

Article

Guidelines for Establishing Safety in Ayahuasca and Ibogaine Administration in Clinical Settings

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Abstract: As the research field with psychedelic substances grows, it is expected to encompass a more extensive cohort of individuals presenting a spectrum of medical conditions, comorbidities, and unique physiological traits, thereby increasing the likelihood of potential adverse events. Furthermore, it is worth noting that there is a scarcity of the specialized literature regarding procedures to ensure the safe management of clinical trials involving psychedelics. Acknowledging this, our research team designed a series of protocols to standardize the care and management of adverse scenarios, ensuring the safety and well-being of research volunteers included in clinical trials conducted by the LEAPS (Laboratory for Studies with Hallucinogens and Psychedelics in Mental Health, linked to the University of São Paulo). These guidelines have been meticulously crafted based on the established guideline philosophy of Hospital das Clínicas de Ribeirão Preto (the university hospital of Universidade de São Paulo), consultation with specialists in the field, and a thorough review of the existing literature. The process resulted in protocols that have been tailored to specifically address the unique requirements and particularities of clinical research with psychedelic substances (in this case, ayahuasca and ibogaine). As a result, these guidelines aim to cover a range of potential issues, encompassing both psychiatric manifestations (e.g., panic attacks, suicidal behavior, and psychotic episodes) and clinical manifestations (e.g., hypertensive crisis and hypoglycemia).

Keywords: ayahuasca; ibogaine; safety guidelines; psychedelics



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1. Introduction

1.1. Ayahuasca

Ayahuasca is a traditional tea used by indigenous peoples from the Amazon basin, notably in Brazil, Peru, Ecuador, and Colombia, for medical and mystical-religious purposes. It is prepared with the prolonged decoction of two plants, the *jagube* vine (*Banisteriopsis caapi*) and the *chacrona*, or ‘queen bush’ (*Psychotria viridis*) [1]. In the mid-1930s, a series of religious groups such as the Santo Daime, Barquinha, and União do Vegetal emerged in Brazil, incorporating the use of ayahuasca as a central sacrament. Subsequently, in the latter half of the century, the dissemination of the psychoactive brew expanded worldwide. Since the 2000s, scientific interest in the substance has grown, with several observational and clinical studies being carried out in order to better understand the effects of ayahuasca tea [2]. Ayahuasca may be classified as a classic hallucinogen since the leaves of the *P. viridis* bush are rich in DMT (*N,N*-dimethyltryptamine), a hallucinogenic tryptamine considered the main psychoactive substance in ayahuasca, acting as a 5-HT_{1A/2A/2C} serotonin receptor

agonist [2,3]. The vine *B. caapi*, in turn, is rich in β -carbolines, such as harmine and tetrahydroharmine (THH), and—in lower concentrations—harmaline, harmol, and harmalol. Harmine, THH, and harmaline are reversible inhibitors of the enzyme monoamine oxidase-A (MAO-A), and THH also has selective serotonin reuptake inhibition activity [3–5]. DMT (present in *P. viridis*) does not have psychoactive properties when ingested orally, due to degradation via MAO-A. However, peripheral inhibition of MAO-A via β -carbolines (especially via harmine) allows DMT to reach the central nervous system and produce psychoactive effects [6]. The literature has described the anxiolytic, antidepressant, and antiaddictive effects of ayahuasca. The main findings related to potential anxiolytic and antidepressant effects were derived from preclinical studies and phase I and phase II clinical trials involving patients diagnosed with major depressive disorder [7–10]. More recently, a pilot, proof-of-concept, randomized, placebo-controlled trial suggested that ayahuasca could modulate anandamide levels in patients with social anxiety disorder [11]. Anti-addictive effects are reported in observational and preclinical studies [12,13]. In addition, other possible beneficial effects on personality traits, cognition, and eating disorders have been reported in observational studies [14].

Overall, there were no reports of serious adverse effects of ayahuasca use in controlled settings, indicating relative safety [15]. Ayahuasca has been shown to be safe for cardiovascular health in healthy volunteers and patients, with only a small increase in blood pressure and heart rate measurements being described during the peak effect, alongside other common and usually mild adverse effects, such as transient nausea, vomiting, and headaches [5,11,15–17]. Furthermore, there are few reports of psychological adverse reactions (PARs) in clinical trials with ayahuasca, which are mostly described through case studies. A descriptive systematic review reported three case series and two case reports describing psychotic episodes associated with ayahuasca ingestion and three case reports describing psychotic episodes associated with smoked DMT [18]. A report described seven cases of acute and challenging psychological experiences after using ayahuasca in ritual settings [19]. A recent study survey based on more than 10,836 subjects found that 60% of the sample reported some kind of mental adverse event, but 88% of them considered that event as part of a positive growth process [20]. These results led the researchers to conclude that the concept of adverse events should be reframed when referring to hallucinogens since part of their action consists precisely of passing through psychologically challenging experiences. Among the controlled studies, there is one report of a PAR, described as a moment of disorientation and anxiety, which was resolved with verbal management [21]. Our group reported only two cases of PARs in the clinical studies carried out during the last 10 years (80 ayahuasca administrations in total); one of them was a young woman with social anxiety disorder, and the other was a healthy young woman [22]. In both cases, it was possible to observe transient anxiety symptoms during the peak of the ayahuasca effect, and only verbal and environmental management was carried out (it was not necessary to use medications) [22]. More recently, the International Center for Ethnobotanical Education, Research and Service (ICEERS) published a global report about ayahuasca consumption and mortality [23]. In this report, between 1994 and 2022, a total of 58 deaths were identified across the world as being possibly related to the consumption of ayahuasca, but it is also highlighted that in many cases, ayahuasca did not even play an indirect role [23]. The authors consider that the number of reported deaths is low compared to the number of people who use ayahuasca around the world each year [23]. Also, most of the cases apparently could have been avoided if they had incorporated rigorous screening, the training of personnel to deal with possible adverse events, and psychological support [23].

1.2. Ibogaine

Ibogaine is one of several alkaloids present in the iboga shrub (*Tabernanthe iboga*), a plant native to Central Africa that has been traditionally used for centuries in traditional medicine by people in countries like Gabon and Cameroon. Iboga is used by members of the Bwiti religion in initiation and religious rituals, usually by chewing or scraping the bark

of its roots, and, at lower doses, its consumption is believed to have stimulating properties, used to mitigate sensations of fatigue, thirst, and hunger [24,25].

Ibogaine was first isolated in 1901, and it was explored as a treatment for asthenia, being commercially available in France from 1939 to 1970 under the name of *Lambarène* as a neuromuscular stimulant. In 1957, Ciba Pharmaceutical (now Novartis) secured a patent for the utilization of ibogaine to reduce tolerance to opioid analgesics. In the late 1950s and during the 1960s, ibogaine was used as an auxiliary tool in psychotherapeutic processes [24,25]. Between the years of 1962 and 1963, a New York psychedelic enthusiast named Howard Lotsof first reported the anti-addictive properties of ibogaine on heroin dependence during recreational use [24–27]. Based on the possible efficacy of ibogaine in the treatment of drug addiction, the Medication Development Division of the National Institute on Drug Abuse (NIDA) in the United States supported preclinical and clinical research on ibogaine, and a phase I/II study with ibogaine on cocaine users was authorized by the Food and Drug Administration (FDA) between 1993 and 1995. However, after the death of a patient in the Netherlands in 1993, in an uncontrolled context (where it was not possible to establish a direct cause between the use of ibogaine and the patient's death), NIDA-funded treatments were suspended, and only research support for preclinical research continued [24–26]. After these events, medical research on ibogaine was reduced, and its use in alternative and non-medical contexts grew until a large network of patients and therapists was formed, where thousands of people sought to treat their drug addictions with ibogaine. It is estimated that in 2006 alone, more than 3000 people were treated with ibogaine in the world, and it is believed that these numbers have been progressively increasing in recent years [27].

Ona and colleagues, through an updated systematic review, analyzed the adverse effects of ibogaine in humans from 2015 to 2020 (the adverse effects from 1990 to 2008 were previously reviewed by Alper and colleagues in 2012 [28]). In the 18 studies analyzed, the authors classified the adverse effects as acute (<24 h), predominantly encompassing cardiological (such as increased QTc interval), gastrointestinal, neurological, and clinical manifestations, or prolonged adverse effects (>24 h), which included persistent cardiac abnormalities as well as the emergence of psychiatric and neurological symptoms. The authors also highlighted the heterogeneity of the products and doses administered [29]. This profile of adverse effects may pose a threat to the safety of iboga consumption. Over 25 fatalities associated with the administration of ibogaine have been reported in the scientific literature, with the majority of these occurrences manifesting within the initial 72 h window [28,30–33]. In most of these cases, the fatality seems to have been caused by the interaction of ibogaine with pre-existing cardiovascular abnormalities or with the concomitant use of other drugs. It is noteworthy that the majority of these cases occurred within uncontrolled settings, under unknown conditions of cardiovascular monitoring and medical supervision, and frequently involved the administration of high or indeterminate doses of ibogaine. Within this frame of reference, Rocha and colleagues conducted a systematic review to assess the utilization of ibogaine in clinical contexts and to analyze the settings [34]. In this review, six articles were included with an additional three studies in the development phase (as documented on [ClinicalTrials.gov](https://www.clinicaltrials.gov) (accessed on 10 December 2020)). The reduced number of studies with different designs, restricted number of samples, and multiple ibogaine dose administrations posed challenges for comprehensive result analysis. However, through a qualitative analysis, it was possible to conclude that it is necessary to use ibogaine in a setting that offers safety to the participant, with cardiac monitoring and medical and psychiatric evaluation throughout the process, in addition to having trained professionals to deal with any side effects. In the article, the authors recommend the systematic recording of the setting in which ibogaine was applied so that it is possible to compare and develop protocols that guarantee safety [34].

A mind map of the main ideas described in this article is displayed in Figure 1 below:

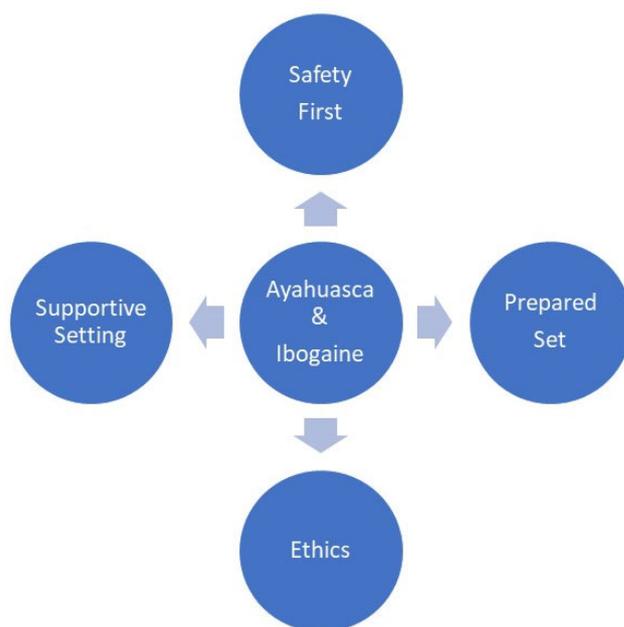


Figure 1. Mind map of the articles' main ideas.

2. Materials and Methods

In the literature, two previous guidelines that address recommendations for the safe use of psychedelics in clinical research settings were identified [35,36]. However, one of them, published 15 years ago, does not specify the required actions during adverse scenarios with psychedelics in detail and is more focused on data from studies with LSD and psilocybin [35]. The other is more focused on clinical trials for the industry and also lacks detailed information on safety procedures in specific situations [36]. Specifically, in the case of ibogaine, there is a guideline to manage the risks of its use in the clinical setting [37]. Therefore, this guideline aims to update the data already published, in addition to developing specific recommendations, establishing protocols to manage serious adverse effects, and establishing standardized care regarding procedures and professional conduct for handling volunteers during experimental sessions involving the administration of ayahuasca and ibogaine. To achieve this objective, our team thoroughly crafted a series of recommendations, covering topics we consider relevant based on our decade of expertise in conducting clinical trials with psychedelic substances, especially focusing on the particularities of ayahuasca and ibogaine. The protocols follow a broader philosophy of modular, independent sets of guidelines constantly published and updated by the clinical staff of Hospital das Clínicas de Ribeirão Preto (the University of São Paulo's affiliated teaching hospital). After deciding the main topics we sought to cover, drafts of the protocols were presented to the team and tested in live scenarios, undergoing several iterations in order to achieve a well-rounded version that is comprehensive and straightforward, ensuring the safety and the physical and psychological well-being of participants within the context of clinical research involving other psychedelic substances.

3. Results

3.1. Screening and Selection

The initial phase of participant selection necessitates a systematic approach to establish a selection procedure that ensures safety during experimental sessions. This phase is marked by the creation of rapport between the researcher and prospective subject and ruling out general potential risks to participant safety. It is imperative to predefine clear exclusion criteria before initiating screening, serving a dual purpose: maintaining sample congruence with study objectives and preventing potential adverse situations from occurring during experimental sessions [36]. Most authors recommend that the presence

of current, past, or familiar psychotic episodes and/or the diagnosis of bipolar affective disorder or schizophrenia be exclusion criteria [35,37]. Currently, due to a lack of evidence of the benefit and safety of those patients, we maintain the recommendation to exclude volunteers with a personal or family history of psychosis conditions from this guideline. However, future protocols could be considered to include subjects with psychotic symptoms if there is a clinical need (for example, to include post-traumatic disorder patients with dissociative symptoms or patients with bipolar disorder).

Moreover, since these are substances that are in the early phases of research, it is also recommended to exclude participants with underlying general medical pathologies, as it is not possible to ensure yet that these substances are safe for these populations. In the case of ibogaine, special attention should be given to the clinical history of cardiac, renal, and hepatic pathologies, and it is recommended to exclude individuals who have a recent history of any of these pathologies [37]. Since ayahuasca and ibogaine are experimental substances whose impact on fetuses and small children has not been studied, pregnant and lactating women should be excluded from participation.

The first step of the screening consists of the researcher approaching the possible volunteer, thoroughly explaining the research protocol, and making an invitation. If the individual shows interest in participating, researchers should conduct a “pre-screening”, asking key questions related to general data, personal and family history of known clinical and psychiatric diagnoses, medications, and substance use. If a researcher identifies any exclusion criteria at this first moment, the possible subject must be dismissed from participating. During this phase, the subject is also required to designate a “safety contact”, usually a close relative or trusted friend, whom the volunteer wishes to be notified by the research team in the event of an emergency or a severe adverse situation.

If the subject is deemed suitable to participate in the study, they should be referred to a qualified professional (a psychiatrist or psychologist) to be evaluated using some structured diagnostic tool, such as the Structured Clinical Interview for DSM-V (SCID-V) or the International Statistical Classification of Diseases and related health problems (ICD) of the World Health Organization (WHO). The SCID application assesses whether an individual meets the disorder diagnostic criteria under investigation or, in studies with healthy individuals, confirms the absence of mental health disorders. The presence of any psychotic or manic episodes, currently or in the past, is carefully evaluated, looking for not only established psychotic disorders (like schizophrenia) and psychotic features in the context of other disorders (i.e., major depressive disorder) but also for scenarios of drug-induced psychosis, psychosis related to pregnancy and childbirth, or due to other medical conditions. Manic episodes are also excluded, including antidepressant-induced mania. The presence of severe dissociative symptoms or severe personality disorders is also excluded. Suicidal thoughts and behaviors are usually included except in special situations, such as when the subject is presenting severe suicidality and is on pharmacological treatment. In these scenarios, we exclude them due to the necessity of withdrawing medication, which may pose a risk to volunteer safety. If any selection criteria are not fulfilled, the individual must be withdrawn from the study; otherwise, the volunteer must be forwarded to the responsible researcher to schedule the experimental session or to carry out other tests that may be included in the screening process. Especially in the case of ibogaine, due to its particularities, liver and kidney function tests, a complete blood count, an electrolyte panel, and an electrocardiogram are also performed and analyzed by a doctor who is responsible for identifying whether the patient’s health is adequate to start the study protocol. Some researchers also suggest using a stress echocardiogram, thallium stress testing, or 24 h Holter monitoring to complement cardiac evaluation [37].

By organizing the screening process this way, we can optimize the flow of possible volunteers in a more resource-efficient manner, as pre-screening can reliably identify major issues concerning participant inclusion and can be performed by any research staff member without the need for specialized training. Pre-screening reliably detects major issues in

participant inclusion, and screening itself enhances the precision of detecting potential exclusion criteria associated with the study design.

3.2. Use of Medications

Medication use is a sensitive issue and must always be openly discussed with the volunteer. We advise that they will be participating in an experimental trial, and the substance used may or may not help them with their disorders. We strongly advise against withdrawing medications for subjects with stable conditions, even those with residual symptoms. In our experience, it is common for people who are stabilized or remitted from their conditions to seek participation in trials with psychedelics with the idea of being permanently free of medications, often against medical advice. We consider including people under these conditions as ethically unacceptable because these people often have misconceptions about the efficacy of psychedelics, driven by media coverage, and, to this date, we have no robust evidence of this efficacy in the long term and no evidence at all for some disorders, so at the moment, the risks may outweigh the benefits.

In general, we do not recommend the inclusion of volunteers using medication and/or with pathologies that are not under control, with special attention to psychotropic drugs [35,37]. In cases where a volunteer is under the care of a healthcare professional unrelated to the study, they are encouraged to discuss their participation with their doctor, explaining the desire to participate and talking about possible risks and benefits. They are told that their doctor can also be in contact with our psychiatrists for further discussions and elucidations if deemed to be necessary. As a research team, the decision to participate in the study is always taken together with the attending physician. In the case of patients who are currently using some continuous medication that must be tapered off, this requirement is informed and discussed with the volunteer at the first meeting, and they are told to discuss this with their doctor, with the research team providing a pre-made report for the attending doctor with information regarding the study, if necessary. Usually, we use a standard timeframe of two weeks for discontinuing antidepressants and five weeks for fluoxetine, and the tapering of other medications is planned individually, considering the specific half-life of each drug. This procedure can be performed either by their attending psychiatrist or, alternatively, the participant can be enrolled in a specialized outpatient program coordinated by our team for this specific purpose. For extreme-risk patients, washouts can be performed in the in-patient ward at the university hospital. In any case, it is explicitly emphasized to the volunteer that any washout process must always be performed under supervision and that the process can only be started following the researcher's instructions.

3.3. Experimental Session

3.3.1. Setting

The setting where studies will take place should be carefully designed to maximize volunteer comfort while also anticipating and addressing any possible adverse situation safely and efficiently [35]. The basic structure for clinical studies with psychedelics in a controlled environment must involve a private room with restricted access only to the research team. This room should be quiet, and the researchers must exert control over environmental stimuli, such as dimmable lighting and temperature control. Additionally, it should offer a comfortable place for the volunteer to rest (an armchair, couch, or bed), easy access to the bathroom, a container for potential vomiting, and readily available sets of clean blankets, sheets, and towels. Before drug administration, it is pivotal to introduce the volunteer to the setting in which he/she will be during the next few hours and ask for their preferences regarding temperature and ambient light to ensure comfort.

In addition, the setting must also be thought out and prepared to deal with possible adverse situations. It is important to have basic nursing supplies readily accessible on-site or in close proximity, such as procedure gloves, materials for checking vital signs, a glucometer, and materials for intravenous infusion (syringes, intravenous catheters, and needles). From

a structural point of view, it is important to have a gas ruler or material for oxygen therapy available, basic medications, and an emergency trolley. Additional precautions must be taken, especially when administering ibogaine, such as a multiparametric monitor and an electrocardiograph, and ensuring that the team is prepared and competent in managing eventual cardiac events, such as an unstable arrhythmia, bradycardia, or cardiac arrest. In any case, it is important to ensure that all materials and structures are checked and tested ahead of the experimental sessions. Although psychiatric interurrences are typically mild and can be controlled with relative ease, it is crucial to plan the setting to address possible severe psychiatric complications, such as psychotic episodes and psychomotor agitation. These measures include furniture positioning in a way that staff can easily enter and leave the room, eliminating any objects that can be harmful to the subject or be used as a weapon, and maintaining spare keys to the bathroom, thereby preventing the volunteer from locking themselves away from the staff [35]. Furthermore, the team must keep the place clean and organized all the time.

3.3.2. Approach the Volunteer

Ideally, all the experimental sessions must be conducted by professionals experienced in conducting experimental psychedelic sessions [36]. Less experienced team members should always be supervised by a more seasoned researcher and should never be left unattended or put in charge of the experimental session. The general recommendations for approaching volunteers are as follows:

- Introduce yourself and all team members at the site before the intervention, even those who are not expected to be in direct contact with the volunteer;
- Inquire about the participant's preferences regarding the intensity of light, temperature, use of blankets, and other comfort items;
- Conduct assessments with 2–3 people;
- Prohibit the volunteers from using their cell phones, especially to solve problems and work-related tasks;
- Provide assistance with bathroom visits and walking, if needed, being attentive to any effects that may lead to potential accidents, such as impaired motor coordination and intense alterations in sensory perception;
- Maintain a calm and gentle approach by speaking softly and pausing and avoiding sudden or unexpected movements;
- Refrain from taking notes during the interaction—your attention should be on the volunteer;
- Facilitate communication—questions must be clear and straightforward;
- Encourage the volunteer to express their feelings in a welcoming and open way. Listen attentively in a non-judgmental or confrontational way and do not guide or interpret their experience;
- Emphasize that the subjective and/or physical effects of the substance are transitory;
- Respond promptly to the individual's needs and requests;
- Identify and remove any individuals who may destabilize the participant;
- Avoid unnecessary physical contact with the volunteer and ask for their permission before any physical contact is made;
- After drug administration and before the start of the effects, the participant may be talkative. Be attentive to when psychoactivity starts and avoid maintaining unnecessary conversations/interactions.

Usually, sessions must be composed of at least three members in order to ensure that there are always two people available to provide continuous assistance. The subject is directly accompanied by one or two researchers, and the team remains in an adjacent room. We recommend at least one researcher with the same gender as the volunteer to be with them all the time [35,36]. In our experience, this cautionary approach is important to minimize volunteer's distress from being in situations of vulnerability, particularly when working with specific populations, such as women with post-traumatic stress disorder. In the event that a researcher involved in the experimental procedure must leave the place,

the team should be notified about their absence so that another member can assume their role. The staff is allowed to engage in conversations with the volunteer if desired, but their primary focus is just to provide support; however, guidance or interpretation of experience is not allowed. This attitude aims to minimize the introduction of confounders or any potential influences that could impact the integrity of the studies. If the volunteer expresses their need for privacy (for example, for crying) and is considered stable (regarding psychoactive effects) by the research team, they can be left alone in the room for a few minutes, but researchers will be alert in the adjacent room and perform regular checking, except in experiments with ibogaine, in which the researchers are required to be close to the volunteer at all times for at least the initial 12 h.

In certain circumstances, the volunteer may face a particularly challenging experience, resulting in feelings of being overwhelmed, confused, or anxious [35]. During these episodes, the established protocol is to provide environmental and verbal management of the situation. The situation should be handled by the most experienced researcher who shares a connection with the volunteer (ideally the one who has established the rapport), preferentially a same-gender researcher in order to provide a greater sense of comfort and avoid triggering potentially distressing situations. Other team members are asked to leave the room, in order to reduce stimuli, but they must be ready to be called to action at any time. During verbal management, it is imperative to adopt a calm attitude, speak softly and assertively, and refrain from sudden movements and touching the volunteer. It is recommended to listen to the volunteer's demands attentively and provide the necessary support, reassuring them that they are under the influence of a substance and that the experience, regardless of how disruptive it may be, eventually will cease and that the team is there to assist them throughout this situation, which is fully expected and under control. Strategies like instructing the volunteer to keep their eyes closed (or open, if the visions are too intense) and focus on breathing can be employed. There may be exceptional situations that may require some form of physical contact to help the volunteer "anchor down" themselves, like a gentle touch on the arm or holding hands. In these cases, the researcher will inform the subject about this possibility before the ingestion of any substance and ask for their permission before any physical contact is made. The volunteer will only be touched after granting permission, and the contact will be terminated as soon as the volunteer feels better. Any other form of physical contact is explicitly prohibited.

3.3.3. Management of Adverse Events and Operational Protocols

Prevention of the occurrence of serious adverse effects is the most important step to ensuring safety. The steps described above, from screening and selection to setting organization and staff behavior, are designed to ensure that the participant's experience is as safe as possible. However, there is always a risk for adverse events to occur. On these occasions, it is imperative to establish a systematic, cohesive approach among all the professionals involved, ensuring the consistent implementation of actions. There are some basic recommendations that should be considered:

- The research team must be prepared to deal with any potential serious adverse event, no matter how infrequent it may be;
- The setting must be well-structured and equipped with the necessary tools to deal with serious adverse effects;
- The clinical team should be aware, and the management protocol should be aligned among the team;
- Regular monitoring of volunteers' health status must be performed according to the study schedule;
- Especially in the case of ibogaine, it is advisable to have a specialist physician or cardiologist perform electrocardiograms and cardiac management if needed.

The research team must be familiarized with the adverse effects profile of the studied substance. In the case of ayahuasca, the most common adverse effects observed in human studies involve headache, nausea, vomiting, and diarrhea [9–11,15,16] as well as autonomic

effects, such as tachycardia and increased blood pressure [5,15,16,21]. There are no reports of serious adverse events in human studies and cases of extreme anxiety and psychotic-like episodes have only been reported rarely in non-experimental settings [18]. Ibogaine has its own particularities, with a main concern related to cardiovascular abnormalities such as bradycardia, hypotension, arteriovenous malformations, aortic aneurysms, and QTc interval prolongation (which can lead to Torsade de Pointes and other arrhythmias), which can last for days after the administration of the drug. Other neurological abnormalities (dysarthria, ataxia, akathisia, and seizures) are also reported [29]. In this case, close supervision and monitoring in a controlled setting are essential during the first 72 h after ibogaine administration [37].

When conducting experiments, it is important for the team to be aware of the occurrence of severe adverse events, so our team developed a set of protocols that focus on managing confusion, anxiety, panic, psychomotor agitation, suicidal behavior, and other clinical aspects (see Supplementary Material). We highlight the need to develop customized guidelines based on the specificities of the team and the research facility and resources available. We advise the guidelines to be straightforward and modular, conveying the necessary information quickly and clearly without needing further reading from somewhere else. Modularity also facilitates the work of regularly updating the protocols. Since these guidelines are designed for rare or hypothetical scenarios, certain situations can expose some inherent flaws or unexpected aspects of the event, which must be addressed through protocol updates. The nature of dealing with rare adverse events demands that, besides structured guidelines, the team must be under continuous education. Training courses and simulated scenarios ensure that the staff is familiar with assessing and responding to these events accordingly so as not to be taken by surprise.

3.4. After the Experimental Session

Although the use of psychedelics is deemed safe and the majority of the side effects occur within hours of the drug intake, some volunteers may experience some adverse situations at the end of the experimental session and in the following days. In our experience, it is common for volunteers to report some kind of psychological distress (feeling emotionally worn out, anxious, or unable to rest) or physical discomfort (headaches or gastrointestinal distress) 24 to 48 h after the experimental session, which usually are self-limited. To monitor psychological distress in the following days of the experimental session, participants were asked to rate their mood using a scale of 0 to 10, indicating how they were feeling on that particular day. This allows for a subjective assessment of their emotional state and detection of potentially risky situations, such as a sudden decrease in rating or a sustained low mood. In such situations, a qualified professional (either a psychiatrist or a psychologist) is put in contact with the volunteer to perform a thorough evaluation [36]. We also recommend the following set of actions to be taken for every participant:

- Ensure, after clinical evaluation, that the participant is in good condition (both physical and psychological) to safely return home before discharging them;
- Ensure that the participant is in the company of someone they trust (such as a close friend or a relative). Discourage them to be alone after the experimental session;
- Encourage resting and light activities. Instruct the participant to avoid intense, stressful, or demanding activities;
- Tell the participants to avoid recreational drugs and keep the tyramine-free diet for another 24 h;
- Contact the volunteer at least 12 and 24 h after the end of the experimental session. Ask for their general condition, adverse effects, and the eventual use of recreational or prescription drugs, focusing on addressing the participant's needs;
- Educate the volunteer about potential adverse reactions and provide contact numbers of the research team to be reached if needed;
- If some severe adverse effect is identified or reported, promptly inform the study coordinator and the psychiatrist in charge.

A summary of the guidelines proposed in this article is displayed in Figure 2 below:

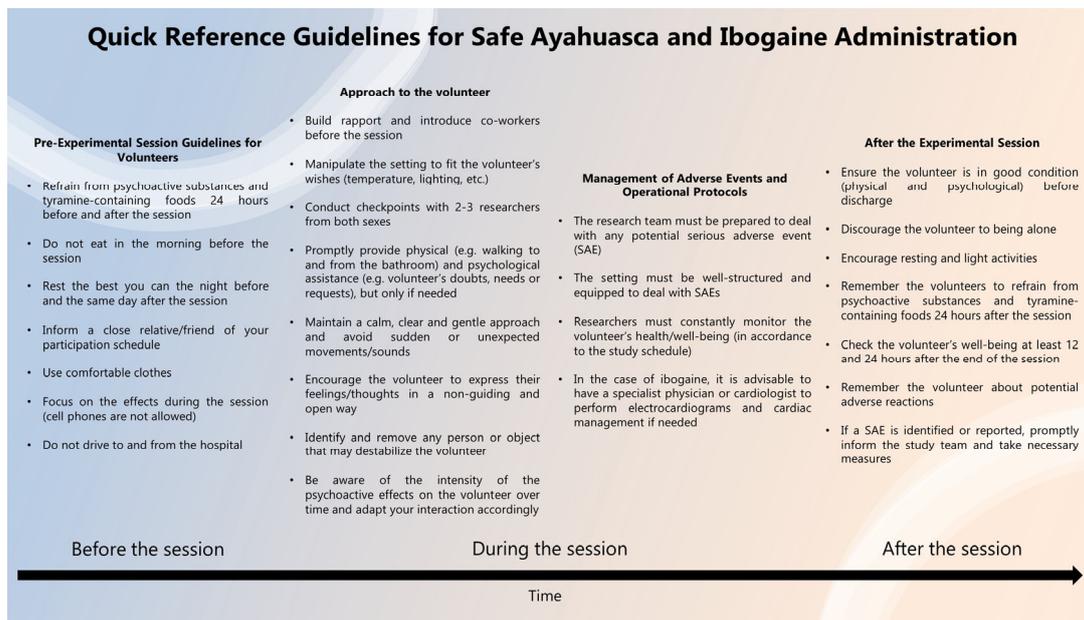


Figure 2. Quick reference guidelines.

4. Discussion

The use of psychedelic substances as a therapeutic tool to address multiple mental disorders is gaining momentum worldwide due to the rising interest of the scientific community, pharmaceutical industry, and media. Overall, the scientific evidence points towards the relative safety and low toxicity of hallucinogens [14,38], although several adverse events have been documented [20,39]. With this growing utilization, it is expected that different populations will start to be treated with these substances, with variations in comorbidities (such as substance use disorders and personality disorders) and sociodemographic, cultural, and economic particularities, which may lead to concerns about safety and undocumented side-effects [40]. However, in addition to knowledge about the effects and mechanisms of action, the researcher and professional perspective of hallucinogens must also be directed to set and setting. The term “set and setting” was proposed by Timothy Leary (1961) and colleagues and encompasses the psychological, environmental, and social factors that affect the psychedelic experience, which leads to understanding substance effects more broadly, including individual preparation and place. Therefore, reflecting on the creation of safety protocols that establish a minimum structure; guiding the work of researchers, therapists, and professionals; and systematizing the actions and care are necessary to expand the use of psychedelics in a safe way. Furthermore, the creation of protocols helps to optimize human and financial resources and facilitates the interpretation of published data.

In 2008, Johnson and colleagues published guidelines regarding hallucinogen use in clinical research [35]. The authors recommended the exclusion of possible volunteers with a personal or family history of psychosis [35]. However, specialists in the field have recently raised doubts about this exclusion criterion, pointing out the absence of scientific evidence to substantiate it [41]. The authors stated that psychedelic-assisted psychotherapy could benefit some individuals with psychotic conditions and is not necessarily contraindicated as long as a high level of support is provided and specific protocols are designed for this population [41]. However, currently, there is insufficient evidence to ensure safety and benefits among this population, so at this moment, we advise against including them, and we highlight the need to develop future specific protocols considering including subjects with other psychiatric conditions. The authors pointed out the importance of creating rapport between the research team and the volunteer before experimental sessions [35]. During experimental sessions, carefully preparing the volunteer and then providing a

safe setting staffed by at least two people during experimental sessions are suggested as important safety measures, and after the session, it is recommended to closely monitor the volunteer, investigating for possible adverse events [35]. Later, in 2023, the U.S. Food and Drug Administration (FDA) published guidelines for the industry regarding research with psychedelic substances (both serotonergic and empathogens) for medical conditions [36]. These guidelines also emphasize the importance of monitoring adverse events and the necessity of continuous observation by at least two professionals (one of them being a healthcare professional with specific training) in order to ensure the volunteer's safety. Furthermore, the authors recommend adequate and well-controlled (AWC) clinical trials as a cornerstone in comparing and analyzing data [36].

In general, the prior literature points to the importance of using ibogaine in controlled settings with medical supervision at least 72 h after administration to ensure the participant's safety [37], while its use in uncontrolled contexts has been associated with a higher rate of occurrence of moderate to severe adverse effects [29,34,42]. However, the few clinical studies conducted with ibogaine provide only a superficial description of the context, which confounds data comparison [34].

Finally, we must acknowledge a limitation of the approach used to prepare the present manuscript: our guideline was based on researcher expertise and not on the consensus of the scientific community. However, our research group is among the most productive and experienced regarding human research with ayahuasca and ibogaine, having conducted human trials during the last 10 years. Thus, our assumptions are rigorously based on scientific evidence, which assures the reliability of these guidelines. Nevertheless, these guidelines should always be reviewed and updated based on the continuous evolution of scientific knowledge on these drugs.

5. Conclusions

The reality of psychedelic use today is a wide spectrum of purposes, different contexts, and cultures. Through the creation of security guidelines, it is possible to systematize the care provided to participants inserted in this new and specific context of clinical research, guarantee a minimum necessary structure, and guide professionals' and researchers' actions. Ensuring safety and well-being is essential for researchers and professionals considering psychedelic-assisted treatment. It highlights the importance of creating a supportive and carefully controlled environment to maximize the therapeutic potential of these substances. Furthermore, it is extremely important that future research develops and describes safety guidelines, facilitating the discussion and design of more refined protocols to be used in clinical research contexts worldwide.

Supplementary Materials: The complete Operational Protocols are available online at <https://www.mdpi.com/article/10.3390/psychoactives2040024/s1> [43–55].

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