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3. An overview of the literature on the pharmacology and neuropsychiatric long term effects of ayahuasca

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Abstract. The last two decades have seen a steady increase in the number of publications devoted to ayahuasca. This fascinating psychotropic plant tea has attracted the attention of biomedical and psychological scientists. Researchers have gathered data on the physiological impact of ayahuasca administration to humans and have assessed the consequences of long term regular use. Acute administration studies have provided information on the fate of the alkaloids in the organism, the modification of vital signs, neuroendocrine and immunological parameters and neurophysiological variables. For the first time, neuroimaging techniques have shown us which brain areas “light up” during the most intense phases of the ayahuasca experience. Also, the popularization of ayahuasca has raised concerns that its regular use may cause neuropsychiatric and addiction-related problems for

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users. An increasing number of studies have tried to address these concerns. In the present chapter we aim to give an overview of the available literature on the human pharmacology of acute ayahuasca intake and on the neuropsychiatric and psychosocial consequences of its long-term use.

1. The human pharmacology of ayahuasca

By temporarily modifying serotonergic neurotransmission, ayahuasca exerts a powerful action on the central nervous system. These neurochemical modifications constitute the basis of the unique experience reported by users. Scientific inquiry into the workings of ayahuasca, and all psychoactive drugs in general, is greatly advanced by the study of these substances in the only species that can accurately report on the diverse facets of the psychedelic-induced experience, i.e., human beings. By administering these compounds in known dosages to carefully selected individuals valuable information has been obtained on their impact on the human body and psyche.

The clinical investigation of ayahuasca was initiated by a field study conducted in the early 1990s by Callaway, Grob, McKenna and colleagues, and aimed to assess the subjective and physiological impact of acute ayahuasca administration in regular users. In the study a 2 ml/kg dose of ayahuasca was given to a group of 15 long-term members of a Brazilian ayahuasca church known as União do Vegetal. Subjective effects were measured with the Hallucinogen Rating Scale (HRS; an instrument originally developed by Strassman and colleagues[1] to assess the effects of intravenous dimethyltryptamine [DMT])[2]. The authors also assessed various physiological parameters and the pharmacokinetic profile of ayahuasca alkaloids[3]. The HRS measurements provided information on six different spheres of the psychedelic-induced experience: *Somaesthesia*, reflecting somatic effects; *Affect*, sensitive to emotional and affective responses; *Volition*, indicating the volunteer's degree of incapacitation; *Cognition*, describing modifications in thought processes or content; *Perception*, measuring visual, auditory, gustatory, and olfactory experiences; and, finally, *Intensity*, which reflects the strength of the overall experience. Scores on the six subscales showed that at the administered dose ayahuasca was able to induce distinct psychedelic effects, with the intensity of the experience falling on "the mild end of the spectrum when contrasted to the highly potent, short-acting intravenous DMT"[2].

This pioneering study found measurable plasma levels of the four main alkaloids (DMT, harmine, harmaline and tetrahydroharmine [THH]), described their pattern of variation with time and how this related with time-dependent modifications which for the most part reached a maximum

between one and two hours and had disappeared at 24 hours after ayahuasca ingestion[3].

More recently, research has been conducted by Riba and coworkers at the Hospital de Sant Pau in Barcelona. Since 1999 this team has performed a series of studies which have tried to better characterize the neuropharmacological profile of ayahuasca. The group started by analyzing the psychometric characteristics of the HRS and obtaining subjective ratings of ayahuasca[4]. A pilot study was then undertaken to assess the tolerability of ayahuasca within a range of dosages, from which safe and pharmacologically effective doses were selected for subsequent studies involving a larger number of volunteers[5]. A method to determine ayahuasca alkaloids in plasma was perfected to now include several metabolites which had not been measured previously in humans[6]. These initial efforts were followed by a series of clinical trials which have provided information on the pharmacokinetics, the subjective and cardiovascular effects of different doses of ayahuasca[7], and various psychophysiological measures[8-11]. For the first time in the centuries-long history of ayahuasca use, the neuroimaging study conducted by this team[12] identified the brain areas specifically involved in the genesis of ayahuasca effects. A review of their studies and findings between 1999 and 2004 can be found in Riba and Barbanoj (2005)[13]. In the last five years the same group has conducted additional studies on the sleep, neuroendocrine and immunological effects of ayahuasca, as well as on the pharmacology of repeated ayahuasca intake. Several of these studies are still pending publication[14].

As would be expected from conventional drugs and somewhat in contrast to popular belief, when administered in a clinical setting and carefully controlling for expectancy (blind designs) ayahuasca was found to act in a dose-dependent manner. This was the case for physiological (cardiovascular), pharmacokinetic and psychological variables (assessed with the HRS; with the ARCI – Addiction Research Centre Inventory, another rating scale to assess subjective effects of drugs; and with VAS – Visual Analogue Scales, a simple method to assess subjective effects of drugs consisting of 100-mm horizontal lines with different labels as “any effect”, “good effects”, “liking”, “visions”, etc., that subjects must mark depending on the intensity of a given effect as experienced while under the effects of the drug). In these studies, DMT plasma concentrations reached their peak coinciding with the maximum intensity of the subjective effects. An unexpected result was the very low levels of harmine found in plasma for the majority of participants. This is suggestive of intense metabolism and also indicative that, at least in some people, the contribution of harmine to the overall central effects of ayahuasca would be small[7]. Ayahuasca induced cardiovascular effects, basically consisting of elevations of

diastolic blood pressure. While these increases were moderate, caution should be exerted by people who have elevated blood pressure or other cardiovascular problems. This is even more relevant considering recent reports in the media concerning the unexplained deaths of people participating in ayahuasca rituals[15-17]. It should be noted that the clinical data which has been published to date is from young healthy volunteers. Safety results might be different in older people or individuals with pre-existing conditions.

At the psychophysiological level ayahuasca induces significant effects, shifting the energy distribution in the electroencephalogram (EEG), i.e., the spontaneous electrical activity of the brain, towards the higher end of the power spectrum. This shift towards the so-called faster frequencies of the EEG can be measured as an increase in the relative power of the EEG beta band[10]. While this effect can be interpreted as reflecting enhanced Central Nervous System (CNS) activity, this activation is unique to psychedelics and different from that induced by traditional psychostimulants. Unpublished data from a study comparing ayahuasca with *d*-amphetamine (*d*-AMPH), a classical psychostimulant enhancing dopaminergic and noradrenergic neurotransmission, show that *d*-AMPH has no effect whatsoever on relative beta power[14]. Whereas both drugs share some sympathomimetic effects, such as increasing pupillary diameter and elevating blood pressure, the distinct effects of ayahuasca on the EEG would relate to its specific serotonergic mechanism. Differences in neurochemical mechanism are also evidenced by ayahuasca, but not *d*-AMPH, significantly increasing prolactin levels (a hormone whose release is enhanced by serotonergic drugs and inhibited by dopaminergic drugs). Despite these differences, both ayahuasca and *d*-AMPH induce a stress-like reaction increasing cortisol levels, the increment induced by ayahuasca being higher. Another interesting finding is that ayahuasca is able to modulate the cell immune system. This effect appears to be non-specific as both ayahuasca and amphetamine induce similar time-dependent modifications on lymphocyte subpopulations: the percentages of CD4 and CD3 cells decrease, while the percentage of NK cells increase. These changes reach a maximum at around 2 hours post-administration and return to baseline levels at 24 hours[14]. No studies have yet assessed the possible impact of these acute physiological modifications on the health of long term ayahuasca users.

Perhaps the most interesting finding from the mentioned clinical trials is the identification of the brain areas where ayahuasca acts. Using the neuroimaging technique SPECT (single photon emission tomography) researchers found that ayahuasca acts almost exclusively on the cerebral cortex without acting on subcortical areas. Ayahuasca increases the activity of the anterior insula bilaterally, with greater intensity in the right

hemisphere. It also hyperactivates the anterior cingulate/frontomedial cortex of the right hemisphere, areas previously known to be implicated in somatic awareness, subjective feeling states, the processing of emotional information and emotional arousal. Additional increases were observed in the left amygdala/parahippocampal gyrus, structures also involved in emotional arousal and the processing of memories[12].

2. Neuropsychiatric long term effects of ayahuasca

Since personality and neuropsychological function are to a great extent regulated by the prefrontal cortex, the study of personality, psychopathological status and neuropsychological functions in long term ayahuasca users is essential to ascertain whether regular ayahuasca use has some impact on mental health.

A few studies have been conducted assessing the consequences of regular ayahuasca use in the long term. The data available is limited and would need replication in larger samples. One preliminary study led by Charles Grob assessed personality and neuropsychological function using the TPQ (Tridimensional Personality Questionnaire) and the WHO-UCLA Auditory Verbal Learning Test. The questionnaires were administered to a sample of 15 regular users with more than 10 years of experience with ayahuasca and to a comparison group of 15 non-users. No personality alterations or neuropsychological deficits were found in the ayahuasca-using subjects, though there were personality differences between groups, which the authors did not interpret as pathological. No information was given as to whether the scores fell within the normal range according to normative data[2]. A typical problem with this kind of studies lies in the interpretation of results. It is difficult to establish whether the scores obtained with the TPQ reflect the impact of ayahuasca use or rather pre-use personality. In the study by Grob and coworkers the authors also used the structured psychiatric interview known as CIDI (Composite International Diagnostic Interview) and found that 11 out of the 15 participants had a history of moderate to severe past alcohol use. Five of them reported episodes of associated violent behavior and a diagnosis of alcohol abuse disorder prior to their involvement with an ayahuasca church. Four subjects also reported previous use of other drugs of abuse, including cocaine and amphetamines, and 8 of the 11 subjects who had a history of alcohol and other drug use and misuse were addicted to nicotine at the time of their first ayahuasca session. According to the authors, all these addiction problems resolved after they began their regular use of ayahuasca. Ayahuasca participants did not meet diagnostic criteria either for

addiction or for any other psychiatric disorder at the moment of the assessment.

A recent study on 32 regular ayahuasca users belonging to the Igreja do Santo Daime in Oregon, USA, did not find psychiatric alterations as measured by a series of rating scales and compared to normative US data. As occurred in the study by Grob and colleagues[2], most of the ayahuasca users had shown some psychiatric disorder or some drug or alcohol abuse disorder in the past, which at the time of the assessment was not present. This was interpreted again as a direct benefit of participating in the Santo Daime ceremonies[18]. Since the subjects in this study were not compared with matched non-users, the findings should be interpreted with caution.

Finally, two papers have been published regarding the long term psychopathological and neuropsychological effects of regular ayahuasca in adolescents. Each study involved 40 adolescents with a two-year history of ayahuasca use, and a comparison group of 40 matched non-users. No statistical differences were found in psychopathology scores[19] or in measures of neuropsychological function[20]. In sum, while no deleterious effects have been demonstrated, due to the small number of studies conducted on regular ayahuasca users the potential impact of sustained ayahuasca use on mental health remains an open question.

3. Additional studies

Several studies have assessed the impact of acute ayahuasca on psychological traits and measures, psychopathology, personality and spirituality, all in a naturalistic context.

In one study of first-time users of ayahuasca in the ritual context of the Brazilian churches of the Santo Daime (19 subjects) and the União do Vegetal (nine subjects), significant reductions of minor psychiatric symptoms and positive changes in behavior were found in the four days following ayahuasca use[21]. Another study found reductions in the scores of panic and hopelessness one hour after ayahuasca ingestion, as compared to baseline[22]. Still in another study, 49 participants without previous experience with ayahuasca attended different ayahuasca ceremonies after which quantitative and qualitative assessments of spiritual experiences were conducted. The rating scales measuring changes in spirituality were not significantly modified after the sessions, though many subjects experienced spiritual themes according to the qualitative data obtained[23]. One study did a six-month follow-up of participants who had consumed ayahuasca for the first time in the context of a Brazilian ayahuasca church (Santo Daime and União do Vegetal). The study found a general improvement in several

psychological measures at the end of the study. Most of the subjects continued to consume ayahuasca after the six-month study period. Additionally, the authors found positive correlations between ayahuasca use and positive psychological attitudes. Ayahuasca use did not appear to cause any adverse effects[24]. Finally, a naturalistic study found that ayahuasca alters binocular rivalry, a perceptual measure of cognitive processing[25].

One recently published study used the Addiction Severity Index (ASI) as a measurement instrument. The ASI is a semi-structured interview designed to assess the impact of drug use in a multi-dimensional fashion. It assesses the participant's Medical Status, Employment/Support, Drug and Alcohol Use, Legal Status, Family/Social Relationships, and Psychiatric Status, and provides general information on the participant's current condition and his/her level of deterioration. The ASI was administered to two different samples of regular ayahuasca users. This study assessed the largest sample studied to date, i.e., a total of 112 regular ayahuasca users. These users belonged to two different ayahuasca churches – the Santo Daime and the Barquinha – and they were assessed in two different settings – jungle and urban-based, respectively. They had a 15-year history of use and they were compared with 115 matched controls. Assessments were repeated one year later as a follow-up. The study concluded that “the ritual use of ayahuasca, as assessed with the ASI in currently active users, does not seem to be associated with the psychosocial problems that other drugs of abuse typically cause”[26]. This research group recently presented a conference paper[27] reporting that they did not find evidence of neuropsychological deficits or personality and psychiatric disorders in their sample.

4. Final remarks

Though no serious adverse events were attributed either to acute or chronic ayahuasca use in the published studies reviewed, a note of caution should be made regarding ayahuasca safety. The clinical trials cited in this chapter were performed in healthy young volunteers who had extensive experience in psychedelic drug use and did not present any sequelae derived from this use. The conclusions cannot be extrapolated to the general population, and especially not to ayahuasca-naive individuals. Ayahuasca has shown to moderately increase several cardiovascular parameters and such increases could have deleterious effects on people with cardiovascular conditions. Furthermore, although only one subject in the clinical trials suffered an episode of disorientation, a case report describes a patient who presented a psychotic breakdown after acute ayahuasca intake. Antipsychotic

medication was needed until its remission, and the same individual suffered a second psychotic crisis after subsequent ayahuasca use[28]. Other cases of psychiatric adverse reactions, including psychotic disorders, have been reported following acute ayahuasca ingestion[29]. It is necessary to take into account the anecdotal evidence available on its potential dangers in order to get a complete picture of the possible negative psychiatric consequences.

Regarding the studies of long term effects, it should be noted that the participant samples studied in the reviewed papers may have suffered from a self-selection bias. This would mean that the assessed individuals may have been those who did not experience any negative neuropsychiatric consequences derived from their maintained ayahuasca use. Subject experiencing adverse consequences might have given up ayahuasca use altogether and would consequently not be accessible to researchers.

To conclude, the scientific investigation of ayahuasca has only found a moderate risk associated to acute ayahuasca administration and has even reported psychological improvements after long-term use. Future investigation into the neuropsychiatric safety of regular ayahuasca use should ideally also include people who used ayahuasca regularly in the past but decided to discontinue its use.

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