposes that while deep psychological dynamics may emerge into awareness during ayahuasca ceremonies, their therapeutic potential depends on trained guidance to bring these potentials to fruition. Lacking qualified assistance in achieving their full integration, important experiences may not produce benefits. Nonetheless, he emphasizes that in the right supportive circumstances, ayahuasca can help provide the insights and personal meanings that can help resolve the underlying dynamics of addiction by triggering visions of the emotional states and traumatic imprints. Successful treatment with ayahuasca requires an experienced person to provide structure and guidance to effectively orient to the visions, the therapeutic purpose, and the development of the experience across sessions.

Formal Assessments of Ayahuasca Treatment Outcomes

Fernández *et al.* [63] have provided evidence of the therapeutic effects of the combination of ayahuasca and ritual by using formal before and after assessments of personality, psychopathology, and neuropsychological conditions. Treatment conditions consisted of biweekly ayahuasca consumption over a period of three to nine months. They interpret the lack of changes on neuropsychological measures as evidence of ayahuasca's safety. Reductions on "Impulsiveness," "Disorderliness," "Anticipatory Worry," and "Shyness with Strangers" subscales provide evidence of therapeutic effects, as did increases in "Self-Directedness," "Responsibility," and

"Purposefulness." The psychopathology subscales of the Symptom Check -List -90 -Revised measuring "Positive Symptoms," "Obsessive–Compulsive," and "Anxiety" showed significant decreases, as did measures of "Apathy," "Disinhibition," and "Executive Dysfunction." Increases of measures of "Transcendent Dimension," "Meaning and Purpose in Life," "Mission in Life," and "Material Values" of the Spiritual Orientation Inventory presented additional evidence of significant spiritual effects from the ritual treatments. The promise provided by ayahuasca ritual therapies is highlighted by these effects in a group of hopeless and problematic drug users with long histories of dependence disorders who had failed in other treatments programs.

A preliminary observational study in a First Nations community in Canada involving the use of a 2-session ayahuasca in the treatment of addictions found improvements in cognitive and behavioral measures associated with diminution of problematic substance use and recovery from addiction [64]. A comparison of pre-treatment and six months follow-up found statistically significant increases in mindfulness, hopefulness and empowerment, as well as quality of life meaning and outlook. While there were declines in self-reported use of alcohol, tobacco and cocaine, reductions in cannabis and opiate use were not found. The self-reports of the participants also found that they experienced lasting changes that they attributed to the ayahuasca retreat. However like other studies, it did not have a design that allowed for assessment of the potential contributions of other non-pharmacological factors such as the ritual, sweat lodges and other features of the retreat setting.

Biochemical and Physiological Mechanisms as a Basis for Ayahuasca's Effects on Addiction

Prickett and Liester [65] propose a variety of biochemical and physiological mechanisms by which ayahuasca might effectively treat addictions. Because of the inclusion of two plant species, the range of potential therapeutic mechanisms of ayahuasca is greater, providing a variety of complementary mechanisms to exert both direct and indirect actions on both dopaminergic and serotonergic systems. Because the effects of DMT appear to reflect the general effects of tryptamines (*e.g.*, DMT, LSD, psilocin, and psilocybin) these therapeutic mechanisms would also be shared with these related substances. The effects of the harmines would be unique to ayahuasca.

The biochemistry of addiction indicates that effective treatment requires two effects: first an increase in the overall levels of serotonin, which would increase dopamine levels sufficiently to attenuate withdrawal symptoms; and secondly a normalization of dopamine levels which can be achieved *via* serotonin's inhibitory effects on the release of dopamine in the mesolimbic dopamine pathways [65]. Ayahuasca can achieve these dual effects through multiple mechanisms that provide opposing mechanisms that both raise and lower dopamine in the mesolimbic dopamine pathway (MDP) [65]. Prickett and Liester [65] refer to this as a neurochemical normalization therapy, providing a treatment for addiction by releasing sufficient dopamine to normalize the levels, but not producing an abrupt spiking that provides reinforcement and susceptibility to addiction.

Prickett and Liester [65] propose an agonist model of the anti-addictive mechanisms of ayahuasca involving the augmentation of release of dopamine in mesolimbic dopamine pathways, resulting in a reduction of craving and withdrawal. Activation of the serotonin neurons in the mesolimbic dopamine pathways by psychedelics can both increase and decrease the release of dopamine as a result of the specific receptors which are activated. Ayahuasca can do both.

Prickett and Liester [65] review primary research establishing these mechanisms in ayahuasca constituents, specifically the beta-carboline alkaloid harmine from *Banisteriopsis* and the DMT normally sourced from *Psychotria viridis*. The beta-carboline alkaloids, which serve as the MAO inhibitor which makes DMT orally active, also have significant biological effects. This stimulates the release of dopamine in presynaptic neurons located in the mesolimbic brain, which cause release of both dopamine and serotonin in the MDP. This potential anti-addictive therapeutic effect may result from effects on the mesolimbic dopamine pathways, which have been implicated as the final common pathway in the development and reinforcement of addictive behaviors from all drugs of abuse,

The beta-carbolines may increase serotonin levels through effects involving the inhibition of MAO enzymes because beta carbolines can block the enzymatic metabolism of catecholamines, resulting in increases in overall dopamine levels. DMT can also bind with most types of serotonin receptors, and consequently effect dopamine as well. Activation of serotonin neurons generally results in a reduction of dopamine release and a reduction of self-administration of drugs of abuse.

DMT's affinity for 5-HT receptors provides a mechanism for dopamine elevation in the MDP. Binding of DMT at serotonin receptors also provides a mechanism for lowering dopamine in MDP by inhibiting dopamine release. While harmine also releases dopamine, it also has a blocking effect on dopamine reuptake into neurons at the synaptic membranes. DMT agonism at sigma-1 receptor receptors can also result in inhibition of dopamine release, reducing the spiking effects which lead to cycles of reinforcement and addiction. This effect of ayahuasca on dopamine in the MDP provides a balance between the low dopamine levels that produce withdrawal symptoms and the elevated levels that lead to addictive behaviors. Thus ayahuasca exerts a normalizing effect on dopamine levels.

"Ayahuasca exerts anti-addictive properties *via* its direct and indirect actions on dopaminergic and serotonergic neurons in the mesolimbic pathway. Ayahuasca raises global 5-HT levels attenuating withdrawal effects and mitigating against potential dopaminergic excess when utilizing DA agonists. Ayahuasca balances DA in the MDP between the low levels associated with withdrawal and the elevated levels associated with initiation and reinforcement of addictive behavior" ([65], p. 118).

Prickett and Liester [65] propose additional physiologic hypotheses for the therapeutic effects of ayahuasca, based in the concept of "neuroplasticity," the ability of neurons to

alter their synaptic connections. They review evidence of a number of mechanisms that can produce neuroplasticity such as: formation of new synapses; elimination of existing synapses; remodeling of dendrites and axons; and up or down regulation of gene expression. The processes of neuroplasticity are thought to underlie an addiction learning process, a pathological or maladaptive learning that results from a "hijacking" of the neural mechanisms underlying learning and memory by the addiction process. This neural learning process results in acquisition of associations and patterns of behavior that contribute to the compulsion and reward cycles which underlie the repeated self-administration of drugs.

Prickett and Liester [65] show how ayahuasca can affect neuroplasticity by effects on a variety of neurochemicals that affect brain plasticity, facilitating adaptive changes in neural architecture by effects of neurochemicals and their pathways and associated processes. Evidence suggests that ayahuasca can affect neurochemical processes that facilitate the disruption of pathological associations which underlie addictive behaviors and responses to triggers and cues which have become wired into the neural networks. Ayahuasca facilitates neurophysiologic changes that promote a neurological rewiring of the brain's reward pathways

Prickett and Liester [65] note that a variety of substances in ayahuasca affect brain derived neurotropic factor (BDNF) and the gabaminergic and glutamaturgic systems. These are involved in producing neuroplastic processes by triggering changes in gene expression which affects the architecture underlying communication between neurons, altering old circuits that supported maladaptive addictive behaviors and allowing for the production of new circuits that can support new more adaptive behaviors. Harmine triggers the release of dopamine in the nucleus accumbens, as does DMT, which functions as an agonist at several types of serotonin neuroreceptors. These effects can lead to altered gene expression that can produce neuroplastic changes that eliminate the pathways that reinforced self administration of drugs.

ASSESSMENT OF THE EFFECTS OF PSYCHEDELICS IN ADDICTIONS TREATMENT

Assessment of novel substances for use in therapies is generally subjected to a series of phases of evaluation by the Food and Drug Administration (FDA) of the United States government. These evaluations are generally construed in Phases I to IV described below [4].

Phase I studies are primarily intended to evaluate safety (toxicity), side effects, and safe dosage range, normally using small groups of healthy subjects. Phase I studies may also rely on patient populations that have the possibility of showing risks (adverse reactions) where none would exist in normal populations. While the double-blind clinical trials are ideal, other forms of evidence can be used to determine toxicity. For instance, as Frecska [4] notes, even when we include the statistics on abuse as opposed to responsible use, there is little evidence of physical harm from the psychedelics.

Phase II trials use small groups of strictly selected patients to further evaluate safety and to determine effectiveness and ideal doses for targeted illnesses. Phase II studies evaluate outcomes in patient populations, but not always with the benefit of the double-blind studies. This leaves open the possibility of placebo effects, but this may be viewed as an acceptable part of a complementary treatment that relies on set and setting effects, including ritual, as a basic part of psychedelic assisted treatment of addictions. Phase II evidence can include studies which include other control features that assess changes in patient conditions evaluated with standard evaluation procedures.

Phase III trials typically use randomized clinical trials with large groups of patients, who may have diverse comorbid conditions. These are done in order to confirm effectiveness, to monitor adverse drug effects and interactions, and compare the effects of the new substances with commonly used treatments. These randomized clinical trials typically use double blind controls to assess the role of placebo or expectancy effects.

Phase IV trials use additional controlled trials to determine further information regarding side effects, safety, long term risks, and benefits, and to perform comparisons with other procedures for the same condition.

It is noteworthy that treatment of patient populations begins with Phase II studies, once issues of toxicity and safety have been determined. In this sense, while Phase II to Phase IV studies are still assessments, they are assessments based on the active use of treatments, albeit not approved for the general patient population. The lack of these further studies in the case of psychedelics is largely due to administrative prohibitions over the last 40 years. Consequently these phases of evaluation for the psychedelic medicines have to be broader, and at times retrospective (in contrast to the prospective design of the premarketing trials of the approved drugs). As Alper and Lotsof [39] point out in their assessment of ibogaine, we need to rely on an integration of various forms of validation through a "triangulation" that combines data derived from: animal research; epidemiological research on general risks and adverse reactions; medical case studies and personal accounts of those who have received these substances as treatments; and process oriented research that assess pre- and post-treatment conditions with a variety of standardized tools. While we still lack the highly esteemed, but sporadically applied double blind clinical trials, there is evidence regarding the effectiveness of psychedelics in the treatment of additions.

LSD

If we assess the effectiveness of LSD as a treatment for alcoholism, we can conclude effectiveness in terms of Phase I and II studies. Krebs and Johansen [15] note the evidence for safety derived from extensive research on animals, as well as human, although they note the potential acute adverse psychiatric events, as well as anxiety and confusion. Their meta-analyses provide robust evidence for Phase II evaluations in establishing a blinded treatment effect. Furthermore, Krebs and Johansen [15] note that comparison of the effectiveness of a single dose of LSD was found to be superior to the effectiveness of daily treatments with approved drugs for alcohol dependence such as naltrexone,

acamprosate, or disulfiram. This is an important sign of potential treatment efficacy, because, as Krebs and Johansen [15, p. 1001) note "It is uncommon for a psychiatric drug to have a positive treatment effect for months after a single dose." Furthermore these are the kinds of evaluations done in Phase III trials. The meta-analyses of double-blind studies also constitute Phase III types of evidence. While there certainly is a need for further studies to refine knowledge regarding ideal dosage levels, any potential side effects, the long term benefits and ideal support to the LSD assisted therapy, there is no sound medical rationale for not immediately using LSD in addictions treatment programs.

Peyote

While further research on specific physiological mechanisms of peyote and its diverse compounds is definitely needed, evidence exists regarding it relative safety and effectiveness. While there are limited toxicology studies, no evidence of physical harm has been found in long-term peyote users [66]. The relative safety of peyote as a treatment is illustrated in the assessments of Halpern *et al*. [66] which compared the neuropsychological, cognitive and psychological status of long-term peyote use of NAC Church members with a comparison group that did not use drugs. Not only were no deficits found for the NAC group, but they were rated higher on the measurements of General Positive Affect and Psychological Well-being from the Rand Mental Health Inventory. Furthermore the extent of lifetime peyote use was positively associated with the Mental Health Index and with significantly lower scores on the scales assessing Anxiety and Loss of Behavioural and Emotional Control. Evidence of Phase II evaluations can be derived from case studies of Peyote Church members [13]. Evidence of Phase III—approved therapeutic use--is found in the practice of the Indian Health Service, a branch of the U.S. Federal Government, approving reimbursement for "road men," the ritual leaders of the NAC who use of peyote for treatment of alcoholism among Native Americans [31].

Further research might consider the problematic issue of sustainable harvest of peyote and instead experiment with synthetic mescaline, considered to be the primary active pharmacological ingredient in peyote. The use of synthetic mescaline would allow for the standardization of doses and provide enhanced possibilities for double blind control trials. The use without the ritual component that is involved in the NAC would allow for determination of the possible strictly pharmacological effects as opposed to the ritual contributions to addiction cessation.

Ibogaine

Many forms of information - including case reports, preclinical toxicological evaluations, initial Phase I trials of safety pharmacokinetics - provide a substantial body of evidence constituting preclinical proof of concept and the equivalence of Phase I and II trials [36, 38, 39, 42]. Based on a review of the literature, Brown [44] concludes that there is a substantial amount of evidence to support the claims for the effects of ibogaine in attenuating withdrawal and reduction of craving in humans, constituting evidence of Phase I and Phase II trials. A wealth of data from preclinical and non-blinded (open-label) clinical studies, combined with data from animal studies, support the long history of anecdotal reports regarding the ability of ibogaine to interrupt addiction and reduce or even eliminate withdrawal symptoms from a variety of drugs, especially the opiates and cocaine.

There are, however, a variety of safety concerns regarding such uses of ibogaine because of a number of deaths in close proximity to ibogaine treatment of addicts [41]. But the fatalities associated with ibogaine use in addiction treatment centers appear to be due to pre-existing medical conditions, specifically poor cardiac health, or as a consequence of using opioids or cocaine shortly before or after the ibogaine dose [44]. In addition to the cardiac risks, people using ibogaine face risks from the lack of standardization of ibogaine doses and lack of standards regarding the manufacture and storage of ibogaine extracts. Nonetheless there is an extensive manual [43] available for screening of patients created by one of the founders of ibogaine therapy, providing insights from several decades of informal clinical observations. These guidelines help to define medical and psychiatric exclusionary criteria, ideal pretreatment laboratory tests such as EKG and liver function tests, the necessary monitoring of patients during the treatment process, and appropriate emergency personnel and medical intervention if necessary. While the original finding regarding the addiction treatment properties of ibogaine were derived from uses of root extracts of the plant, what has recently been the most common form of treatment in ibogaine clinics is derived from the synthesized ibogaine hydrochloride salt. It is not just ibogaine but also several related compounds (noribogaine, 18-MC) that have the ability to alleviate withdrawal symptoms. Some of these other compounds may be more promising treatment avenues given the risks associated with ibogaine.

Ayahuasca

The evidence of the safety of ayahuasca is derived from several studies, including studies of the health and well being of youth and long term members of the ayahuasca churches [46, 57, 67-69]. There is also considerable Phase II evidence [46, 59, 60] and the publications reviewed above from [49]. While the nature of ayahuasca makes double-bind studies more challenging, not only is the use of freeze-dried sample possible, but there is the possibility of using synthetic or extracted versions of the major ingredients that have been implicated in ayahuasca's therapeutic mechanisms, the DMT and harmine. Distinguishing the therapeutic effects of each will need to be done with pure DMT and harmaline and harmine, and without ritual.

The current lack of such studies should not be seen as reasons for curtailing treatments with ayahuasca, however. Not only have ayahuasca treatment programs for drug addicts shown considerable promise, formal assessments support further use. While randomized controlled trials are needed, these should not be seen as necessary to justify further use. Ideal double-blind clinical trials may be forever beyond the methodological possibility given the importance attributed to ritual elements. Consequently, double-blind clinical studies will be particularly challenging in terms of appropriate pharmacological and ritual control conditions.

But such studies are to separate drug effects from set and setting-such as ritual. It is, however, these combined physiological and ritual elements of ayahuasca can affect addiction outcomes. The evidence for ayahuasca as an effective treatment for addictions is from practices that espouse a view that emphasizes the interaction of sacrament with physiological effects with the ritual and interpersonal dynamics of therapy. This widely recognized treatment effect is from practices that espouse an interaction of ritual and pharmacological effects, not to mention spiritual influences from the point of view of many. These shamanistic approaches attribute therapeutic effects to a variety of factors, including pharmacological as well as psychological, but most significantly the interactions of the biological and personal levels with the spiritual.

CONCLUSION: POLICY DIRECTIONS IN THERAPEUTIC DEVELOPMENT

The effects of psychedelics in reducing addictive behaviors clearly have biological bases, but their therapeutic potentials are best viewed in terms of biopsychosocial interactions, where the physiological effects are molded by ritual, set and setting. While there are therapeutic processes that derive strictly from physiological mechanisms, the therapeutic effects can also be further extended as psychophysiological processes, where the biological dynamics predispose certain psychological, and psychosocial and spiritual effects. Prominent effects of the psychedelics derive from their ability to function as non-specific facilitators of the dynamics derived from set and setting-the expectations embodied in social factors, the ritual process and the personal and interpersonal expectations regarding the treatment process and outcome.

As Alper and Lotsof [39] point out in their assessment of ibogaine, we find validation of the effectiveness of these substances in the treatment of addictions from triangulation and synthesis of many forms of evidence-animal studies, laboratory data, medical case studies, personal case accounts, and case series. Treatment practices involving ritual and clinical use of the sacred plants peyote, ibogaine, and ayahuasca, as well as synthetic analogues such as LSD, have shown exceptional potential as part of substance abuse rehabilitation strategies. The evidence reviewed here show that the psychedelics in general have evidence of treatment effectiveness from Phase I and Phase II equivalents, as well as Phase III evidence in the case of LSD.

The lack of effective use of these therapies is a direct consequence of the United States' federal prohibitions, which were extended by international treaty to most of the world. Nonetheless, this U.S federal prohibition on psychedelics is considered by many to lack constitutional grounds, since there is no article in the constitutions or amendments to the constitution that allow the federal government to regulate what we put into our bodies [70]. Remember, it took the "Prohibition Act", a U.S. Constitutional Amendment, to restrict the use of alcohol by the U.S. federal government. After Timothy Leary won his U.S. Supreme Court case regarding the illegality of federal laws regarding marijuana, the Nixon administration made an end-run on the constitution and regulated such substances through the channels of administrative law. This processes of placing them in Schedule 1 - substances considered to be without evidence of medical efficacy and with a high potential risk for abuse - has however, been achieved through political actions rather than on the basis of scientific evaluations [70].

So how can we proceed? Winkelman and Roberts [71] have provided an overview of the multiple levels of society at which we need to act to change the current political climate that regulates these substances. Political pressure on federal regulatory agencies remains a central approach for opening up experimental use of these substances. This pressure involves many forms of action, including general education, education of the media, activities in public health and policy organizations, private funding of research and perhaps even corporate developments. What remains key is applying the cumulative scientific, clinical, ethnographic and cross-cultural evidence regarding the immense potentials of these substances to public education to facilitate professional, media and popular pressure to effect administrative changes in federal regulation.

Fenney [72] expands our understanding of the possible permissible uses of these substances. The constitutional and legislative provisions relating to protection of religious freedoms and the federal government's special protections of the religious rights of the Indian nations has resulted in a variety of legal precedents affecting the rights to use peyote and other psychoactive sacramentals. The federal rulings regarding Native Americans' rights to use peyote have established rights for members of federally recognized tribes. Fenney contends that our legal system cannot logically-or perhaps even legally-deny the same rights to other ethnic groups in society. The inconsistencies in rulings leads Fenney to conclude that the use of peyote or by extension any psychoactive sacramental, cannot be restricted to specific groups, Indian or otherwise, as long as they are sincere believers. In addition, other venues for increasing opportunities for the use of these sacred medicines may be found in the development of religious based uses such as the Uniao do Vegetal and Santo Daime churches which use ayahuasca as a sacrament.

Education, public policy development, and collective political action, rather than just more science, is necessary for changing opportunities for their use in treatment of some of the most ravaging social diseases of our times such as the addictions to alcohol, tobacco, methamphetamines and opiates and their synthetic derivatives. The acknowledged success rates of the conventional addictions treatment industry is not much different from the spontaneous remission rate. In contrast, the case study and other evidence effectiveness of the psychointegrators, particularly peyote, ibogaine, ayahuasca, and LSD, is substantial for those who are willing to consider the evidence.

Halpern [14] points out that given the limited efficacy of current treatments for drug addiction, the use of psychedelic substances for treatment of drug dependence is an ethical responsibility of the medical field. These treatment approaches are more ethical than maintenance/treatment programs employing drugs of high abuse or substitutes (*e.g.,* methadone treatment) because of their abuse and overdose potential. While it is clear that physical injuries or psychological harm may result from unsupervised use in

inappropriate settings, this does not seem to be the case for professional application of these substances as treatments for addiction. To the author's knowledge, there exist no studies of the use of psychedelics in addictions treatment that have indicated general risks for patient populations, under conditions of appropriate screening and adequate supervision. To the contrary there is substantial evidence that these substances have extremely high safety profiles [4].

Physicians have a moral imperative to seek the applications of these more effective tools for the treatment for these devastating psychosocial diseases associated with addiction. The existing evidence indicates the justification for further well-controlled Phase III clinical studies into the effects of psychedelics in addiction treatment. It should be noted however, that Phase III studies would be, according to the FDA criteria of phase III trials, involve studies on patient populations receiving these substances as treatments. The use of actual patients who may have diverse comorbid conditions, assessed in randomized clinical trials, is done in order to confirm effectiveness and to monitor possible adverse drug effects and drug interactions.

Because of the great cost of a Phase III studies, and the imitations on patenting natural substances, we won't see these developments without changes in the government funding or industry approaches to make these substantial investments. Even where there are approved drugs that also have a demonstrated effectiveness in addictions treatment, such as ketamine, the drug industry is disinterested in further clinical trials. Ketamine is already classified as a Schedule III drug, with approved uses. Phase I, Phase II and Phase III clinical trials in the ketamine psychedelic psychotherapeutic treatment of alcoholism and opioid dependence have been carried out, and currently there is research that constitutes the beginning of Phase IV see [73, 74]. But the drug company which owns the patent on ketamine is not interested in the further development of a treatment that requires only one or two doses lifetime, and consequently with negligible potential revenues.

Psychotherapists have a limited range of therapeutic options for the use of psychedelics. Boire [70] provides guidelines for adapting to the legal constraints on the psychotherapeutic use of these substance created by the current administrative and professional regulations. Boire outlines a "medical necessity defense," a justification for using a substance as an alternative when lawful medical treatments have been found to be ineffective. Individual users may also be able to make such claims directly. Boire contends that one can base a valid defense asserting that although the treatment is prohibited by Schedule I classification, its use reduces the patient's severe suffering without causing disproportionate harm to others (patient, other people, or to the State's interest). The general failure of the addictions treatment industry might justify similar conclusions about the applications of psychedelics to the treatment of addictions. As far as medical treatment of addiction with psychedelics is concerned, there should be no evidentiary concerns regarding general safety and effectiveness if treatments follow well established guidelines for patient screening, preparation, support, processing and follow-up *e.g.,* [75].

If medicine does not offer these remedies, perhaps patients themselves will being to take increasing efforts to avail themselves to these treatments. A recent study [76] found that naturalistic hallucinogen use reduced recidivism among a group of individuals with a history of substance use and high rates of recidivism who were under supervision in a community corrections program. The personal use of hallucinogens was associated with prosocial behavior and a reduced likelihood of failure due to noncompliance with legal and program requirements and an increased abstinence from alcohol and other drug use.

CONFLICT OF INTEREST

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