Responsible Ceremonial Medicine: A Review of Current Evidence, Safety Protocols, and Ethical Considerations for Professional Practice

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Abstract

The therapeutic potential of classic psychedelic compounds, particularly psilocybin and ayahuasca, has been supported by a growing body of clinical evidence published in high-impact journals including the New England Journal of Medicine, JAMA, and Nature Neuroscience. Over 134 clinical trials with psilocybin have been registered, with results demonstrating significant antidepressant effects in treatment-resistant populations. Parallel research with ayahuasca has shown rapid and sustained reductions in depressive symptoms. However, the same body of evidence consistently demonstrates that therapeutic outcomes depend critically on the professional context of administration: psychological screening, therapeutic preparation, professional accompaniment, and post-experience integration. This review examines the current state of clinical evidence for psilocybin and ayahuasca, the neurobiological mechanisms underlying their therapeutic effects, established safety protocols and adverse event profiles, and the ethical and cultural considerations essential to responsible professional practice. The article argues that the three-phase model (preparation, experience, integration) documented in leading clinical trials constitutes the minimum professional standard, and that personality-informed approaches may enhance treatment specificity. Implications for the development of professional ceremonial medicine practice in Latin America are discussed.

Keywords: psilocybin, ayahuasca, psychedelic-assisted therapy, ceremonial medicine, harm reduction, neuroplasticity, set and setting, therapeutic framework, safety protocols, cultural ethics, plant medicine, transpersonal psychology, treatment-resistant depression

1. Introduction

The past two decades have witnessed a remarkable resurgence of scientific interest in the therapeutic applications of classic psychedelic compounds. What Indigenous cultures of Mesoamerica, the Amazon Basin, and other regions have utilized as tools for healing and knowledge for centuries is now being examined through the lens of modern clinical research, with results that have generated significant attention in mainstream medicine.

As of 2024, over 134 clinical trials with psilocybin alone have been registered on ClinicalTrials.gov, spanning 54 potential therapeutic indications (Norring & Spigarelli, 2024). Results in major depressive disorder (MDD) and treatment-resistant depression (TRD) have been published in the *New England Journal of Medicine* (Goodwin et al., 2022; Carhart-Harris et al., 2021), *JAMA*

(Raison et al., 2023), and *JAMA Psychiatry* (Davis et al., 2021). Research with ayahuasca, while more limited in controlled trials, has demonstrated equally promising results in depression (Palhano-Fontes et al., 2019) and has generated growing longitudinal evidence (Camargos et al., 2026).

This review examines the available evidence with critical rigor, the safety protocols that research has established, and the ethical considerations that inform responsible professional practice. As a licensed clinical psychologist in Costa Rica and a graduate of the Vital Program (USA) in psychedelic-assisted therapy, I write from the intersection of clinical training, direct ceremonial experience, and a commitment to evidence-based practice that respects the cultural origins of these therapeutic modalities.

2. Clinical Evidence: Psilocybin

The landmark trial by Goodwin et al. (2022), published in the *New England Journal of Medicine*, evaluated single-dose psilocybin (1 mg, 10 mg, or 25 mg) in 233 participants with treatment-resistant depression across 22 sites in 10 countries. The 25 mg dose produced significant reductions on the MADRS depression scale at 3 weeks compared to the 1 mg control, though effects attenuated by week 12, indicating the need for more robust follow-up protocols and potentially repeated dosing strategies.

Davis et al. (2021) reported in *JAMA Psychiatry* that two psilocybin sessions (20 mg and 30 mg) with psychotherapeutic support produced a 71% response rate at 4 weeks in participants with MDD, with 54% achieving remission. Raison et al. (2023) confirmed these findings in a placebo-controlled trial published in *JAMA*, reporting a 69% response rate at 48 hours post-administration. Carhart-Harris et al. (2021) compared psilocybin with escitalopram in a 6-week trial, finding comparable efficacy on the primary outcome but superior results for psilocybin on secondary measures of well-being and emotional processing.

Rosenblat et al. (2024) extended the evidence to more complex clinical populations, including participants with high treatment resistance, significant comorbidities, and bipolar II disorder. Their randomized trial demonstrated that psilocybin-assisted psychotherapy maintained significant antidepressant effects in this challenging population, with repeated doses associated with greater therapeutic benefit. These findings suggest that the clinical utility of psilocybin may extend beyond the relatively homogeneous populations studied in earlier trials.

3. Clinical Evidence: Ayahuasca

Palhano-Fontes et al. (2019) conducted the first randomized, placebo-controlled trial of ayahuasca in treatment-resistant depression, published in *Psychological Medicine*. Twenty-nine participants received a single dose of ayahuasca or placebo. Significant antidepressant effects were observed at day 7, with rapid onset within hours of administration. This trial provided the first controlled evidence supporting the traditional use of ayahuasca for mood disorders.

More recently, Camargos et al. (2026) published a longitudinal observational study of 280 adults with depressive disorders assessed at six time points over 180 days following ritualistic ayahuasca use. Significant reductions in MADRS scores were observed, with the most pronounced improvements emerging within the first two weeks post-intervention and substantial improvements maintained across the full 6-month period. While the observational design limits causal inference, the sample size and

longitudinal scope represent an important contribution to the evidence base.

4. Neurobiological Mechanisms

Recent research has identified specific neurobiological mechanisms underlying the therapeutic effects of psychedelic compounds. Moliner et al. (2023) demonstrated in *Nature Neuroscience* that psychedelics promote neuronal plasticity by directly binding to the TrkB receptor of brain-derived neurotrophic factor (BDNF), independent of their serotonergic activity. This finding suggests a mechanism through which single or few doses can produce sustained therapeutic effects: by opening a window of enhanced neuroplasticity during which new patterns of thought, emotion, and behavior can be established.

Morales-García et al. (2020) documented that N,N-dimethyltryptamine (DMT), the primary psychoactive component of ayahuasca, regulates adult neurogenesis both in vitro and in vivo. These findings expand the potential mechanisms beyond acute experiential effects to include structural neurobiological changes that may contribute to lasting therapeutic benefit.

5. Safety Profile and Adverse Events

The systematic review by Freitas et al. (2025), published in the *Australian & New Zealand Journal of Psychiatry*, analyzed 24 articles on the safety of psilocybin-assisted psychotherapy in clinical populations. The most commonly reported adverse events during sessions included transient blood pressure elevation, headache, nausea, vomiting, fatigue, and anxiety. Post-session adverse events included headache and emotional sensitivity. Suicidal ideation was observed infrequently and predominantly in participants with prior history of suicidal ideation or attempts. Critically, no deaths were attributed to psilocybin in any of the reviewed studies.

The authors note significant heterogeneity in adverse event definition, measurement, and reporting across studies, and recommend standardization to enable more robust safety comparisons. They conclude that the safety of psilocybin-assisted psychotherapy is generally supported by available data, while emphasizing the importance of screening for suicidality history and ongoing monitoring.

Johnson, Richards, and Griffiths (2008) established foundational safety guidelines for human hallucinogen research that have informed subsequent clinical trials. Key recommendations include exclusion of individuals with personal or family history of psychotic disorders, careful evaluation of medication interactions (particularly serotonergic agents), assessment of cardiovascular risk factors, and the provision of trained professional support throughout the experience. These guidelines constitute the minimum safety standard for any professional application of psychedelic compounds.

6. The Three-Phase Model as Professional Standard

Clinical trials with the most robust outcomes share a common structural feature: a three-phase model consisting of preparation, experience, and integration. This model, documented in the protocols of Johns Hopkins University, Imperial College London, and COMPASS Pathways, has emerged as the de facto standard for professional psychedelic-assisted therapy.

The **preparation phase** includes comprehensive psychological evaluation, medical and medication history review, psychoeducation about the experience, and establishment of therapeutic alliance. In clinical practice, this phase may be enhanced by personality-informed assessment, such as Enneagram-based mapping of resistance patterns and vulnerability profiles, which can inform individualized preparation strategies.

The **experience phase** requires a controlled environment with continuous professional accompaniment, medical safety protocols, and an adequate participant-to-facilitator ratio. The concept of set and setting (Leary, Metzner, & Alpert, 1964) has been empirically validated as a critical determinant of outcomes. The therapeutic relationship and environmental factors function as active therapeutic variables, not merely contextual background.

The **integration phase** is arguably the most critical and the most frequently neglected component in non-professional settings. Horton et al. (2021) identified integration as a core psychotherapeutic component of psilocybin-assisted therapy, noting that without structured post-experience processing, even profound experiential material may fail to translate into lasting behavioral and psychological change.

7. Ethical and Cultural Considerations

The expansion of Western interest in psychedelic plant medicines generates legitimate ethical tensions. These substances are not pharmaceutical innovations but cultural patrimony of Indigenous traditions with centuries of structured practice. Responsible professional engagement requires acknowledgment of cultural origins, avoidance of appropriative practices, and transparency about the relationship between clinical and traditional frameworks.

A coherent ethical position involves working in dialogue with traditional knowledge systems while maintaining the standards of clinical professionalism. This means neither dismissing traditional frameworks as pre-scientific superstition nor uncritically adopting ceremonial practices without adequate cultural competence and authorization. The professional framework is psychotherapeutic, informed by clinical research, with genuine respect for the traditions that developed and preserved these therapeutic modalities.

Transparency about the limitations of current evidence constitutes another essential ethical requirement. While the research is promising, Phase 3 trials remain incomplete, studied populations are relatively small and often homogeneous, and long-term safety data are limited. Ethical practice demands presenting data accurately, not as marketing material.

8. Limitations and Future Directions

Several limitations of the current evidence base must be acknowledged. First, the majority of psilocybin trials have been conducted with relatively homogeneous populations in Western clinical settings, limiting generalizability. Second, blinding remains a significant methodological challenge, as the perceptual effects of psychedelic compounds make true placebo conditions difficult to achieve (Norring & Spigarelli, 2024). Third, the contribution of the therapeutic component versus the pharmacological component remains inadequately disaggregated in most trial designs.

Future research priorities include: (a) larger, adequately powered Phase 3 trials with active comparator conditions; (b) development of standardized adverse event reporting frameworks; (c) longitudinal studies tracking outcomes beyond 12 months; (d) investigation of personality-informed treatment matching to optimize therapeutic specificity; and (e) research conducted in Latin American and other non-Western settings where traditional use of these compounds has the longest history.

9. Conclusion

The clinical evidence for the therapeutic potential of psilocybin and ayahuasca is substantial and growing, published in the highest-impact medical journals and supported by identified neurobiological mechanisms. This evidence justifies informed optimism about the role of these compounds within professional therapeutic frameworks. However, the same evidence consistently demonstrates that outcomes are inseparable from context: screening, preparation, professional accompaniment, and integration are not optional additions but essential components of the therapeutic intervention itself.

The development of responsible ceremonial medicine practice requires clinicians trained in both evidence-based psychotherapy and the specific competencies of psychedelic-assisted therapy. It requires institutional frameworks that prioritize safety over access, clinical evaluation over marketing, and cultural respect over commercial extraction. The question for the field is not whether these compounds have therapeutic value, the evidence increasingly confirms that they do, but whether the professional infrastructure exists to deliver that value safely, ethically, and effectively.

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