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Editorial

Beyond Enthusiasm: Ayahuasca and the Future of Depression Research

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This is a preliminary, unedited version of a manuscript that has been accepted for publication in the Brazilian Journal of Psychiatry. As a service to our readers, we are providing this early version of the manuscript. The manuscript will still undergo copyediting, typesetting, and review of the resulting proof before it is published in final form. The final version may present slight differences in relation to the present version.

Beyond enthusiasm: Ayahuasca and the future of depression research

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Few topics in contemporary psychiatry generate as much fascination, hope, and discomfort as the therapeutic use of psychedelics. For some, they represent a long-awaited disruption in the treatment of depression, a field in which many patients still experience partial response, relapse, or treatment resistance despite decades of pharmacological innovation. For others, the enthusiasm surrounding psychedelics has moved faster than the evidence, creating a risk that cultural excitement may be mistaken for clinical certainty. Ayahuasca sits precisely at the center of this tension.

Ayahuasca is a complex Amazonian brew traditionally prepared from Banisteriopsis caapi and Psychotria viridis. Its psychoactive profile depends mainly on the interaction between N,N-dimethyltryptamine (DMT) and β-carboline alkaloids such as harmine, harmaline, and tetrahydroharmine [1]. This combination allows orally ingested DMT to become psychoactive through monoamine oxidase-A inhibition, while also engaging neurobiological systems relevant to mood regulation, emotional processing, and neuroplasticity [2]. These mechanisms include serotonergic signaling, especially through 5-HT2A receptors, glutamatergic modulation, sigma-1 receptor pathways, inflammatory regulation, and possible effects on brain-derived neurotrophic factor and synaptic plasticity.

Depression remains one of the most burdensome psychiatric conditions worldwide, and the need for faster-acting and more durable interventions is evident.

In this context, the possibility that a single ayahuasca session could produce rapid reductions in depressive symptoms is scientifically compelling. However, psychiatry must be careful with compelling ideas. A biologically plausible intervention is not necessarily an evidence-based treatment. At present, ayahuasca should be viewed as a promising experimental intervention for depressive symptoms, not as an established antidepressant therapy.

The strongest signal comes from the Brazilian randomized placebo-controlled trial conducted by Palhano-Fontes et al. [3], in which patients with treatment-resistant depression receiving ayahuasca showed greater reductions in depressive symptoms than those receiving placebo during the first week after administration. This trial remains a landmark because it moved the field beyond observational reports and open-label designs. It also placed Brazilian psychiatry at the center of one of the most important scientific discussions in psychedelic medicine.

Galvão-Coelho et al. [4] published a meta-analysis on classic serotonergic psychedelics for mood and depressive symptoms, including studies with psilocybin, LSD, and ayahuasca. The authors identified 12 eligible studies with 257 participants, including randomized controlled trials involving psilocybin, LSD, and only one ayahuasca trial. Their findings suggested significant improvements in mood and depressive symptoms at acute, medium-term, and longer-term time points. However, the ayahuasca-specific evidence within the meta-analysis was necessarily limited because only one ayahuasca randomized controlled trial was available.

This fragility does not make the field unimportant. On the contrary, it makes it scientifically urgent. Ayahuasca research now faces a decisive methodological challenge: how to preserve the seriousness of the antidepressant signal while avoiding premature clinical claims. Open-label trials and large cross-sectional surveys consistently suggest reductions in depressive and anxiety symptoms after ayahuasca use [5-7]. These findings are valuable because they show that the phenomenon is not confined to a single laboratory setting. Yet they are also vulnerable to selection bias, expectancy effects, uncontrolled therapeutic context, regression to the mean, and the possibility that participants who benefit are more likely to remain engaged and report favorable outcomes. Such studies are useful for hypothesis generation, but they cannot substitute for well-powered randomized controlled trials.

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The problem of blinding is perhaps the most difficult issue in psychedelic psychiatry. Ayahuasca produces unmistakable subjective and bodily effects. Participants may experience intense perceptual changes, emotional release, nausea, changes in self-perception, and altered meaning-making. These effects make it difficult for participants to remain unaware of whether they received ayahuasca or placebo. Even research staff may infer allocation indirectly from behavior, speech, physiological responses, or the intensity of the acute experience. This is not a minor technical issue. If blinding fails, expectancy can become entangled with pharmacology, and the measured antidepressant effect may partly reflect what participants believe has happened to them.

Future trials must take this problem seriously, moving beyond the mere claim of a double-blind design to formally assess whether blinding was actually preserved. Participants and assessors should be asked to guess allocation, and these guesses should be reported. Active placebos should be designed to mimic at least some somatic or psychoactive features of ayahuasca without reproducing its full psychedelic profile and the expectancy should be measured before and after dosing.

This challenge is even more complex because ayahuasca is rarely experienced as a “drug effect” alone. It is often embedded in ritual, music, preparation, interpersonal support, cultural meaning, and post-session integration. These elements may not be noise around the intervention; they may be part of the intervention itself. Placebo-controlled research in ayahuasca group-retreat settings has shown that set and setting are important determinants of mental health outcomes, reinforcing that context is not peripheral in psychedelic research. The central question, therefore, is not simply whether ayahuasca works, but what exactly is working?

Safety considerations should remain central in ayahuasca research. Although severe psychiatric complications seem to be uncommon under controlled conditions, available safety data and case-based evidence suggest that adverse psychological reactions may occur in vulnerable individuals, including transient psychotic symptoms, manic activation, or paranoid reactions. These risks are particularly relevant for participants with personal or familial susceptibility to psychotic or bipolar disorders, unstable psychiatric conditions, concomitant substance use [8].

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Finally, ayahuasca should not be romanticized as an ancient cure, nor reduced to a pharmacological curiosity. It should be studied as a complex intervention at the intersection of neurobiology, subjective experience, culture, and psychiatric suffering.

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