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Hypotheses Regarding the Mechanisms of Ayahuasca in the Treatment of Addictions

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Abstract — Ayahuasca is a medicinal plant mixture utilized by indigenous peoples throughout the Amazon River basin for healing purposes. The "vine of the soul" or "vine of death," as it is known in South America, contains a combination of monoamine oxidase inhibitors and N,N-dimethyltryptamine (DMT). When ingested together, these medicines produce profound alterations in consciousness. Increasingly, ayahuasca is being utilized to treat addictions. However, the mechanism of action by which ayahuasca treats addictions remains unclear. We offer four hypotheses to explain possible biochemical, physiological, psychological, and transcendent mechanisms by which ayahuasca may exert its anti-addiction effects.

Keywords — ayahuasca, addiction, N, N-dimethyltryptamine (DMT), monoamine oxidase inhibitors, mesolimbic pathway, transcendent experience

For at least four thousand years, indigenous peoples of South America have utilized a plant admixture known as "ayahuasca" for healing and spiritual purposes (Naranjo 1986). This brew is prepared by boiling two or more plants found in the Amazon rain forest until a concentrated liquid remains. This liquid is then ingested orally and the results are said to facilitate healing, prophesy, and divination (Schultes, Hofmann & Ratsch 1998: 124). Recently, this medicine has been utilized to treat addictions (Mabit 2007). For example, The Takiwasi Center in Tarapoto, Peru was established by Jacques Mabit, M.D. in September 1992 to utilize ayahuasca for the treatment of addictions (Mabit 1996).

The term "ayahuasca" is derived from the Quechua language (Metzner 2006: 1). "Quechua" refers both to a collection of related indigenous groups in South America as well as the common language they speak. Quechua people are found primarily in Ecuador, Peru, Bolivia, Chile, and Argentina.

The term "ayahuasca" is derived from the Quechua roots *aya* meaning "dead person, spirit, soul, or ancestor" and *huasca* meaning "rope or vine" (Metzner 2006:1). Thus, common translations of the term *ayahuasca* are "vine of the soul" or "vine of the dead" (Grob 2002: 185; Metzner 2006: 1). These translations also incorporate ayahuasca's purported ability to transport individuals who ingest this medicine beyond time and space. Ayahuasca is known by many different names in South America including: caapi, yaje, and hoasca (Brazil) (Schultes 1982: 124). At least 72 different indigenous groups in South America currently use ayahuasca (Beyer 2009: 209).

Recently, a growing body of literature has touted ayahuasca as a treatment for addictions. A 2010 story from the Voice of America described ayahuasca's potential to treat alcohol and drug addictions (Celeste 2010). Articles supporting ayahuasca's anti-addiction properties

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have appeared in newsletters (Mabit 1996), books (Mabit 2007), and the esteemed medical journal, *The Lancet* (Morris 2008).

HISTORY OF AYAHUASCA USE

Archaeological evidence dates the earliest use of ayahuasca by indigenous people to more than four thousand years ago. This evidence includes pottery vessels, snuffing trays, and tubes that indicate plant hallucinogens were used in the Ecuadorian Amazon as early as 1500 - 2000 B.C.E. (Naranjo 1986).

Europeans first became aware of this medicinal plant when Spanish and Portuguese explorers ventured into the Amazon rain forest early in the sixteenth century. These explorers encountered indigenous people who ingested a plant mixture that when drunk would "deprive of the senses, because it is very powerful, and by this means they communicate with the devil, because he talks to them when they are deprived of judgment with the said drink, and deceive them with different hallucinations, and they attribute it to a god they say is inside the seed" (as quoted by Guerra 1971). Believing the effects to be the work of the devil, the Holy Inquisition of 1616 condemned the ceremonial ingestion of hallucinogenic plant medicines (Grob 2002: 189). Individuals who openly utilized ayahuasca and other plant medicines risked accusations of heresy and witchcraft, charges that could result in horrible tortures and death (Grob 2002: 266).

In the modern era, the first written documentation of ayahuasca use occurred in 1851 when the British botanist Richard Spruce encountered indigenous Tukanos in Brazil drinking ayahuasca (Schultes 1982). The first published report of the use of ayahuasca occurred in 1858 when the Ecuadoran geographer Manuel Villavicencio wrote about ayahuasca being used in the Rio Napo region (Metzner 2006).

In the 1920s, Brazilian churches began using ayahuasca as a part of their religious ceremonies. Today, three Brazilian churches use ayahuasca as their primary sacrament. These churches are: (1) Santo Daime, (2) the Uniao de Vegetal (UDV), and (3) Barquinia (Labate, Santana de Rose & Guimaraes dos Santos 2008; Metzner 2006). In 2005, Brazilian churches were found in 23 different countries including Germany, Spain, Holland, Canada, Mexico, and the USA, as well as countries in Africa, Asia, and Central America.

Due in part to the difficulty of obtaining ayahuasca's active ingredients, medicines similar to ayahuasca are now being synthesized around the world via nontraditional methods, particularly in Western countries. These methods involve either: (1) combining synthetic ingredients rather than utilizing plants substrates, or (2) substituting other plant sources for the active ingredients found in the plants from the Amazon rain forest (Schultes, Hofmann & Ratsch 1998:137).

BIOCHEMISTRY OF AYAHUASCA

Traditionally, ayahuasca is prepared by boiling the bark or vine of the plant *Banisteriopsis caapi* with one of up to 75 different plants, most often *Psychotria viridis* (Harner 1973). Other commonly used plants come from the Solanaecous genera, which includes tobacco and the Brugmansia species (Metzner 2006: 41). For a detailed discussion and listing of other constituents of ayahuasca please see Beyer 2009, Appendix A and Schultes, Hofmann & Ratsch 1998: 124.

Banisteriopsis caapi is a South American jungle vine of the Malpighiaceae family (Ratsch 2005: 86). In the Quechua language, it is known as *chacruna* (Beyer 2009: 389). This plant contains beta-carboline alkaloids including harmine, harmaline, and tetrahydroharmine that serve as potent monoamine oxidase inhibitors (MAOIs) (Metzner 2006: 49).

MAOIs are a variety of naturally occurring and synthetically produced chemicals whose primary uses in Western medicine are to treat Parkinson's disease and major depressive disorder (Stahl 2008: 574, 579, 582). MAOIs exert their therapeutic effects by blocking the activity of enzymes known as "monoamine oxidases," a family of enzymes that catalyze the oxidation of endogenous and exogenous monoamines.

Monoamines are a group of chemically similar molecules that serve as neurotransmitters and neuromodulators. They contain one amino group connected to an aromatic ring by a two-carbon chain. Monoamines include catecholamines (e.g. dopamine, norepinephrine, and epinephrine), tryptamines (e.g. serotonin, melatonin, and DMT), and trace amines (e.g. tyramine, histamine, and thyronamines). When ingested orally, monoamines are generally degraded by monoamine oxidase enzymes found in the gastrointestinal tract. However, in the presence of MAOIs, these monoamines are not metabolized to simpler compounds in the gastrointestinal tract (McKenna, Towers & Abbott 1984:195).

Psychotria viridis is a shrub from the coffee family, Rubiaceae (Ratsch 2005: 456). The leaves of this plant contain many alkaloids, N,N-dimethyltryptamine (DMT) being the predominant psychoactive constituent. DMT is a naturally occurring tryptamine alkaloid, which is found throughout the plant and animal kingdoms (Strassman 2001: 42). DMT is also a short acting, potent medicine that induces a rapidly altered state of consciousness when smoked or snorted (Strassman 2001).

First synthesized in 1931 by a Canadian chemist, DMT was isolated from a South American tree 15 years later by

a Brazilian ethnobotanist (Strassman 2001: 44). DMT is now known to exist in hundreds of plant species worldwide. In 1965, a German team isolated DMT from human blood and in 1972, NIH scientist and Nobel Prize winner Julius Axelrod discovered DMT in human brain tissue (Strassman 2001: 48).

DMT is structurally similar to serotonin and other indole ring containing molecules. It is a relatively small molecule, 188 molecular units, only slightly larger than the glucose molecule (Strassman 2001: 52). It is easily synthesized from indole or tryptamine in vitro, and a simple two-step process from L-tryptophan has been proposed for biosynthesis in vivo (Shulgin & Shulgin 1997: 412–414). DMT shows an affinity for serotonergic receptors, with agonist actions documented at the 5-HT2a and 5-HT2c sites (Stahl 2008: 990.)

When ingested orally, DMT is broken down by the enzyme monoamine oxidase in the gastrointestinal tract into the inactive compound indoleacetic acid (McKenna, Towers & Abbott 1984: 195; Shulgin & Shulgin 1997: 420). However, DMT remains active when ingested orally in the presence of MAOIs, such as those found in *Banisteriopsis caapi* (Mabit 2007: 87).

THE AYAHUASCA EXPERIENCE

The experience produced by ayahuasca can be divided into three phases (Beyer 2009: 229). The first phase involves vivid visual imagery that may include geometric designs, lights, animals, scenes from nature, and other imagery that may shift or move. Sensations of dizziness and nausea with vomiting may also occur during this phase. The second phase is said to consist of contact with the spirit world. Plant and animal spirit teachers are said to appear and communicate helpful information or lessons. In this phase, the types of information that may be obtained include the whereabouts of missing relatives or lost objects. The third phase involves a fading of visions, a decrease in nausea, and a state of physical lassitude. Brief visions may be experienced in this final phase as well (Beyer 2009: 229–230).

EFFECTS OF AYAHUASCA

The effects of ayahuasca can be divided into biochemical, physiologic, psychological, and transcendent categories.

Biochemical Effects

Three unique biochemical effects of ayahuasca have been identified thus far. These biochemical effects result from the actions of ayahuasca's primary active ingredients, DMT and the MAOIs acting in concert.

The first of ayahuasca's biochemical effects relates to DMT's action on the serotonin system. DMT is an agonist at most serotonin receptions, including 5HT2A receptors, which are the putative site of the action of hallucinogenic drugs such as LSD and psilocybin (Stahl 2008: 990). DMT also binds to other serotonin receptors including 5HT1A and 5HT2C receptors (Stahl 2008: 990). Chronic use of ayahuasca has been associated with an increased number of serotonin receptors on platelets (Callaway et al. 1994). The clinical significance of this finding is not yet known.

Second, the MAOIs found in ayahuasca increase monoamine levels including dopamine, serotonin, and norepinephrine by preventing breakdown of these amines by MAO enzymes. Increased dopamine levels in the mesolimbic pathway have been associated with a sensation of pleasure (Stahl 2008: 272).

Third, ayahuasca is associated with alterations in hormone levels. Increased levels of prolactin, cortisol, and growth hormone have been found within 120 minutes of ingestion of ayahuasca (dos Santos et al. 2011; Callaway et al. 1999). The significance of increased prolactin levels will be discussed in the next section.

Physiologic Effects

The physiologic effects of ayahuasca typically last six to 12 hours. These effects occur in a state of lucidity in which there is no loss of clarity of thought (Beyer 2009: 232). Effects on the gastrointestinal tract include nausea (Riba et al. 2001: 89), vomiting (Beyer 2009: 213; Harner 1973: 12), and diarrhea (Schultes, Hofmann & Ratsch 1998: 129). Neurologic effects include: tremors (Schultes, Hofmann & Ratsch 1998: 129), dizziness (Schultes, Hofmann & Ratsch 1998: 126), mydriasis (dilation of the pupils) (Callaway et al. 1999; Schultes, Hofmann & Ratsch 1998: 129), synesthesia (Beyer 2009: 233), and tingling sensations (Riba et al. 2001: 89). Cardiovascular symptoms include: increased heart rate (Schultes, Hofmann & Ratsch 1998: 129) and blood pressure (Riba et al. 2001: 88). Metabolic changes include changes in perception of body temperature and skin sensitivity (Riba et al. 2001: 89).

Psychological Effects

Ayahuasca's psychological effects include alterations in perception, emotions, and thinking. Typically, no loss of consciousness is associated with ayahuasca ingestion. However, profound alterations in consciousness may occur (Riba et al. 2001: 93).

Perceptual alterations frequently include visual imagery that occurs while the individual is awake but the eyes are closed. Common images include jungle animals such as snakes and jaguars (Grob 2002: 200; Metzner 2006: 14 & 77, 1999; Riba et al. 2001: 89; Harner 1973: 160–165). Visions of geometric patterns may also occur (Grob 2002: 198; Schultes, Hofmann & Ratsch 1998: 126–129).

Alterations in auditory perceptions are common. These may involve sounds of flowing water, falling rain, people singing, a brass band, or voices speaking (Beyer 2009: 236; Riba et al. 2001: 90; Metzner 2006: 133). Some individuals report a capacity to communicate with nature (Metzner 2006: 139).

The emotional effects of ayahuasca may include intensified emotional reactions. Happiness, sadness, awe, amazement, anxiety, and fear have all been reported. Some individuals experience contradictory feelings simultaneously (Riba et al. 2001: 89–90). Feelings of rejuvenation and hope are reported (Grob 2002: 198). In addition, a lingering state of well-being can persist even after perceptual, cognitive, and affective effects dissipate (Riba et al. 2001: 88).

Reported cognitive effects include an enhanced rate of thinking. Thoughts often center on personal psychological content and may provide new insight into personal concerns (Riba et al. 2001: 90). When memories are experienced, they generally relate to personal matters (Riba et al. 2001: 90).

Transcendent Effects

Ayahuasca users often report experiences that are described as "transcendent." These aspects of the experience may include visions of a spiritual reality, an altered sense of space and time, ineffability, intuitive insights, out of body experiences, and feelings of oneness with the universe (Grob 2002). A dissolution of boundaries between one's self and others may result in feelings of unity with nature (Grob 2002: 197–198). Feelings of oneness with the universe are also common (Riba et al. 2001: 90).

Ayahuasca experiencers often report visions of distant or supernatural realms. These realms are populated by deities, demons, or spirit beings (Beyer 2009: 110–111, 240–242; Grob 2002: 200; Metzner 2006: 77; Harner 1973: 165–168).

The sense of time may be altered (Beyer 2009: 233; Harner 1973: 12). Such alterations may include a feeling of timelessness, a sensation of time speeding up or slowing down, or a sensation of traveling through time into the past or the future (Beyer 2009: 158–159; Grob 2002: 197).

Individuals may have difficulty communicating their experience to others. This difficulty may be due, in part, to the fact that their experience is outside of the perceptual framework of others who have not had similar experiences. This has been described as a sense of the ineffable (Grob 2002: 198).

Intuitive insights may be experienced during the ayahuasca experience (Metzner 2006: 15). Such insights include information about the location of missing relatives or lost objects (Beyer 2009: 229).

Individuals who have ingested ayahuasca frequently report experiencing their consciousness being separate from their body. An altered sense of space may be reported (Harner 1973: 12). Individuals may experience a sensation of traveling through space (Beyer 2009: 158–159; Grob 2002: 199; Riba et al. 2001: 90; Metzner 2006: 77, 1973: 158–160; Harner 1973: 168–169).

THEORIES OF ADDICTION TREATMENT WITH AYAHUASCA

Addiction is a complex, multifactorial phenomenon in which biochemical, physiological, psychological, and transcendent factors may all play a role. Ayahuasca appears to treat addictions by facilitating changes at each of these levels. We offer the following four hypotheses to explain how ayahuasca treats addictions at each of these levels.

Biochemical Theory

Various theories of addictions exist. One theory proposes that release of dopamine in the mesolimbic system by various drugs of abuse reinforces the use of these drugs (Pierce & Kumaresan 2006). In fact, Pierce has suggested that the mesolimbic dopamine system is the final common pathway for the reinforcing effect of all drugs of abuse (Pierce & Kumaresan 2006). The mesolimbic dopamine pathway, which is also known as the "reward pathway" or "pleasure center," is also involved in motivation, pleasure, and reward (Stahl 2008: 272).

Excessive or repetitive administration of drugs that increase dopamine also produce positive psychotic symptoms, such as delusions or hallucinations. On the other hand, drugs that decrease dopamine will reduce or stop psychotic symptoms. All antipsychotic drugs currently in use are predominantly blockers of the D2 dopamine receptor, which effectively reduces dopamine's effects on the brain (Stahl 2008: 273).

In summary, drugs that increase dopamine in the brain are associated with pleasure, reward, and addiction. Excessive or repetitive dopamine release is associated with positive symptoms of psychosis.

Hypothesis #1 is that *ayahuasca exerts its anti-addictive properties by reducing brain dopamine levels in the mesolimbic pathway. This occurs via ayahuasca's effects on serotonin receptors.*

Two lines of evidence support the theory that ayahuasca reduces dopamine in the mesolimbic pathway. First, DMT is a potent 5HT2A agonist (Stahl 2008: 990). The beta-carbolines (MAOIs) in ayahuasca are partial agonists at the 5HT2A receptor as well (Glennon et al. 2000). It is known that stimulation of 5HT2A receptors reduces dopamine release in the mesolimbic, nigrostriatal, and mesocortical pathways (Stahl 2008). This occurs via two mechanisms. The first mechanism involves a direct connection between serotonin neurons and dopamine neurons. Agonism of postsynaptic 5HT2A receptors by serotonin on dopamine neurons has a direct inhibitory

action on the release of dopamine. The second mechanism involves indirect connections between serotonergic neurons and dopaminergic neurons via GABA interneurons (Stahl 2008: 351). Agonism at postsynaptic serotonin receptors excites GABA interneurons. These GABA interneurons then inhibit dopamine release. Inhibition of dopamine release via 5HT2A receptor agonism has been supported by radioreceptor labeling and positron emission tomography (PET) scans.

When imaging studies are performed on patients with schizophrenia who have been treated with atypical antipsychotic medications, binding at 5HT2A receptors is observed and dopamine release is reduced (Stahl 2008: 358). Atypical antipsychotics are 5HT2A receptor antagonists. Typical antipsychotic medications have little action at serotonin receptors.

Imaging of dopamine receptors in the nigrostriatal pathway under the influence of a typical antipsychotic drug reveals an almost total blockade (approaching 90% of receptor sites). However, when the same imaging procedure is utilized under the influence of an atypical antipsychotic drug, which has 5HT2A antagonist effects in addition to dopamine antagonistic effects, the blockade of dopamine receptors is significantly attenuated (∼%70) (Stahl 2008: 351–358). These imaging results demonstrate that antagonism of 5HT2A receptors due to administration of an atypical antipsychotic drug results in a relative increase in dopamine levels. This increase in dopamine, especially in the nigrostriatal pathway, is suggested as the explanation for the reduced appearance of extra pyramidal side effects (EPS) when using atypical versus typical antipsychotic medications (Stahl 2008: 351).

The theory that ayahuasca reduces brain dopamine levels is supported by a second line of evidence—the finding of increased prolactin levels in users of ayahuasca (McKenna, Callaway & Grob 1998). Dopamine is known to be the primary regulator of prolactin release from lactotrophs in the anterior pituitary. This regulation is mediated by dopamine's inhibitory action on prolactin release. It is also known that 5HT2A agonism promotes prolactin release from the anterior pituitary (Stahl 2008: 362). Thus, elevated prolactin levels in ayahuasca users are indicative of decreased dopamine levels, which likely result from 5HT2A receptor agonism.

Ayahuasca is hypothesized to reduce activity in the reward or pleasure center of the brain by inhibiting dopamine release. The net effect of this would be a reduction in the pleasure or reward effect associated with addictive drugs and associated stimuli.

As reduced binding of dopamine at postsynaptic neurons is an effect shared by the DMT in ayahuasca and antipsychotic drugs, their pharmacologic differences and similarities should be discussed. Antipsychotic medications have been investigated as a treatment for addiction due to their dopaminergic blocking actions in the mesolimbic pathway (Ray, Heydari & Zorick 2010). Typical antipsychotics, with their almost total blockade of D2 receptors, may cause a phenomenon known as *mesolimbic dopaminergic supersensitivity* or MDS (Carvalho et al. 2009). MDS is thought to be the result of a compensatory up regulation of dopamine receptors due to the potent receptor blockade of the typical antipsychotics (as demonstrated by the PET scans discussed above). This results in an increased sensitivity to dopaminergic stimulation. Studies exploring schizophrenics with nicotine addiction treated with long-term typical antipsychotic medication reveal that basal cigarette smoking increased and patients' ability to quit smoking decreased (Matthews, Wilson & Mitchell 2011). MDS may explain why typical antipsychotics do not show significant efficacy as anti-addictive medicines despite lowering dopamine in the mesolimbic or reward pathway (Carvalho et al. 2009).

Atypical antipsychotics, however, have been shown to possess anti-addictive properties and do not show a proclivity towards MDS development (Ray, Heydari & Zorick 2010; Martinotti et al. 2008; Kampman et al. 2007; Benaliouad, Kapur & Rompre 2006). Schizophrenics with nicotine addiction treated with atypical antipsychotics smoked fewer cigarettes and were able to quit smoking more easily, even when not specifically attempting abstinence (Matthews, Wilson & Mitchell 2011). This may be related to a lower affinity for the D2 receptor as well as a synergistic increase in dopamine release due to 5HT2A antagonism. The result is an attenuated dopaminergic blockade (Ray, Heydari & Zorick 2010).

The effects of dopamine on postsynaptic neurons may be influenced by three variables: (1) the amount of dopamine released from presynaptic neurons, (2) the number of dopamine receptors on postsynaptic neurons, and (3) the availability or blockade of dopamine receptors on postsynaptic neurons. The interplay between these three variables may help explain the differing effects of ayahuasca, typical antipsychotics, and atypical antipsychotics at dopaminergic neurons.

DMT is an agonist at 5HT2A receptors. Binding of DMT at 5HT2A receptors decreases the release of dopamine. Atypical antipsychotics act as antagonists at 5HT2A receptors, causing an increase in the release of dopamine. Typical antipsychotics have no affinity for 5HT2A receptors.

DMT does not bind to D2 receptors. As mentioned above, atypical antipsychotics have been found to block 70% to 80% of D2 receptors in the nigrostriatial pathway whereas typical antipsychotics block nearly 90% of these same receptors (Stahl 2008: 351–358). The combination of increased dopamine release along with partial blockade of D2 receptors is suggested to explain the reduced appearance of EPS when using atypical antipsychotic medications (Stahl 2008: 351).

A third variable modulating dopamine's effect is the number of dopamine receptors on the postsynaptic neuron. The ability of typical antipsychotics to block nearly all the postsynaptic D2 receptors may lead to MDS (Carvalho et al. 2009). Atypical antipsychotics do not show a proclivity towards MDS development (Ray, Heydari & Zorick 2010; Martinotti et al. 2008; Kampman et al. 2007; Benaliouad, Kapur & Rompre 2006). This reduced risk of MDS may be related to the atypical antipsychotics' lower affinity for the D2 receptor as well as their stimulation of increased dopamine release via antagonism at 5HT2A receptors. Atypical antipsychotics thus exert an attenuated dopamine effect relative to typical antipsychotics (Ray, Heydari & Zorick 2010). DMT would not be expected to cause MDS. Its inhibitory effect on the release of dopamine and its lack of affinity for postsynaptic D2 receptors would not be consistent with MDS or an increase in postsynaptic dopamine receptors.

The differing effects of typical and atypical antipsychotics on dopaminergic neurons may help explain not only their varying rates of EPS, but also their differing anti-addictive properties. Although both typical and atypical antipsychotic drugs reduce dopaminergic activity in the mesolimbic pathway, they do so to varying degrees. This difference in dopaminergic activity may be responsible for their differing anti-addictive effects. Typical antipsychotics do not show significant anti-addictive properties despite lowering dopamine levels in the mesolimbic pathway (Carvalho et al. 2009). Atypical antipsychotics, on the other hand, have been shown to possess anti-addictive properties (Ray, Heydari & Zorick 2010; Kampman et al. 2007).

Another factor that may play a role in the anti-addictive effects of these medications is the frequency of dosing. The direct blockade of D2 receptors by antipsychotics is generally produced with daily dosing. It is possible that the less frequent dosing of ayahuasca, in traditional settings, may contribute to its different effects (e.g. reduced risk of MDS and increased anti-addictive effects).

The net effect of ayahuasca at dopaminergic neurons is reduced activity in the reward or pleasure center of the brain. This is hypothesized to result in a reduction in the pleasure or reward effects associated with addictive drugs.

Physiological Theory

Dopamine exerts varying effects in the brain depending upon the location, the specific types of dopamine receptors activated, and the level of dopamine. For example, reduced dopamine synthesis in the niagra striata is associated with Parkinson's disease and reduced dopamine in the prefrontal cortex is associated with attention-deficit/hyperactivity disorder (Stahl 2008: 277, 885). Increases in dopamine levels produced by pharmacologic intervention may ameliorate the symptoms of these disorders, but in excess may also lead to psychosis.

Dopamine is the primary neurotransmitter involved in the mesolimbic pathway. The mesolimbic pathway involves three critical brain areas. These are the ventral tegmental area (VTA), the nucleus accumbens, and the prefrontal cortex.

The VTA is a group of neurons which release dopamine when exposed to internal or external cues associated with an addictive behavior. The nucleus accumbens is a group of cell bodies that receive dopamine from the VTA and communicate with the prefrontal cortex. The prefrontal cortex is an area of the brain associated with an individual's personality, executive functioning, social functioning, and motivation. The prefrontal cortex communicates with the VTA directly and indirectly through the amygdala completing the classic "reward circuit" (Stahl 2008: 945–954).

Release of dopamine in the mesolimbic pathway has been associated with synaptic plasticity, a process in which connections between neurons are altered. Synaptic plasticity has been associated with learning, and more recently with the development and maintenance of addiction (Saal et al. 2003; Berke & Hyman 2000). Release of dopamine in the ventral tegmental area has been hypothesized to reorganize neuronal circuits, leading to addictive behaviors (Mameli & Luscher 2011). These changes are thought to be primarily related to changes in the amygdala, which has been implicated in learning having to do with reward, fear, and other emotional responses to stimuli. Stahl refers to this dopamine-fueled process as "diabolical learning." Through repeated use of a drug of abuse, or any addictive behavior, repeatedly increased levels of dopamine from the VTA to the amygdala result in adaptive neural architecture changes associated with conditioned and learned responses. These plastic changes result in activation of the reward circuitry when exposure to internal or external cues are experienced that were associated with the addictive behavior. Ultimately, this process is thought to mediate the psychological withdrawal, craving, and intense desire to experience the addicted behavior again and again. The reward circuitry has been, according to Stahl, "hijacked" by the addiction process (Stahl 2008: 945–950). Using pharmaco-neuroimaging, reversible structural remodeling has been shown to occur in striatal pathways within hours after acute blockade of D2 receptors (Tost et al. 2010). Although the mesolimbic pathway has not, to our knowledge, been investigated in this way, it is possible that similar structural and functional changes in neural architecture occur in this pathway as well. These experiments have shown that neuro-plastic changes in dopaminergic pathways are attainable in the timeframe for which ayahuasca and DMT exert their effects. This leads to our second hypothesis.

Hypothesis #2 is that *reduced dopamine levels in the mesolimbic pathway associated with ayahuasca interfere with the synaptic plasticity associated with the development and maintenance of addictions.*

Psychological Theory

The psychological effects of ayahuasca include changes in perceptions, emotions, ideation, and behavior.

Early research with hallucinogenic drugs, such as LSD-25, focused on their ability to produce a schizophrenic-like state, the so-called "psychotomimetic effect" (Hoffer & Osmond 1967: 36, 128). It was believed these drugs provided an opportunity to study mental illnesses such as schizophrenia, an idea known as the "model psychosis concept" (Hoffer & Osmond 1967: 83; Hoffman 2009: 73).

However, some individuals who ingested hallucinogenic substances reported experiences that were very different from mental illness. For example, some patients were able to talk about their problems more easily during LSD-induced states and were able to reevaluate the emotional meaning of their symptoms (Busch & Johnson 1950). Additional studies found that LSD improved depression, increased one's sense of well-being, reduced compulsions, and reduced anxiety (Hoffer & Osmond 1967: 197). Individuals who ingested LSD were also found to exhibit enhanced rapport with their therapists and gained increased access to previously repressed memories (Hoffman 2009: 74). LSD was also found to alleviate pain in terminally ill cancer patients (Hoffman 2009: 77). LSD was even reported to produce religious and mystical experiences (Hoffman 2009: 115; Pahnke 1963).

Such experiences lead to questions about the model psychosis concept (Hollister 1962). In fact, Manfred Bleuler claimed that psychotomimetic drugs "contributed nothing to the understanding of the pathogenesis of schizophrenia" (Bleuler 1959 quoted in Grob 2002: 272). In 1957, the British psychiatrist Humphrey Osmond suggested the term "psychedelics" be used to replace the older term "hallucinogens" based upon these drugs' ability to produce life-changing visions and a "mind manifesting" or "mind expanding" state (Hoffman 2009: 75; Osmond 1957).

Along with the Canadian psychiatrist, Abram Hoffer, Osmond initially began studying LSD with the intention of using it to produce a schizophrenic-like state to study psychosis. However, they later came upon the idea of using LSD to create a model of delirium tremens. This led to their conjecture that LSD could be used to treat alcoholism. They believed administering LSD to alcoholic patients would cause them to experience a state similar to delirium tremens. They hoped this would be such an unpleasant experience that patients would no longer drink alcohol. Hoffer and Osmond later discovered that a similar approach had already been employed by members of the Native American Church of North America. Church members used peyote to take away the desire for alcohol (Slotkin 1956).

From their studies, Hoffer and Osmond (1967: 159) learned that the environment and the attitude of the people around the person had a profound influence upon the individual's reaction to LSD. This led to the recognition of the importance of the set (i.e. the expectations, motivations, and intentions of the individual) and setting (i.e. physical and interpersonal environment) upon the individual's experiences with hallucinogens (Grof 2008: 102).

Awareness of LSD's beneficial effects led some researchers to begin exploring the use of this medicine as an aid to psychotherapy (Grof 2008: 26; Hoffer & Osmond 1967: 150). Several treatment models were employed. The "psycholytic therapy" model involved the administration of small doses of LSD at one to two week intervals. A psychodynamic therapy approach was utilized to understand and integrate the phenomena resulting from the LSD sessions (Grof 2008: 35; Hoffman 2009: 75).

The use of LSD and peyote to treat alcoholism parallels the use of ayahuasca to treat addictions. It is believed by those who utilize ayahuasca that this medicine allows access to unconscious emotional issues, thus reducing the likelihood of using alcohol in the future (Yamberla 2010).

Ayahuasca is also believed to help individuals heal traumas by allowing them to recognize how past experiences have influenced present-day experiences. Furthermore, it is believed that ayahuasca gives individuals an opportunity to experience the potential future outcomes of their choices, including the choice to use alcohol and/or illicit drugs (Yamberla 2010). This facilitates improved decision-making, including the decision to abstain from addictive substances.

Hypothesis #3 is that *ayahuasca treats addictions by helping resolve traumas, encourage the understanding of potential outcomes of choices, and improving decision-making*.

Transcendent Theory

In addition to its biochemical, physiological, and psychological effects, ayahuasca may exert anti-addictive properties via a fourth mechanism. Ayahuasca is reported by those who drink it to provide a transcendent experience (Hoffer & Osmond 1967: 125).

Transcendent experiences have been previously reported to help individuals overcome addictions. The story of Bill W., the founder of Alcoholics Anonymous, is one example). Hospitalized for intractable alcoholism, Bill had a transcendent experience that resulted in his giving up alcohol. He explained:

> Lying there in conflict, I dropped into black depression. Momentarily my prideful obstinacy was crushed. I cried out, "Now I'm ready to do anything". . . Expecting naught, I made this frantic appeal: "If there be a God, will he show himself!" The result was instant, electric, beyond description. The place lit up, blinding white. I knew only ecstasy and seemed on a mountain. A great wind blew, enveloping and permeating me. It was not of air, but of Spirit. Blazing, came the tremendous thought, "You are a free man!" Then ecstasy subsided. Still on

> the bed, I was now in another world of consciousness which was suffused by a Presence. One with the Universe, a great peace stole over me and I thought, "So this is the God of the preachers; this is the Great Reality." But reason returned, my modern education took over. Obviously I had gone crazy. I became terribly frightened (Wilson 1994: 260).

After this experience, Bill W. never took another drink.

Utilizing plant medicines to provide transcendent experiences represents a unique, although not entirely novel paradigm for the treatment of addiction. Ingestion of hallucinogenic drugs, such as LSD and mescaline, has also been reported to facilitate transcendent experiences (Grof 2008: 85; Huxley 1977). In addition to the previously described "psycholytic therapy" model employing LSD, another model termed the "psychedelic therapy" model was developed by Hoffer and Osmond (Hoffman, 2009: 75). This model utilized generally one, but sometimes as many as three, relatively high dose sessions with LSD. This approach was intended to induce a so-called "psychedelic peak experience" which would assist the individual in overcoming their addiction (Grof 2008: 36–39). Studies performed in the 1960s reported that about 50% of individuals who were treated with LSD utilizing this model were able to remain sober or significantly reduce their use of alcohol (Hoffer 1970). Due to a combination of social and political pressures, research with LSD and other psychedelics was terminated by the 1970s. Recently, however, research into the potential benefits of LSD and other psychedelics has gradually resumed (Mangini 1998).

Hypothesis #4 is that a*yahuasca treats addictions by facilitating transcendent experiences*.

SUMMARY

Ayahuasca is a medicine that is increasingly being used to treat addictions. We propose that ayahuasca exerts its anti-addictive properties via four unique but interrelated mechanisms. These include biochemical, physiological, psychological, and transcendent pathways. Further study is needed to explore the potential benefits and adverse effects of this medicine.

REFERENCES

Benaliouad, F.; Kapur, S.; & Rompre, P.P. 2006. Blockade of 5-HTa receptors reduces haloperidol-induced attenuation of reward. *Neuropsychopharmacology* 32 (3): 551–61.

Berke, J.D. & Hyman, S.E. 2000. Addiction, dopamine, and the molecular mechanisms of memory. *Neuron* 25: 515–32.

Beyer, S.V. 2009. *Singing to the Plants: A Guide to Mestizo Shamanism in the Upper Amazon*. Albuquerque: University of New Mexico Press.

Busch, A.K. & Johnson, W.C. 1950. L.S.D. 25 as an aid in psychotherapy. *Disease of the Nervous System* 11: 241–43.

Callaway, J.C.; McKenna, D.J.; Grob, C.S.; Brito, G.S.; Raymon, L.P.; Poland, R.E.; Andrade, E.N.; Andrade, E.O. & Mash, D.C. 1999. Pharmacology of Hoasca alkaloids in healthy humans. *Journal of Ethnopharmacology* 65 (3): 243–56.

Callaway, J.C.; Airaksinen, M.M.; McKenna, D.J.; Brito, G.S. & Grob, C.S. 1994. Platelet serotonin uptake sites increased in drinkers of ayahuasca. *Psychopharmacology* 116: 385–87.

Carvalho, R.C; Fukushiro, D.F.; Helfer, D.C.; Callefaro-Filho, D.; Trombin, T.F.; Zanlorenci, L.H.; Sanday, l.: Sivla, R.H.; & Frussa-Filho, R. 2009. Long-term haloperidol treatment (but not risperidone) enhances addiction-related behaviors in mice; role of dopamine D2 receptors. *Addiction Biology* 14 (3): 283–93.

Celeste, E. 2010. Potent jungle vine brew has potential to treat addiction. *Voice of America*. Available at http://www.voanews.com/english/news/health/Potent-Jungle-Vine-Brew-Has-Potential-to-Treat-Addiction-88923322.html.

dos Santos, R.G.; Valle, M.; Bouso, J.C.; Nomdedeu, J.F.; Rodriguez-Espinosa, J.; McIlhenny, E.H.; Barker, S.A.; Barbanoj, M.J.; Riba, J. 2011. Autonomic, neuroendocrine, and immunological effects of ayahuasca: A comparative study with D-amphetamine. *Journal of Clinical Psychopharmacology* 31: 1–10.

Glennon, R.A.; Dukat, M.; Grella, B.; Hong, S.; Costantino, L.; Teitler, M.; Smith, C.; Egan, C.; Davis, K. & Mattson, M.V. 2000. Binding of β-carbolines and related agents at serotonin (5-HT_2 and 5-HT_{1A}), dopamine (D_2) and benzodiazepine receptors. *Drug and Alcohol Dependence* 60 (2): 121–32.

Grof, S. 2008. *LSD Psychotherapy*. Ben Lomond, CA: Multidisciplinary Association for Psychedelic Studies.

Grob, C.S. (Ed.) 2002. *Hallucinogens: A Reader*. New York: Jeremy P. Tarcher/Putnam.

Guerra, F. 1971. *The Pre-Columbian Mind*. London: Seminar Press.

Harner, M. 1973. *Hallucinogens and Shamanism*. New York: Oxford University Press.

Hoffer, A. 1970. Treatment of alcoholism with psychedelic therapy. In: B. Aaronson & H. Osmond (Eds.) *Psychedelics: The Uses and Implications of Psychedelic Drugs*. New York: Doubleday & Company.

Hoffer, A. & Osmond, H. 1967. *The Hallucinogens*. New York: Academic Press.

Hofmann, A. 2009. *LSD: My Problem Child*. Santa Cruz, CA: Multidisciplinary Association for Psychedelic Studies.

Hollister, L.E. 1962. Drug-induced psychoses and schizophrenic reactions. *Annals of the New York Academy of Sciences* 96: 80–88.

Huxley, A. 1977. *Doors of Perception: Heaven and Hell*. New York: HarperCollins.

Kampman, K.M.; Pettinati, H.M.; Lynch, K.G.; Whittingham, T.; Macfadden, W.; Dackis, C.; Tirado, C.; Oslin, D.W.; Sparkman, T. & O'Brien, C.P. 2007. A double-blind, placebo controlled pilot trial of quetiapine for the treatment of Type A and Type B alcoholism. *Journal of Clinical Psychopharmacology* 27 (4): 344–51.

Labate, B.C.; Santana de Rose, I. & Guimaraes dos Santos, R. 2008. *Ayahuasca Religions: A Comprehensive Bibliography & Critical Essays*. Santa Cruz, CA: Multidisciplinary Association of Psychedelic Studies.

Mabit, J. 2007. Ayahuasca in the treatment of addictions. In: T.B. Robert & M.J. Winkelman (Eds.) *Psychedelic Medicine. Vol. 2: New Evidence for Hallucinogenic Substances as Treatments*. Westport, CT: Praeger.

Mabit, J. 1996. Takiwasi: Ayahuasca and shamanism in addiction therapy. *Newsletter for the Multidisciplinary Association for Psychedelic Studies* 6 (3): 24–31.

Mameli, M. & Luscher, C. 2011. Synaptic plasticity and addiction: Learning mechanisms gone awry. *Neuropharmacology* 61 (7): 1052–59.

Mangini, M. 1998. Treatment of alcoholism using psychedelic drugs: A review of the program of research. *Journal of Psychoactive Drugs* 30 (4): 381–418.

Martinotti, G.; Andreoli, S.; Di Nicola, M.; Di Giannantonio, M.; Sarchiapone, M.; & Janiri, L. 2008. Quetiapine decreses alcohol consumption, craving, and psychiatric symptoms in dually diagnosed alcoholics. *Human Psychopharmacology* 23 (5): 417–24.

Matthews, A.M.; Wilson, V.B. & Mitchell, S.H. 2011. The role of antipsychotics in smoking and smoking cessation. *CNS Drugs* 25 (4): 299–315.

McKenna, D.J.; Callaway, J.C. & Grob, C.S. 1998. The scientific investigation of ayahuasca: A review of past and current research. *Heffter Review of Psychedelic Research* 1: 65–76.

McKenna, D.J.; Towers, G.H.N. & Abbott, F. 1984. Monoamine oxidase inhibitors in South American hallucinogenic plants: Tryptamine and B-carobline constituents of ayahuasca. *Journal of Ethnopharmacology* 10: 195–223.

Metzner, R. 2006. *Sacred Vine of Spirits: Ayahuasca*. Rochester, VT: Inner Traditions.

Morris, K. 2007. Research on psychedelics moves into the mainstream. *Lancet* 371: 1491–92.

Naranjo, P. 1986. El ayahuasca in la arqueologia ecuatoriana. *America Indigena* 46: 117–28.

Osmond, H. 1957. A review of the clinical effects of psychotomimetic agents. *Annals of the New York Academy of Sciences* 66: 418–34.

Pahnke, W. 1963. Drugs and mysticism: An analysis of the relationship between psychedelic drugs and the mystical consciousness. Ph.D. dissertation, Harvard University.

Pierce, R.C. & Kumaresan, V. 2006. The mesolimbic dopamine system: The final common pathway for the reinforcing effect of drugs of abuse? *Neuroscience and Biobehavioral Reviews* 30: 216–38.

Ratsch, C. 2005. *The Encyclopedia of Psychoactive Plants: Enthnopharmacology and Its Applications*. Rochester, VT: Inner Traditions.

Ray, L.A.; Heydari, A.; & Zorick, T. 2010. Quetiapine for the treatment of alcoholism: Scientific rationale and review of the literature. *Drug and Alcohol Review* 29 (5): 568–75.

Riba, J.; Rodriguez-Fornells, A.; Urbano, G.; Morte, A.; Antonijoan, R.; Montero, M.; Callaway, J.C. & Barbanoj, M.J. 2001. Subjective effects and tolerability of the South American psychoactive beverage ayahuasca in healthy volunteers. *Psychopharmacology* 154: 85–95.

Saal, D.; Dong. Y.; Bonci, A. & Malenka, R.C. 2003. Drugs of abuse and stress trigger a common synaptic adaptation in dopamine neurons. *Neuron* 37 (4): 577–82.

Schultes, R.E. 1982. The beta-carboline hallucinogens of South America. *Journal of Psychoactive Drugs* 14: 205–19.

Schultes, R.E.; Hofmann, A. & Ratsch, C. 1998. *Plants of the Gods: Their Sacred, Healing, and Hallucinogenic Powers*. Rochester, VT: Healing Arts Press.

Shulgin, A. & Shulgin, A. 1997. *Tihkal, the Continuation*. Berkeley, CA: Transform Press.

Slotkin, J.S. 1956. *The Peyote Religion*. Glenco, IL: Free Press.

Stahl, S.M. 2008. *Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications*. Cambridge, NY: Cambridge University Press.

Strassman, R. 2001. *DMT: The Spirit Molecule*. Rochester, VT: Park Street Press.

Tost, H.; Braus, D.F.; Hakimi, S.; Ruf, M.; Vollmlert, C.; Hohn, F. & Meyer-Lindenberg, A. 2010. Acute D2 receptor blockade induces rapid, reversible remodeling in human cortical-striatal circuits. *Nature Neuroscience* 13 (8): 920–22.

Wilson, W. 1994. The society of Alcoholics Anonymous. *American Journal of Psychiatry*. Supplement, 151: 259–262. Read at the 105th annual meeting of the American Psychiatric Association, Montreal, Quebec, May 23–27, 1949.

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