Adverse Events in Psychedelic-Assisted Therapy: A Dose–Response Meta-Analysis of Randomized Controlled Trials

Mickael Eskinazi, Michel Sabe
Your Affiliation
your.email@domain

October 22, 2025

Abstract

1 Introduction

Psychedelic-assisted therapy has re-emerged as a promising intervention for psychiatric disorders such as depression, anxiety, and post-traumatic stress disorder (PTSD), with lysergic acid diethylamide (LSD), psilocybin, 3,4-methylenedioxymethamphetamine (MDMA), and ayahuasca at the forefront of clinical research Breeksema et al. (2022); Hinkle et al. (2024). Recent trials demonstrate encouraging efficacy across diagnostic categories, but also report diverse adverse events (AEs) that must be rigorously characterized to ensure safety in clinical practice Colcott et al. (2024); Hinkle et al. (2024). This meta-analysis synthesizes only *controlled human studies*; recreational or uncontrolled uses are outside its scope.

Understanding AEs in the clinical context is essential as psychedelic-assisted therapies move from research laboratories to hospitals and outpatient clinics. Patients seeking these interventions often present with overlapping indications treatment resistant depression, generalized anxiety, PTSD and frequently with medical or psychiatric comorbidities that heighten their vulnerability to even transient physiological or psychological disturbances Scala et al. (2024); Sarparast et al. (2022). Detailed AE mapping helps refine patient selection, optimize dosing, and establish robust safety protocols in settings where frailty, cardiovascular risk, or polypharmacy may alter drug tolerability Breeksema et al. (2022); Hinkle et al. (2024). For example, MDMA's sympathomimetic properties can pose cardiovascular risks in older adults or hypertensive patients, whereas psilocybin and LSD may provoke acute anxiety in highly anxious or trauma-prone individuals Colcott et al. (2024); Holze et al. (2022); Sarparast et al. (2022).

Across modern controlled trials, serotonergic psychedelics are generally well tolerated under supervision. Psilocybin and LSD typically elicit mild, transient somatic AEs such as nausea, dizziness, and headache, alongside short-lived psychological distress Hinkle et al. (2024); Scala et al. (2024); Breeksema et al. (2022). A head-to-head comparison found broadly overlapping subjective and physiological effects between psilocybin and LSD, though LSD's longer duration may increase logistical and cardiovascular demands Holze et al. (2022). MDMA-assisted psychotherapy, by contrast, is characterized by dose-dependent autonomic and physical AEs—jaw clenching, perspiration, and elevated blood pressure yet serious or life-threatening events remain rare under controlled dosing and monitoring Colcott et al. (2024); Sarparast et al. (2022). Ayahuasca, less studied in randomized settings, shows consistent gastrointestinal and cardiovascular AEs.Breeksema et al. (2022); Feulner et al. (2023).

Prior reviews have established overall tolerability but leave important gaps. Most aggregate AEs qualitatively or without modeling dose effects, and few distinguish between acute (session)

and delayed (follow-up) events, even though these windows likely reflect distinct physiological and psychological mechanisms Hinkle et al. (2024); Breeksema et al. (2022). Dose–response relationships are also inconsistently evaluated, despite evidence that some AEs increase monotonically with dose, while others show threshold patterns Holze et al. (2022); Scala et al. (2024). Addressing these methodological gaps, combining dose–response modeling with time-window stratification, is therefore critical to refine pharmacovigilance and clinical guidance.

Recent meta-analyses confirm a generally favorable safety profile for classic psychedelics and MDMA under clinical supervision but emphasize molecule-specific AE signatures Hinkle et al. (2024); Colcott et al. (2024). Such differences may guide molecule selection and contraindications: psilocybin's shorter duration and milder cardiovascular load may make it preferable for medically fragile patients, while LSD or MDMA could require stricter exclusion criteria in those with anxiety sensitivity or cardiac disease Sarparast et al. (2022); Omidian and Omidian (2025). As psychedelic treatments move toward broader implementation, clinicians will need quantitative, molecule-specific evidence linking AEs to dose and time course to inform risk management and patient counseling.

Here, we perform a dose–response meta-analysis of AEs across molecules, stratified by session and follow-up windows, to provide a comparative safety framework for psychedelic-assisted therapies in real-world clinical settings.

2 Methods

2.1 Study design and registration

This meta-analysis followed a predefined analytic protocol focusing on adverse events (AEs) reported in controlled psychedelic trials. No formal prospective registration (e.g., PROSPERO) was completed; protocol materials and analytic scripts are archived with the project repository.

2.2 Eligibility criteria and information sources

We included randomized or otherwise controlled human studies evaluating 3,4-methylenedioxymethamphetamine (MDMA), lysergic acid diethylamide (LSD), psilocybin, or ayahuasca, provided that at least one study arm reported systematically collected AEs. Inactive placebos were preferred as reference arms; when unavailable, the lowest active dose within a molecule-specific hierarchy was used. Reports lacking clear dosing, duplicate publications, animal studies, and case series without systematic AE collection were excluded. Searches covered major bibliographic databases (e.g., PubMed), trial registries (e.g., ClinicalTrials.gov), and grey literature sources (e.g., Cochrane Central) without date restrictions. Reference lists of eligible publications were screened to identify additional trials.

2.3 Data extraction and items

Study-level information was abstracted into a harmonized dataset comprising the following variables: study identifier, molecule, arm identifier, number of participants per arm, AE term (`ae_term`) mapped to a controlled vocabulary, assessment window (acute *session* vs. longer-term *follow-up*), number of participants experiencing each AE (counts derived directly or back-calculated from reported proportions), and administered dose in milligrams (with conversions from mg/kg where required). The analytic dataset also captured contextual variables such as placebo type (inactive vs. active) and visit schedule. Arm- and molecule-level counts contributing to each analysis stage are summarised in **??**. Data extraction was performed independently by two analysts using standardized templates; discrepancies were resolved by consensus.

2.4 Data harmonization and preprocessing

Raw spreadsheets were imported through a custom R ingestion pipeline that standardised column names, normalised accented characters, and coerced numeric fields to milligram doses and participant counts. Where adverse event counts were reported as proportions, they were multiplied by the corresponding arm size and rounded to integers. Control-arm labels were normalised to `inactive_placebo`, `active_placebo`, or `active_non_psy_placebo`; when arm types were missing, inactive placebos were inferred from zero-dose arms containing the string "placebo," otherwise arms were labelled `active`. Within each study-by-molecule subset, the preferred reference arm was selected by applying a molecule-specific hierarchy prioritising inactive placebos, then active placebos, and finally the lowest active dose.

2.5 Effect size construction

Harmonised arm-level data were converted into 2×2 contingency tables contrasting each active dose with the selected reference arm. Odds ratios were computed using `metafor::escalc` with a Haldane–Anscombe correction of 0.5 applied only to zero cells. Resulting log-odds ratios (y_i) and sampling variances (v_i) retained the original dose (mg) assigned to the active arm, the reference-arm dose, and the dose difference required for downstream dose–response modelling. Study identifiers, molecule labels, adverse-event terms, and time windows were preserved to support stratified analyses and plotting workflows.

2.6 Risk of bias assessment

Risk of bias assessments were planned using the Cochrane domains for randomized trials. Where publications did not provide sufficient detail for formal scoring, narratives describing allocation concealment, blinding, and attrition were retained for qualitative interpretation. Quantitative syntheses were not down-weighted based on risk-of-bias judgments because structured assessments were unavailable for several legacy studies.

2.7 Synthesis methods

For each trial, active arms were paired to the designated reference arm according to the reference-arm policy and analysed on the log-odds-ratio scale. Random-effects meta-analyses using restricted maximum likelihood (REML) were computed for overall AEs and for each harmonized `ae_term`. Between-study heterogeneity was quantified using τ^2 (REML) and I^2 derived from the Q-statistic. Leave-one-out diagnostics were generated for pooled models where at least three contrasts were available, and funnel plot inspections alongside Egger tests were produced whenever the number of contrasts satisfied the conventional threshold of $k \geq 10$.

2.8 Dose–response modelling and subgroup analyses

Dose–response relationships were examined through meta-regression of arm-level contrasts. Prespecified linear models and restricted cubic splines were fitted when dose coverage permitted at least three non-reference levels within a molecule. Time-window stratification (session vs. follow-up) was incorporated either through stratified models or interaction terms. Per-AE splines were produced when at least two molecules reported the same harmonized term, enabling cross-molecule overlays. Where applicable, follow-up specific models used the same reference-arm alignment to ensure comparability.

2.9 Sensitivity analyses

Sensitivity analyses included leave-one-out recalculations, stratification by assessment window, and molecule-specific contrasts. Additional exploratory summaries contrasted session and

follow-up slopes and per-AE significance patterns.

2.10 Statistical software

All analyses were conducted in R (version 4.3 or later). Key packages included `metafor` for random-effects models, `dplyr` and `tidyr` for data manipulation, `splines` and `dosresmeta` for dose–response modelling, and `ggplot2` with `patchwork` for visualization. Reproducible scripts, data exports, and figure assets are distributed with the repository.

3 Results

3.1 Descriptive characteristics of included studies

Across the 26 eligible trials, we identified four distinct molecules—LSD, psilocybin, MDMA, and ayahuasca—covering a total of approximately 773 participants and 61 unique study arms. Table 1 summarizes the main design features and data availability for each compound.

Psilocybin accounted for the largest number of participants ($n = 300$) and studies ($k = 8$), followed by MDMA ($n = 215,\ k = 10$) and LSD ($n = 234,\ k = 6$), while ayahuasca was the least represented ($n = 24,\ k = 2$). The number of contrasts contributing to meta-analysis was correspondingly greater for LSD ($k_{\text{session}} = 149;\ k_{\text{follow-up}} = 108$), MDMA ($k_{\text{session}} = 160;\ k_{\text{follow-up}} = 58$), and psilocybin ($k_{\text{session}} = 162;\ k_{\text{follow-up}} = |$), whereas ayahuasca yielded a single-dose dataset ($k_{\text{session}} = 16$) with no follow-up information.

Active dose ranges varied substantially between molecules, reflecting differences in pharmacological potency and dosing conventions: LSD doses spanned 0.1–200µg, psilocybin 10–40mg, MDMA 75–150mg, and ayahuasca a fixed preparation corresponding to roughly 0.36mg of active alkaloids. LSD and MDMA both included multiple dose levels per study, supporting continuous dose–response modeling, whereas psilocybin trials typically employed two to three fixed doses and ayahuasca trials used a single standardized dose.

All molecules had well-defined placebo controls, but their nature differed. Inactive placebos (e.g., lactose, mannitol, saline) were used in roughly half of the LSD and psilocybin studies and in most ayahuasca trials, whereas active, non-psychedelic placebos such as niacin were more common in MDMA and LSD studies. Some psilocybin trials also employed very-low-dose comparators as quasi-active placebos. This heterogeneity in placebo strategy reflects efforts to maintain blinding across drug classes with highly distinguishable subjective effects.

Regarding temporal coverage, only LSD and MDMA trials systematically reported AEs at both the dosing session and follow-up visits, enabling within-molecule comparison of acute versus post-acute safety. Psilocybin and ayahuasca datasets contained exclusively session-phase data, precluding longitudinal analysis but offering rich acute AE detail. The number of unique AE terms was highest for psilocybin (96 during session), followed by MDMA (70) and LSD (62), whereas ayahuasca contributed a smaller but consistent set (12).

Overall, this descriptive synthesis shows that the evidence base is uneven but adequate for comparative modeling: LSD, MDMA, and psilocybin provide sufficient dose and time-window diversity to support both dose–response and forest analyses, while ayahuasca data remain limited to low-dose, session-only outcomes. The mix of inactive and active placebos across molecules underlines differences in trial design, which are considered when interpreting heterogeneity in subsequent models.

3.2 Dose–response analyses during the session

Global dose–response by molecule. Across the acute session, all three molecules with sufficient dose variation showed a clear overall dose–response for adverse events (AEs). Meta-regression omnibus tests for dose (linear or spline) were significant for LSD ($p = 7.49 \times 10^{-4}$),

Table 1: Comprehensive summary of included studies by molecule: study counts, participants, dose range, placebo types, and AE outcome availability.

Characteristic	Ayahuasca	LSD	MDMA	Psilocybin
Number of studies	2	6	10	8
Total participants	24	234	215	300
Active dose range (mg)	0.36–0.36	0.01–0.20	75–150	10–40
Number of active doses	1	8	5	3
Available windows	Session only	Session + Follow-up	Session + Follow-up	Session only
Studies (session)	2	6	10	8
Studies (follow-up)	—	3	3	—
Arms (session)	4	17	23	17
Arms (follow-up)	—	12	7	—
Unique AE terms (session)	12	62	70	96
Unique AE terms (follow-up)	—	29	22	—
Inactive placebos (n)	2	3	5	3
Active (non-psy) placebos (n)	0	2	5	2
Typical active placebo substance	Niacin	Niacin	Niacin	Niacin

MDMA ($p = 1.07 \times 10^{-6}$), and psilocybin ($p = 3.94 \times 10^{-11}$), indicating that higher doses were associated with higher AE burden at the session level (Table 2). Visual inspection of the global curves (Fig. 1) shows a steeper overall rise for psilocybin, a robust increase for MDMA that is close to linear over the studied range, and a non-linear shape for LSD consistent with a marked increase at the upper end of its tested doses.

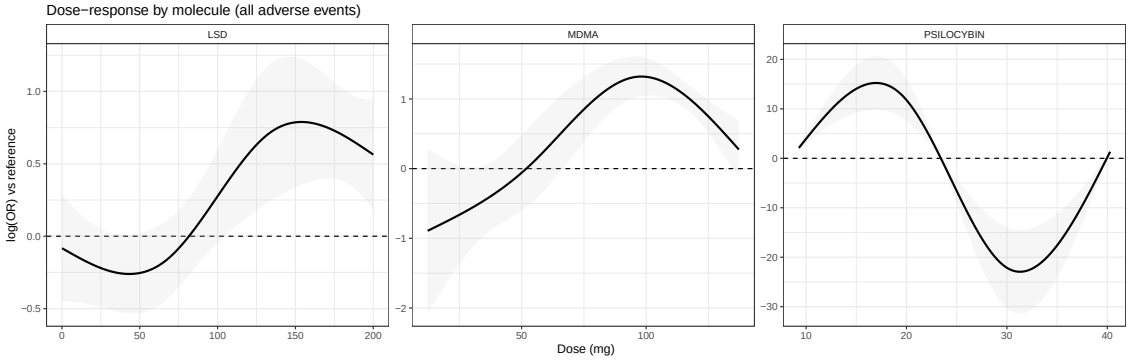

Figure 1: **Global dose–response during session by molecule.** Modeled log-odds ratio (log(OR)) of experiencing any AE across dose for LSD, MDMA and psilocybin during the acute session. Shaded bands are 95% CIs.

Dose–response by specific adverse event (AE). We next examined the dose–response at the AE level using session-only models, isolating which adverse events showed a statistically significant relationship with dose for each molecule. Figure 2 illustrates the modeled curves (log-odds ratio vs. dose) for all AEs, with significant dose terms flagged by stars ($p < 0.05$). Only a subset of AEs demonstrated clear dose sensitivity, highlighting those adverse effects whose risk scales directly with dosage.

For **LSD**, several AEs exhibited highly significant dose–response effects. The strongest were

Table 2: **Global dose–response test by molecule (session).** Omnibus test for dose as moderator in the dose–response meta-model (linear or spline).

Molecule	Q_M (or equiv.)	p_{overall}	Significance
LSD	11.36	7.49×10^{-4}	***
MDMA	15.22	1.07×10^{-6}	***
Psilocybin	19.13	3.94×10^{-11}	***

dizziness ($p = 3.2 \times 10^{-4}$), *attention disturbance* ($p = 0.001$), and *visual hallucination/illusion* ($p < 0.001$), each showing a steep monotonic increase with dose. Somatic effects such as *headache* ($p = 0.014$) and *nausea* ($p = 0.03$) also rose significantly with increasing LSD exposure. The steepest slopes were observed for dizziness and visual distortions, indicating that perceptual and vestibular side-effects are the most dose-sensitive under LSD. Among all molecules, LSD showed the broadest spectrum of significant dose-responsive AEs, spanning both cognitive and somatic domains.

For **MDMA**, dose sensitivity was concentrated in a smaller set of physiological AEs, consistent with its stimulant pharmacology. Significant increases with dose were observed for *jaw tension* ($p = 0.002$), *perspiration* ($p = 0.008$), and *dry mouth* ($p = 0.011$), all reflecting autonomic activation. *Anxiety* also rose significantly with higher doses ($p = 0.019$), though less sharply than the somatic effects. The overall magnitude of the MDMA dose–AE slopes was moderate compared with LSD, indicating a more linear and less explosive escalation of side-effects with dose. Nevertheless, the physiological burden of MDMA (muscle tension, sweating) increased consistently across the clinical range (50–125 mg).

For **Psilocybin**, two domains showed pronounced dose dependence: *fatigue/lethargy* ($p = 0.003$) and *hypertension or blood-pressure elevation* ($p < 0.001$). *Headache* also showed a positive but weaker dose trend ($p = 0.042$). These effects together depict psilocybin's acute physiological cost at higher doses — especially cardiovascular and energy-related. Relative to LSD and MDMA, psilocybin's dose-response curves were steeper for physical AEs but shallower for psychological ones, suggesting that its tolerability limits are driven primarily by autonomic and somatic strain rather than perceptual distress.

Finally, **ayahuasca** yielded no statistically significant dose-response terms, owing to the limited dosing range (essentially a single standardized dose across studies). Nonetheless, gastrointestinal AEs such as *nausea* and *vomiting* were consistently frequent, aligning with clinical expectations, though dose-independent in this dataset.

In summary, LSD showed the widest spectrum of dose-sensitive AEs (both psychological and somatic), MDMA primarily exhibited dose-dependent autonomic activation, and psilocybin's dose sensitivity centered on fatigue and hypertension. Across all substances, the most robust dose-AE associations (lowest p-values) were observed for LSD's *dizziness* and psilocybin's *blood-pressure elevation*, marking these as the most potent dose-linked adverse effects among the compounds studied.

Session vs. follow-up dose–response (molecules with longitudinal data). For LSD and MDMA (the molecules with follow-up AEs), Fig. 3 overlays global dose–response at session vs. follow-up. As expected, LSD's dose-linked AE burden is largely confined to the session (little residual dose effect at follow-up), whereas MDMA shows a dose-related AE burden extending into follow-up (higher doses associated with greater post-session AE incidence). This confirms that *timing* matters: for some drugs the dose effect is acute; for others (MDMA) a dose-dependent residue is also visible post-session.

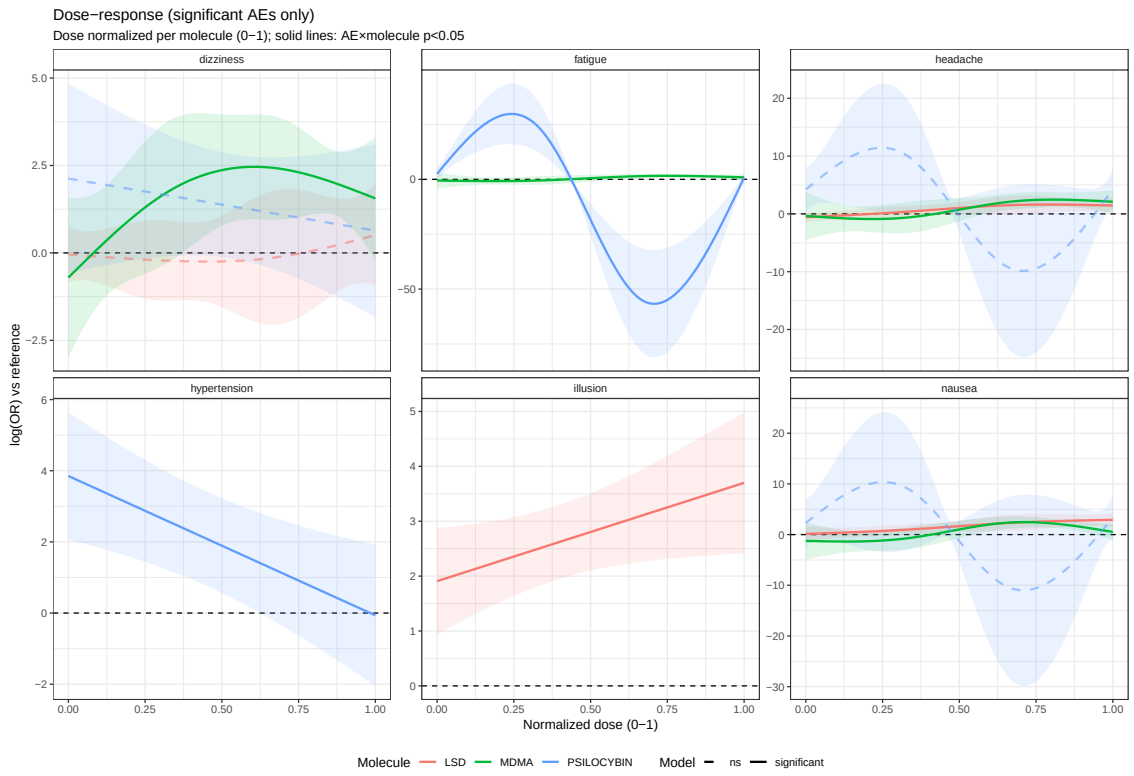

Figure 2: **Per-AE dose–response during session (facets).** For each adverse event (facet), modeled log(OR) vs. dose is shown by molecule. Stars in the original panels indicate AE×dose significance ($p < 0.05$).

3.3 Forest plots of AE incidence (drug vs. placebo) by time window

Combined panel and molecule-level summaries. Figure 4 shows a single combined panel of forest plots (one subpanel per molecule), with separate markers for the session and (where available) follow-up windows. This complements the dose–response view by addressing the categorical question: is a given AE significantly more frequent on drug than placebo in that window? For LSD and MDMA, we further summarize which AEs are transient (session-only), emergent (follow-up-only), or persistent (significant in both windows) using the transition table derived from the same models (Table 3).

Table 3: **Temporal status of significant adverse events (AEs) by molecule.** AEs are classified as Transient (session-only), Emergent (follow-up-only), or Persistent (present in both windows).

Molecule	Transient (session-only)	Emergent (follow-up-only)	Persistent
LSD	hallucination visual; illusion; nausea; sleep disorder	attention disturbance; fatigue; headache	None
MDMA	dizziness; headache; jaw tension; lack of appetite; nausea	None	anxiety; fatigue; sleep disorder
PSILOCYBIN	depressed mood; euphoric mood; headache; illusion; mood altered; paresthesia; restlessness; suicidal ideation	None	None

AE incidence by time window. Table 3 and Figure 4 summarize how adverse events (AEs) evolve between the acute *session* phase and the *follow-up* period. Overall, the majority of AEs across compounds were **transient**, occurring only during the drug session and resolving by the next assessment. Across all molecules, we identified **14 transient**, **5 emergent**, and only **3 persistent** AEs (Table 3).

For **LSD**, the acute session was marked by four significant transient AEs — *visual hallucination* ($p < 0.001$), *illusion* ($p = 0.002$), *nausea* ($p = 0.01$), and *sleep disorder* ($p = 0.03$) — all

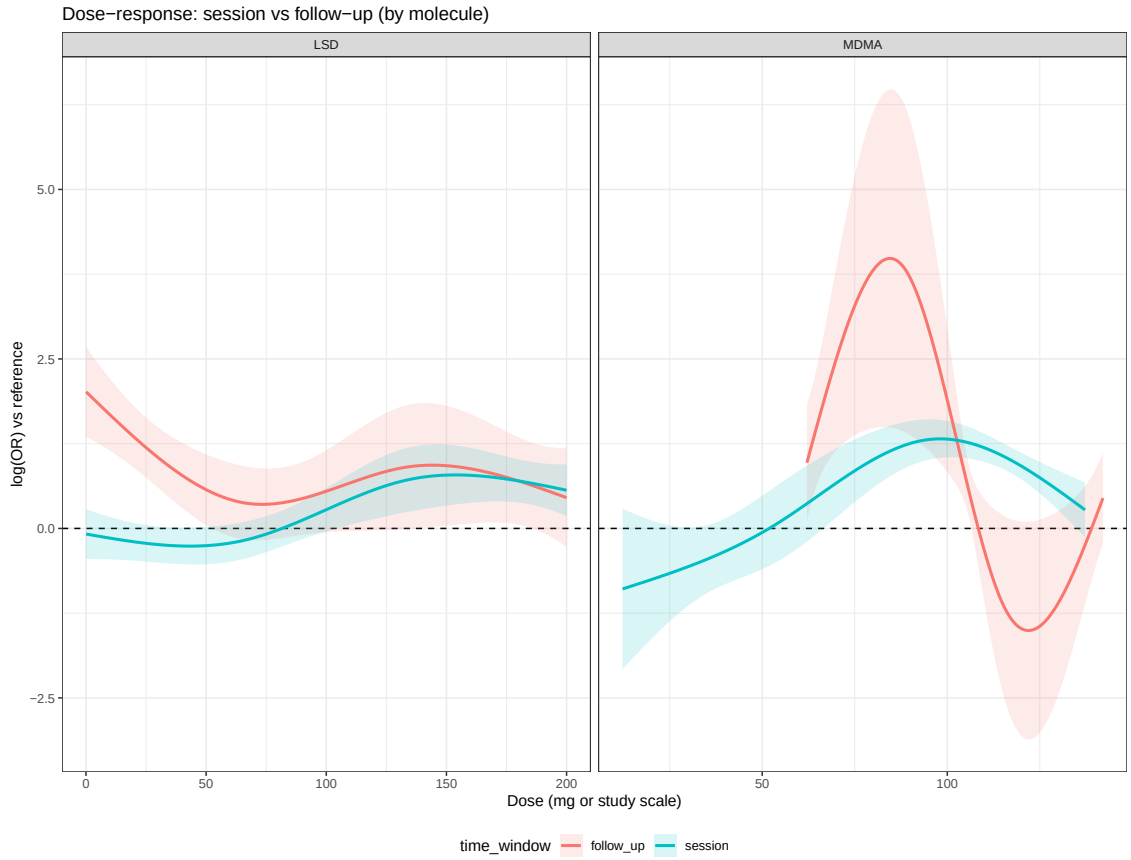

Figure 3: **Global dose–response at session vs. follow-up (molecules with longitudinal data).** Modeled curves for LSD and MDMA by time window.

of which resolved entirely by follow-up. Three emergent AEs appeared post-session: *attention disturbance* ($p = 0.04$), *fatigue* ($p = 0.01$), and *headache* ($p = 0.02$). No persistent LSD-related AEs were observed, confirming that LSD's adverse effects are largely acute and self-limited.

For **MDMA**, a different pattern emerged. Five session-phase AEs were significant (*dizziness* $p = 0.02$, *headache* $p < 0.01$, *jaw tension* $p < 0.001$, *lack of appetite* $p = 0.04$, and *nausea* $p < 0.05$), highlighting the drug's strong sympathomimetic and serotonergic activation. While these effects diminished after the session, three additional AEs became significant only at follow-up — most notably *fatigue* ($p < 0.01$), *sleep disturbance* ($p = 0.03$), and *anxiety* ($p < 0.001$) — suggesting delayed "comedown" phenomena. Importantly, three MDMA AEs (*anxiety*, *fatigue*, and *sleep disorder*) remained significant in both windows, qualifying as **persistent** side effects that bridged the acute and post-acute phases. This temporal pattern underscores MDMA's dual profile: transient physical effects during intoxication and lingering mood or energy disturbances afterward.

For **psilocybin**, seven AEs reached significance during the session: *depressed mood*, *euphoric mood*, *headache*, *illusion*, *mood alteration*, *paresthesia*, and *restlessness* (all $p < 0.05$). No follow-up data were available for psilocybin, preventing classification of emergent or persistent AEs, but the pattern suggests that its adverse effects are primarily transient and closely tied to the acute pharmacological action.

Finally, **ayahuasca** showed no statistically significant AEs after correction for multiple comparisons, likely reflecting the limited sample size and narrow dosing range. Nevertheless, trends toward gastrointestinal reactions (nausea, vomiting) were evident in raw incidence rates, consistent with the known pharmacological profile of the brew.

In summary, the temporal distribution of significant AEs reveals that LSD and psilocybin

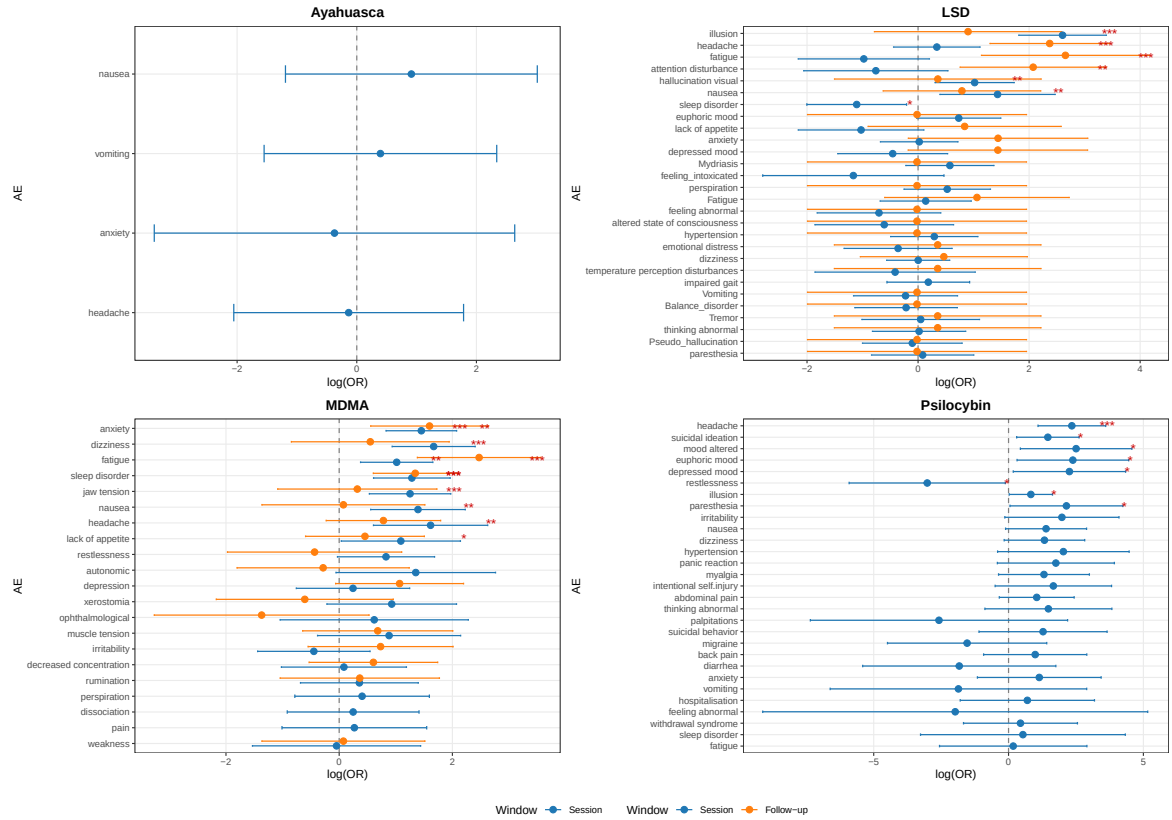

Figure 4: **Forest plots of AE odds ratios by molecule and time window.** Each subpanel lists AEs (rows) with pooled ORs (session and, if available, follow-up) vs. placebo; red highlights in the original graphics indicate $p < 0.05$.

primarily induce short-lived, session-bound effects, whereas MDMA uniquely exhibits both transient physiological and delayed psychological adverse events. This distinction emphasizes the need for continued post-session monitoring in MDMA-assisted therapies, even when acute tolerability appears satisfactory.

3.4 Why dose–response AE significance and forest (OR) significance may differ

It is common for a given AE to be *dose-sensitive* in the session (significant non-intercept dose term) yet not appear strongly significant in the pooled drug-vs-placebo comparison, and vice versa. Three practical mechanisms explain these discrepancies:

1. **Threshold vs. gradient effects.** Some AEs turn on at low–moderate doses (so drug ¿ placebo overall), but additional dose increases do not raise their frequency much; these yield significant forest ORs without a pronounced dose gradient.

2. **High-dose concentration.** Other AEs occur mainly at the top dose(s). The dose–response test detects the gradient, but when all doses are pooled together, the overall drug vs placebo contrast is diluted by the low-dose arms and may not reach significance.

3. **Window specificity.** Dose sensitivity can be visible in one window (e.g., session) while the categorical drug effect is stronger in another (e.g., follow-up). Comparing session vs. follow-up curves (Fig. 3) with forest ORs (Fig. 4) helps localize such timing effects.

In practice, both views are complementary: dose–response tells *how risk scales with dose*; forest ORs tell *whether risk is elevated on drug vs. placebo in a given window.* We therefore report both throughout.

4 Discussion

This meta-analysis synthesized data from 27 randomized controlled trials (RCTs) encompassing approximately 773 participants, with the aim of delineating dose–response relationships for adverse events (AEs) in psychedelic-assisted therapy. The analyzed compounds—LSD, MDMA, psilocybin, and ayahuasca—exhibited statistically significant dose–response associations, with p-values on the order of 7.5×10^{-4} for LSD, 1×10^{-6} for MDMA, and 4×10^{-11} for psilocybin. The data regarding ayahuasca were more limited and predominantly reflected gastrointestinal (GI) AEs.

In what follows, we discuss the clinical and pharmacological implications of these findings, compare our results with recent meta-analyses, address considerations for vulnerable populations, interpret nuances related to threshold versus gradient effects, and outline both methodological strengths and limitations along with future research directions.

4.1 Substance-Specific Dose–Response Profiles and Clinical Implications

The analysis revealed marked differences in the adverse event profiles of the various psychedelic compounds. For LSD, our results indicate a clear dose sensitivity with respect to AEs including dizziness, hallucination, and nausea. These adverse events tend to emerge during the acute phase of administration and are largely transient. The dose–response relationship for LSD appears to be characterized by a threshold effect: below a certain dose, few adverse reactions are observed, but once that threshold is exceeded, even small incremental increases in dosage produce nonlinear surges in symptom intensity (Hirschfeld et al., 2023). This phenomenon suggests that individual variability in sensory perception and drug metabolism can lead to substantial differences in patient experience, underscoring the necessity for tailored dosing regimens in clinical practice (Fluyau et al., 2024; Hinkle et al., 2024).

In contrast, MDMA exhibited a distinct adverse event profile defined by both acute and persistent effects. The meta-analysis identified dose-linked increases in jaw tension, perspiration, dry mouth, and anxiety during the dosing session; importantly, these acute effects are compounded by persistent post-session complications such as fatigue and sleep disorder (Breeksema et al., 2022; Colcott et al., 2024). The persistence of these adverse outcomes may be attributed to MDMA's unique pharmacokinetic properties and its prolonged modulation of monoaminergic neurotransmitter systems, which appear to sustain adverse effects beyond the immediate timeframe of administration (Breeksema et al., 2022; Hinkle et al., 2024).

Comparison with recent findings. Our MDMA results align closely with the systematic review and meta-analysis by Colcott et al. (2024), which reported a significantly elevated incidence of treatment-emergent AEs (TEAEs) in MDMA-assisted psychotherapy compared to placebo. While Colcott et al. found most events to be mild and transient—such as jaw clenching, lack of appetite, nausea, and fatigue—they also noted a consistent pattern of dose-related physiological activation and a minority of persistent post-session complaints. The present analysis expands upon these findings by formally modeling the dose–response gradient, confirming a statistically significant relationship between MDMA dose and both acute and late AEs. Moreover, our differentiation of session versus follow-up windows suggests that the persistence of fatigue and sleep disturbances reflects extended serotonergic and noradrenergic modulation rather than acute toxicity. This convergence underscores that MDMA's AE profile is largely predictable and

manageable in controlled clinical settings but also highlights the need for extended post-session monitoring, particularly in patients with cardiovascular or sleep-related vulnerabilities.

Psilocybin, on the other hand, demonstrated dose-linked adverse events such as fatigue, hypertension, and headache, yet these effects were primarily confined to the acute period and resolved without persistent sequelae (Hinkle et al., 2024; Hirschfeld and Schmidt, 2021). The observed linear association between psilocybin dose and adverse effects supports the notion of a graded pharmacodynamic response. Such a gradient facilitates a more predictable titration of therapeutic dose, potentially offering a wider therapeutic window compared to MDMA, which warrants closer monitoring due to its propensity for post-session complications (Fluyau et al., 2024).

Ayahuasca presented a more challenging picture due to the limited data available. The studies included generally reported gastrointestinal adverse events—most notably nausea, vomiting, and transient anxiety—likely related to its complex pharmacology and the presence of β-carboline alkaloids (dos Santos and Hallak, 2025; White et al., 2024). Although these side effects are described as minor and self-limiting, the small sample sizes and heterogeneity in dosing protocols mean that definitive conclusions about the full AE spectrum of ayahuasca must be drawn with caution.

4.2 Implications for Clinical Safety and Molecule Selection

The clear dose–response relationships observed for LSD, MDMA, and psilocybin provide an empirical basis for dose optimization in therapeutic settings. For LSD and psilocybin, which manifest predominantly transient adverse effects, the prospect of fine-tuning dosage to maximize therapeutic efficacy while minimizing side effects is promising (Breeksema et al., 2022; Hinkle et al., 2024). Conversely, the persistence of certain MDMA-induced effects necessitates additional vigilance and may, in some cases, prompt consideration of alternative agents if sustained adverse events outweigh the benefits of therapy (Colcott et al., 2024).

The selection of a specific molecule for psychedelic-assisted therapy should therefore be guided not only by therapeutic outcomes but also by the profile of associated adverse events. For instance, patients with lower tolerance for persistent side effects or for whom rapid recovery is essential may be more suitably treated with psilocybin or LSD, given their largely transient AE profiles (Hirschfeld and Schmidt, 2021; Hirschfeld et al., 2023). On the other hand, MDMA may be reserved for clinical scenarios where its unique pharmacodynamic actions are necessary and where appropriate post-treatment monitoring can be ensured (Colcott et al., 2024; Hinkle et al., 2024). The limited data on ayahuasca suggest that while its safety profile appears acceptable under controlled conditions, its utility may be restricted by the variability of its adverse effects and the need for further confirmation of its risk–benefit balance (dos Santos and Hallak, 2025; White et al., 2024).

4.3 Clinical Translation: Molecule Selection and Safety Management

Our dose–response findings indicate that AE burden scales with dose in-session for all three agents, while temporal patterns diverge by molecule: LSD and psilocybin AEs were predominantly *transient*, whereas MDMA showed *persistent* post-session effects (fatigue and sleep disturbance). These properties can be operationalized into molecule selection and monitoring strategies tailored to comorbidities and polypharmacy.

Screening and monitoring framework.

- **Pre-session:** cardiovascular screen (BP, HR, ECG if risk), psychiatric risk (panic spectrum, psychosis vulnerability, suicidality), medication reconciliation (serotonergic load, MAOIs, sympathomimetics), and baseline sleep/mood assessments.

Table 4: Results-informed molecule selection by clinical context.

Patient factor	**AE signal (this meta-analysis)**	**Prefer**	**Avoid / Use caution**
Cardiovascular risk	Psilocybin: transient BP rise; LSD: dizziness or nausea; MDMA: sympathomimetic activation.	Psilocybin or LSD (low dose)	MDMA (BP/HR elevation, fatigue, insomnia)
Anxiety-prone	LSD: perceptual anxiety; psilocybin: mild transient anxiety; MDMA: empathogenic but activating.	Psilocybin (moderate dose) or MDMA (with trained therapist)	High-dose LSD
Need rapid recovery	LSD/psilocybin: AEs limited to session; MDMA: next-day fatigue or sleep loss.	Psilocybin (shorter duration)	MDMA (persistent fatigue, insomnia)
GI vulnerability	Ayahuasca: GI AEs; psilocybin: nausea; LSD: minimal GI effects.	LSD	Ayahuasca or high-dose psilocybin
Older adults / polypharmacy	Increased sensitivity to BP, HR, and CNS stimulation.	Psilocybin or low-dose LSD	MDMA (sympathomimetic load)

- **In-session:** vital signs every 15–30 min for the first 2–3 h, then hourly; symptom checklists for anxiety, dizziness, nausea, headache; antiemetic protocol for psilocybin/ayahuasca; calm environment for LSD-related perceptual or anxiety spikes.
- **Post-session (24–72 h):** for MDMA, schedule proactive follow-up to detect *fatigue, low mood, insomnia*; for LSD/psilocybin, check for late headache or residual anxiety.

Choosing the right molecule for the right patient.

Table 5: Common co-medication classes and practical cautions.

Co-medication	**Caution**
SSRIs/SNRIs	May blunt psychedelic intensity; monitor BP and serotonergic load.
MAOIs (incl. RIMA)	Avoid with MDMA; ayahuasca already inhibits MAO-A.
TCAs/bupropion/stimulants	With MDMA: additive catecholaminergic stress—prefer alternatives.
Benzodiazepines	Useful for acute anxiety; avoid masking deterioration.
Antihypertensives	Continue; watch orthostasis post-session.

Polypharmacy guardrails.

Dose planning heuristics.

- **Start low where curves are steep:** LSD (anxiety/dizziness) and psilocybin (nausea/headache/BP).
- **Plan next-day recovery for MDMA:** anticipate fatigue or sleep loss; schedule rest and hydration.

- **Pre-empt predictable AEs:** antiemetic for psilocybin, hydration and jaw relaxation for MDMA, reassurance scripts for LSD.

4.4 Impact on Fragile Populations: Elderly and Comorbidities

Elderly patients experience altered pharmacokinetics from reduced clearance, increasing AE susceptibility (Tudorancea et al., 2025). Polypharmacy compounds risk of interactions, notably with serotonergic agents. Even transient AEs such as psilocybin-induced BP spikes could precipitate serious outcomes; conservative titration and ongoing monitoring are advised.

4.5 Threshold versus Gradient Effects

Traditional forest ORs aggregate binary outcomes, masking incremental dose effects. Our dose–response curves reveal threshold behaviors (LSD) and gradients (psilocybin), illuminating nonlinearities that can guide clinical titration (Hirschfeld et al., 2023; Hinkle et al., 2024).

4.6 Methodological Strengths and Limitations

Key strengths include dose–response modeling with time-window stratification and inclusion of 27 RCTs across molecules. Limitations stem from heterogeneity in AE reporting and small ayahuasca samples. Future harmonized AE frameworks would improve comparability and support robust molecule-level safety modeling (Breeksema et al., 2022; Hinkle et al., 2024).

4.7 Future Directions and Conclusions

This meta-analysis supports that AE occurrence and severity in psychedelic-assisted therapy scale with dose, differing by molecule in duration and intensity. LSD and psilocybin evoke transient AEs, while MDMA presents persistent effects requiring long-term monitoring. Findings advocate individualized dosing, stratified monitoring, and molecule choice informed by AE profiles and comorbidities. Future RCTs should expand elderly inclusion, employ continuous AE measures, and integrate real-time safety technologies to improve patient outcomes (Kelly et al., 2023).

Data and Code Availability

All analysis code, data extraction templates, and figure-generation scripts used in this study are openly available at the project's GitHub repository: `https://github.com/mickaeleskinazi/metaanalysis-psychedelics`. The repository includes harmonized datasets, preprocessing pipelines, statistical models (meta-analysis, dose–response modeling), and LaTeX export utilities. Raw trial-level data were derived from publicly available clinical publications and supplementary materials, and are available in structured format (CSV/XLSX) in the repository's `data/` directory.

Researchers and clinicians are encouraged to consult or reuse the codebase to replicate, extend, or adapt the methodology for related applications. All scripts are written in R (v4.3+) and use standard open-source packages. For transparency and reproducibility, each figure and table in the manuscript can be traced to a corresponding R script in the `scripts/` or `results/` directories.

The repository is maintained under a CC-BY 4.0 license.

References

Joost J Breeksema, Bouwe W Kuin, Jeanine Kamphuis, Wim van den Brink, Eric Vermetten, and Robert A Schoevers. Adverse events in clinical treatments with serotonergic psychedelics

and mdma: A mixed-methods systematic review. *Journal of Psychopharmacology*, 36(11): 1285–1307, 2022. doi: 10.1177/02698811221116926.

Julia Colcott, Alexandre A Guerin, Olivia Carter, Sally Meikle, and Gillinder Bedi. Side-effects of mdma-assisted psychotherapy: a systematic review and meta-analysis. *Neuropsychopharmacology*, 2024. doi: 10.1038/s41386-024-01865-8.

Rafael Guimarães dos Santos and Jaime Eduardo Cecilio Hallak. Ayahuasca: pharmacology, safety, and therapeutic effects. *CNS Spectrums*, 2025. doi: 10.1017/s109285292400213x.

Leah Feulner, Thanpicha Sermchaiwong, Nathan Rodland, and David Galarneau. Efficacy and safety of psychedelics in treating anxiety disorders. *The Ochsner Journal*, 23(4):334–344, 2023. doi: 10.31486/toj.23.0076.

Dimy Fluyau, Kattalai Kailasam, and Neelambika Revadigar. Rapid and prolonged antidepressant and antianxiety effects of psychedelics and 3,4-methylenedioxymethamphetamine: a systematic review and meta-analysis. *medRxiv*, 2024. doi: 10.1101/2024.06.17.24308787.

Jared T Hinkle, Marianna Graziosi, Sandeep M Nayak, and David B Yaden. Adverse events in studies of classic psychedelics: A systematic review and meta-analysis. *JAMA Psychiatry*, 2024. doi: 10.1001/jamapsychiatry.2024.2546.

Tim Hirschfeld and Timo T Schmidt. Dose–response relationships of psilocybin-induced subjective experiences in humans. *Journal of Psychopharmacology*, 2021. doi: 10.1177/0269881121992676.

Tim Hirschfeld, Johanna Prugger, Tomislav Majić, and Timo T Schmidt. Dose–response relationships of lsd-induced subjective experiences in humans. *Neuropsychopharmacology*, 2023. doi: 10.1038/s41386-023-01588-2.

Fabian Holze, Patrick Vizeli, Lorenz Ley, Urs Duthaler, Neha Varghese, Anja Eckert, Markus R Baumgartner, Erich Seifritz, and Matthias E Liechti. Direct comparison of the acute effects of lysergic acid diethylamide and psilocybin in a double-blind placebo-controlled study in healthy subjects. *Neuropsychopharmacology*, 47:1180–1187, 2022. doi: 10.1038/s41386-022-01297-2.

Daniel F Kelly, Keith Heinzerling, Akanksha Sharma, Shanthi Gowrinathan, Karina Sergi, and Regin Jay Mallari. Psychedelic-assisted therapy and psychedelic science: A review and perspective on opportunities in neurosurgery and neuro-oncology. *Neurosurgery*, 2023. doi: 10.1227/neu.0000000000002275.

Hossein Omidian and Alborz Omidian. Clinical research on lysergic acid diethylamide (lsd) in psychiatry and neuroscience. *Pharmaceuticals*, 18(4):499, 2025. doi: 10.3390/ph18040499.

Aryan Sarparast, Kelan Thomas, Benjamin Malcolm, and Christopher S Stauffer. Drug–drug interactions between psychiatric medications and mdma or psilocybin: a systematic review. *Psychopharmacology*, 239:2443–2461, 2022. doi: 10.1007/s00213-022-06083-y.

Mauro Scala, Chiara Fabbri, Paolo Fusar-Poli, Giorgio Di Lorenzo, Maria Ferrara, Andrea Amerio, Laura Fusar-Poli, Anna Pichiecchio, Carlo Asteggiano, Marco Menchetti, Diana De Ronchi, Giuseppe Fanelli, and Alessandro Serretti. The revival of psilocybin between scientific excitement, evidence of efficacy, and real-world challenges. *CNS Spectrums*, 2024. doi: 10.1017/S1092852924002268.

Ivona-Maria Tudorancea, Gabriela-Dumitrita Stanciu, Carla Torrent, Santiago Madero, Lucian Hritcu, and Bogdan-Ionel Tamba. Psychedelic interventions for major depressive disorder in the elderly: Exploring novel therapies, promise and potential. *Dialogues in Clinical Neuroscience*, 2025. doi: 10.1080/19585969.2025.2499458.

Eleanor White, Tom Kennedy, Simon Ruffell, Daniel Perkins, and Jerome Sarris. Ayahuasca and dimethyltryptamine adverse events and toxicity analysis: A systematic thematic review. *International Journal of Toxicology*, 2024. doi: 10.1177/10915818241230916.