Adverse Events in Studies of Classic Psychedelics: A Systematic Review and Meta-Analysis

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Adverse Events in Studies of Classic Psychedelics
A Systematic Review and Meta-Analysis

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IMPORTANCE A clear and comprehensive understanding of risks associated with psychedelic-assisted therapy is necessary as investigators extend its application to new populations and indications.

OBJECTIVE To assess adverse events (AEs) associated with classic psychedelics, particularly serious AEs (SAEs) and nonserious AEs (NSAEs) requiring medical or psychiatric evaluation.

DATA SOURCES The search for potentially eligible studies was conducted in the Scopus, MEDLINE, PsycINFO, and Web of Science databases from inception through February 8, 2024.

STUDY SELECTION Two independent reviewers screened articles of classic psychedelics (lysergic acid diethylamide [LSD], psilocybin, dimethyltryptamine [DMT], and 5-methoxy-N,N-dimethyltryptamine [5-MeO-DMT]) involving administration in clinical or research contexts.

DATA EXTRACTION AND SYNTHESIS AE data were extracted and synthesized by 2 reviewers and were used for random-effects meta-analysis of AE frequency and heterogeneity. Risk of bias assessment focused on AE ascertainment (eg, systematic assessment and quality of follow-up).

MAIN OUTCOMES AND MEASURES A hybrid approach was used for capture of all reported AEs following high-dose classic psychedelic exposure and confirmatory capture of AEs of special interest, including suicidality, psychotic disorder, manic symptoms, cardiovascular events, and hallucinogen persisting perception disorder. AEs were stratified by timescale and study population type. Forest plots of common AEs were generated, and the proportions of participants affected by SAEs or NSAEs requiring medical intervention were summarized descriptively.

RESULTS A total of 214 unique studies were included, of which 114 (53.3%) reported analyzable AE data for 3504 total participants. SAEs were reported for no healthy participants and for approximately 4% of participants with preexisting neuropsychiatric disorders; among these SAEs were worsening depression, suicidal behavior, psychosis, and convulsive episodes. NSAEs requiring medical intervention (eg, paranoia, headache) were similarly rare. In contemporary research settings, there were no reports of deaths by suicide, persistent psychotic disorders, or hallucinogen persisting perception disorders following administration of high-dose classic psychedelics. However, there was significant heterogeneity in the quality of AE monitoring and reporting. Of 68 analyzed studies published since 2005, only 16 (23.5%) described systematic approaches to AE assessment, and 20 studies (29.4%) reported all AEs, as opposed to only adverse drug reactions. Meta-analyses of prevalence for common AEs (eg, headache, anxiety, nausea, fatigue, and dizziness) yielded comparable results for psilocybin and LSD.

CONCLUSIONS AND RELEVANCE In this systematic review and meta-analysis, classic psychedelics were generally well tolerated in clinical or research settings according to the existing literature, although SAEs did occur. These results provide estimates of common AE frequencies and indicate that certain catastrophic events reported in recreational or nonclinical contexts have yet to be reported in contemporary trial participants. Careful, ongoing, and improved pharmacovigilance is required to understand the risk and benefit profiles of these substances and to communicate such risks to prospective study participants and the public.

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Multimedia

Supplemental content

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The medical uses of classic or serotonergic psychedelics—psilocybin, lysergic acid diethylamide (LSD), mescaline, dimethyltryptamine (DMT), and 5-methoxy-N,N-DMT (5-MeO-DMT)—feature prominently in discussions of contemporary psychiatry. Academic discourse continues to call for investigation of the benefits and harms of clinical psychedelic applications to calibrate expectations.[1-4] Therefore, it is critical to develop a comprehensive understanding of adverse events (AEs) that clinicians and patients may encounter during and following clinical psychedelic administration.

Prospective participants in classic psychedelic studies are informed of symptoms (eg, fear, panic, dysphoria, paranoia, and headaches) they could experience, as well as possible serious complications (eg, psychosis, suicidal ideation, and hypertensive emergency). However, contemporary meta-analytic data regarding these complications' frequency in research or clinical settings are limited. Early landmark studies providing risk estimates based on surveys of LSD-prescribing psychotherapists,[5,6] inpatient experimental regimens,[7,8] emergency department clinicians,[9] or a combination of these sources[10] are not generalizable to frameworks implementing widely adopted safety guidelines.[11]

Clarifying the risks of classic psychedelics is of immediate medical, scientific, and ethical relevance. Accurate AE estimates would improve informed consent discussions and provide a benchmark for novel applications of psychedelic-assisted therapy or novel psychedelic-related agents.[12,13] Therefore, we performed a systematic review of literature on classic psychedelic administration in clinical or research settings and a meta-analysis of published AE data. Of special interest were events meeting the International Conference on Harmonization (ICH) criteria for serious AEs (SAEs) and nonserious AEs (NSAEs) severe enough to require medical intervention or treatment. Our scope was limited to studies referencing psilocybin, LSD, DMT, and 5-MeO-DMT, which are the classic psychedelics most actively studied.

Key Points

Question What is the nature, frequency, and severity of adverse events (AEs) reported in studies of classic psychedelic administration in monitored clinical or research settings?

Findings Reports of serious AEs (SAEs) and nonserious AEs (NSAEs) requiring medical or psychiatric attention in classic psychedelic research were rare. In this systematic review and meta-analysis of 3504 participants from 114 studies, SAEs were reported for no healthy participants and approximately 4% of participants with preexisting neuropsychiatric disorders; however, for most studies, there was concern for underdetection or incomplete AE reporting.

Meaning Classic psychedelics were generally well tolerated in clinical or research environments according to existing literature, although SAEs and medically significant NSAEs did occur, which demonstrates the importance of improved pharmacovigilance to understand and quantify the risk and benefit profiles of classic psychedelic substances.

Methods

Study Design, Eligibility Criteria, and Search Strategy

The study protocol was preregistered in PROSPERO (CRD42023411107) and designed per the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guidelines.[14] The systematic review was designed to aggregate all peer-reviewed literature involving administration of classic psychedelics in clinical or research settings. A complete list of inclusion and exclusion criteria is provided in the eMethods in Supplement 1. Studies of human participants who were monitored following administration of LSD, psilocybin, DMT, or 5-MeO-DMT were eligible for inclusion. Institutional review board approval was not sought because, in cases where individual-level data were discussed, data were deidentified and means for reidentification were not considered reasonably possible.

We searched the Scopus, MEDLINE, PsycINFO, and Web of Science databases from their earliest available studies through February 8, 2024. Where reported, we reviewed US National Institutes of Health (NIH) ClinicalTrials.gov AE data. A sample search strategy is provided in the eMethods in Supplement 1.

Screening was conducted using Covidence (Veritas Health Innovation). Abstracts and full texts were screened by 2 independent coders (J.T.H. and M.G.). Disagreement was resolved through discussion and adjudication by other authors (S.M.N. and D.B.Y.) if needed.

Outcomes of Interest

We adopted a hybrid approach for exploratory capture of all reported AEs and confirmatory capture of prespecified AEs.[15] ICH consensus AE terminology was adopted, including the distinction between seriousness and severity—that is, an AE is considered serious if it is life-threatening or results in death, inpatient hospitalization, or prolongation of existing hospitalization; results in significant disability or incapacity; constitutes a congenital defect; or requires intervention to prevent 1 of these outcomes. Key outcomes included SAEs and NSAEs severe enough to require medical intervention (eg, restricted medication, physician evaluation, or intravenous infusions) as opposed to self-limited or participant-managed AEs. SAEs were quantified separately, mirroring the format of the NIH ClinicalTrials.gov platform. Prespecified AEs of special interest were psychotic disorder, manic symptoms, suicidal ideation or behavior, cardiovascular events, and hallucinogen persisting perception disorder. We calculated these AEs' frequencies separately among NSAEs requiring medical intervention. Study authors were contacted by email to clarify specifics of reported AEs when necessary.

AEs were stratified by population, including the following categories: (1) healthy participants without active medical or neuropsychiatric disorders; (2) outpatient participants with neuropsychiatric disorders; and (3) inpatient participants requiring continuous hospital or facility care for a neuropsychiatric condition (including psychotic disorders) at the time of psychedelic exposure. AEs were also stratified by timescale as (1) acute (typical period of subjective effects); (2) sub-

acute (between the acute period resolution and 48 hours post-administration); or (3) delayed events (after 48 hours). Acute and subacute events were infrequently differentiated and were therefore pooled for analysis as early events.

To avoid underestimation of AEs associated with conventional dosing, we restricted analysis to psychedelic dose ranges (eg, LSD, ≥30 µg; psilocybin, >3 mg/70 kg oral or any intravenous dose; and intravenous DMT, ≥0.2 mg/kg). AEs with significant symptomatologic overlap were grouped (eg, gastrointestinal upset and abdominal pain) and the more frequent AE was tabulated.

Statistical Analysis

Statistical analysis was performed in R version 4.2.2 (The R Foundation). The R package meta[16] was used to calculate meta-analytic estimates of specific AE rates and heterogeneity (I^2). For each AE, a random intercept logistic regression model calculated an overall proportion with 95% CIs with the inverse variance method. In cases where a single study reported proportions for separate groups of participants, the random-effects model was organized as a 3-level model (ie, study, participant group, and participant) with study identifier as a clustering variable to account for within-study correlations. Meta-analysis was only performed for AEs for which data from at least 3 independent studies were available for analysis.

Risk of Bias Assessment

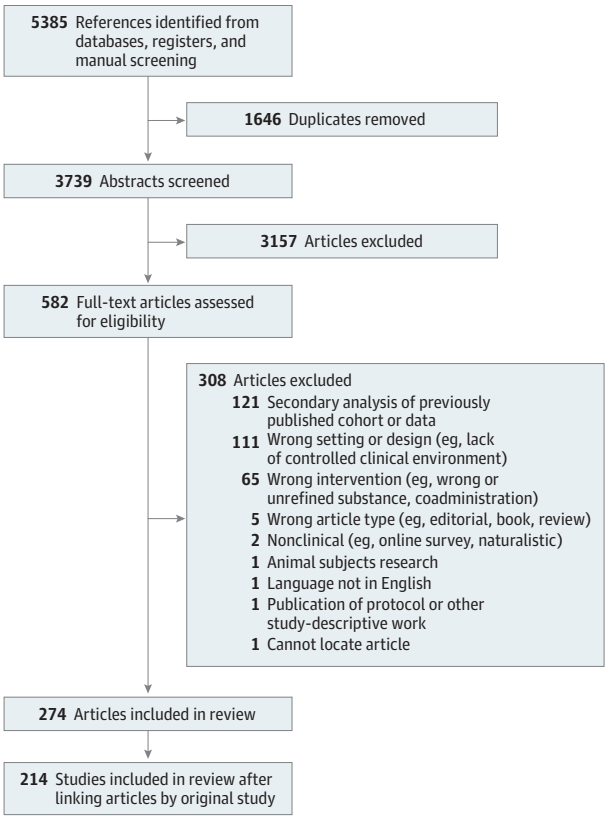
Because of the diversity of study designs included for this review, we modified the Newcastle-Ottawa Scale for cohort studies[17] to assess risk of bias in the ascertainment of AE outcomes (eMethods in Supplement 1). We created 2 items related to ascertainment: all events reported (ie, whether all AEs were described as opposed to a subset, such as suspected adverse drug reactions) and severity framework (ie, whether a system for assessing severity was described).

Results

The search strategy (**Figure 1**) identified 3739 unique records, of which 274 met inclusion criteria. Articles published using the same dataset were merged, resulting in 214 unique studies. Among these, 114 studies (53.3%) reported AEs experienced by 155 groups of participants (N = 3504). Study characteristics are presented in eTable 1 in Supplement 1. After stratification, there were 95 groups of healthy participants (n = 1726), 39 groups of outpatient participants (n = 934), and 21 groups of inpatient participants (n = 844). All inpatient studies were conducted between 1951 and 1972. Of 844 inpatient participants, at least 139 (16.5%) had schizophrenia or another psychotic disorder. Primary diagnoses (where known) for inpatient participants and drug administration schedule and dosage are provided in eTable 2 in Supplement 1. The distribution of study drug by year (**Figure 2**) visualizes trends in psychedelic research.

Rates of SAEs and NSAEs requiring medical intervention, stratified by study population and timescale, are summarized in **Table 1**. In the 2 identified studies of 5-MeO-DMT, 1 in healthy participants (n = 22)[18] and the other among participants with treatment-resistant depression (n = 16),[19] no SAEs or NSAEs of medical or psychiatric significance were reported.

Figure 1. PRISMA Flowchart of Literature Search



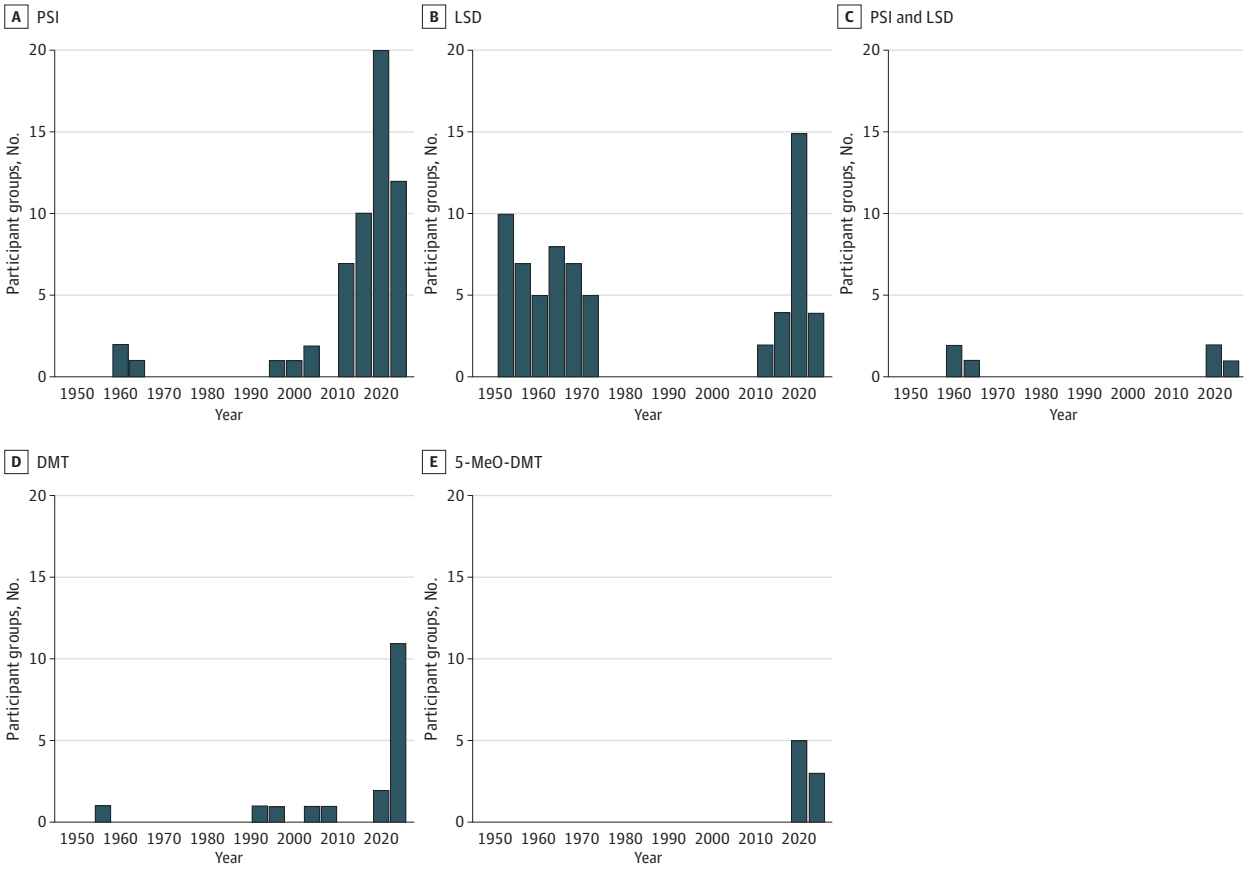
SAEs

Early SAEs

In studies of healthy participants administered psilocybin (n = 659), LSD (n = 372) or DMT (n = 139), no early SAEs were reported. No outpatient participants administered psilocybin (n = 618) experienced an early SAE. Among 128 outpatient participants given LSD, 1 participant (0.8%) who received LSD, 200 ug, in a study for anxiety[20] experienced an acute and subacute SAE involving "acute transient anxiety and delusions" refractory to lorazepam, requiring olanzapine and overnight observation. Symptoms resolved by morning without recurrence; the participant later received a second reduced LSD dose, 100 µg. In DMT studies,[21] 1 participant of 6 (16.7%) with depression and a clinical history suggestive of orthostasis experienced a substantial blood pressure drop, which was reported as an SAE.

Early SAEs were reported for 11 of 517 (2.1%) psychiatric inpatient participants who were administered LSD. There were 4 reported episodes of psychosis terminated with electroconvulsive therapy; at least 2 affected participants had prior psychotic episodes.[22] Provoking doses were unclear, but 150 participants received doses of LSD, up to 2000 µg (roughly 10-fold the current norms of a therapeutic dose), in up to 10

Figure 2. Articles Reporting Adverse Event Data by Year and Study Drug



Participant groups refers to independent groups of participants (n = 155) assigned to receive the same dosing regimen of the same psychedelic(s). For example, in a study with 2 groups of participants (1 given psilocybin and the other given LSD [or given different doses of the same psychedelic]), the groups would be separated for analysis by participant group and drug. The PSI and LSD condition refers to participants given LSD and psilocybin on separate study occasions (ie, no coadministration). 5-MeO-DMT indicates 5-methoxy-N,N-dimethyltryptamine; DMT, dimethyltryptamine; LSD, lysergic acid diethylamide; PSI, psilocybin.

sessions. Another participant in this study with preexisting epilepsy who was not taking anticonvulsants experienced a seizure.[22] Two participants in studies of LSD for alcohol use disorder also had seizures (1 having a history of delirium tremens), and a third participant experienced confusion, delaying discharge.[23,24] Again, provoking doses were not specified, but maximum doses were 600 to 800 µg. Finally, a study of 65 inpatient participants with treatment-resistant psychotic disorders who were given LSD without a concomitant antipsychotic noted 3 serious complications of mania with psychotic features following doses between 40 and 73 µg in participants with prior "affective psychosis": 1 participant developed mania with psychotic features after 3 LSD doses, which persisted for 3.5 months; another participant became paranoid after 1 LSD dose and attempted suicide 3 days later, then developed manic symptoms lasting at least 4 months; and the third participant developed alternating manic and depressive symptoms with psychotic features after 1 LSD dose, which lasted up to 4 months. All required inpatient antipsychotic therapy to recover to their pre-LSD state.[25]

Delayed-Phase SAEs

Follow-up periods to monitor for delayed SAEs varied by study population and drug, but the median (range) follow-up period was approximately 12 (1-60) weeks. No SAEs were noted during follow-up of healthy participants administered LSD (n = 258), psilocybin (n = 319), or DMT (n = 109).

Of outpatient participants given LSD, 8 of 155 (5.2%) experienced SAEs during follow-up, although the relation to the study drug was unclear. One outpatient participant died of aortic stenosis 5 months after administration of LSD.[26] The remaining 7 SAEs occurred in 2 studies[20,27] and were deemed unrelated to LSD: 2 pregnancies followed by spontaneous abortion; a planned nasal surgery; a radial fracture at a personal event unrelated to the study procedures; a suspected transient ischemic attack (2 weeks following LSD dose in a participant with Marfan syndrome and at least 4 prior suspected transient ischemic attack episodes); and 2 events (death and esophageal cancer metastasis) during a 1-year follow-up period that were attributed to preexisting life-threatening illnesses (typically cancer or severe autoimmune disease).

Table 1. Rates of SAEs and NSAEs Requiring Medical or Psychiatric Intervention in Psychedelic Studies

Population	Phase[a]	LSD			Psilocybin			DMT		
		Groups (participants), No.	Follow-up, median (range), wk	Outcomes, No. (%)[b]	Groups (participants), No.	Follow-up, median (range), wk	Outcomes, No. (%)[b]	Groups (participants), No.	Follow-up, median (range), wk	Outcomes, No. (%)[b]
SAEs										
Outcome: any										
Healthy	Early	22 (372)	NA	0	29 (659)	NA	0	14 (139)	NA	0
	Delayed	8 (258)	8.5 (1-52)	0	14 (379)	13 (1-60)	0	12 (109)	4 (1-52)	0
Outpatient	Early	6 (128)	NA	1 (0.8)	25 (618)	NA	0	1 (6)	NA	1 (16.7)
	Delayed	6 (155)	52 (1-52)	8 (5.2)	24 (584)	14 (4-52)	23 (3.9)	1 (6)	1 (1-1)	0
Inpatient	Early	8 (517)	NA	11 (2.1)	NA	NA	NA	NA	NA	NA
	Delayed	11 (611)	26 (1-52)	9 (1.5)	NA	NA	NA	NA	NA	NA
NSAEs requiring medical or psychiatric intervention										
Outcome: suicidality										
Healthy	Early	18 (321)	NA	0	26 (618)	NA	0	14 (139)	NA	0
	Delayed	8 (258)	8.5 (1-52)	0	14 (379)	13 (1-60)	0	12 (109)	4 (1-52)	0
Outpatient	Early	5 (97)	NA	0	23 (464)	NA	1 (0.2)	1 (6)	NA	0
	Delayed	5 (118)	52 (1-52)	0	20 (553)	14.5 (6-52)	3 (0.5)	1 (6)	1 (1-1)	0
Inpatient	Early	4 (158)	NA	0	NA	NA	NA	NA	NA	NA
	Delayed	6 (427)	24 (4-52)	0	NA	NA	NA	NA	NA	NA
Outcome: psychotic disorder										
Healthy	Early	13 (284)	NA	1 (0.4)	27 (631)	NA	1 (0.2)	14 (139)	NA	0
	Delayed	8 (258)	8.5 (1-52)	0	14 (379)	13 (1-60)	0	12 (109)	4 (1-52)	0
Outpatient	Early	5 (97)	NA	1 (1)	25 (618)	NA	1 (0.2)	1 (6)	NA	0 (0%)
	Delayed	5 (118)	52 (1-52)	1 (0.8)	22 (573)	14 (3-52)	0	1 (6)	1 (1-1)	0
Inpatient	Early	4 (237)	NA	0	NA	NA	NA	NA	NA	NA
	Delayed	4 (115)	30 (4-52)	0	NA	NA	NA	NA	NA	NA
Outcome: manic symptoms										
Healthy	Early	18 (340)	NA	2 (0.6)	27 (632)	NA	0	14 (139)	NA	0
	Delayed	8 (258)	8.5 (1-52)	0	14 (379)	13 (1-60)	0	12 (109)	4 (1-52)	0
Outpatient	Early	3 (53)	NA	0	25 (618)	NA	0	1 (6)	NA	0
	Delayed	5 (118)	52 (1-52)	0	20 (553)	14.5 (3-52)	0	1 (6)	1 (1-1)	0
Inpatient	Early	1 (65)	NA	0	NA	NA	NA	NA	NA	NA
	Delayed	2 (93)	6 (4-8)	0	NA	NA	NA	NA	NA	NA
Outcome: cardiac events										
Healthy	Early	8 (181)	NA	0	26 (628)	NA	3 (0.5)	11 (108)	NA	3 (2.8)
	Delayed	6 (147)	15 (1-52)	0	14 (379)	13 (1-60)	0	12 (109)	4 (1-52)	1 (0.9)
Outpatient	Early	3 (53)	NA	0	25 (618)	NA	1 (0.2)	1 (6)	NA	0
	Delayed	6 (155)	52 (1-52)	0	21 (558)	14 (3-52)	0	1 (6)	1 (1-1)	0
Inpatient	Early	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Delayed	1 (28)	8 (8-8)	0	NA	NA	NA	NA	NA	NA
Outcome: HPPD										
Healthy	Early	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Delayed	8 (324)	17 (1-134)	0	13 (371)	26 (1-134)	0	11 (97)	4 (1-52)	0
Outpatient	Early	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Delayed	4 (96)	52 (1-52)	0	21 (555)	14 (6-52)	0	1 (6)	1 (1-1)	0
Inpatient	Early	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Delayed	1 (28)	8 (8-8)	0	NA	NA	NA	NA	NA	NA

(continued)

Table 1. Rates of SAEs and NSAEs Requiring Medical or Psychiatric Intervention in Psychedelic Studies (continued)

Population	Phase[a]	LSD			Psilocybin			DMT		
		Groups (participants), No.	Follow-up, median (range), wk	Outcomes, No. (%)[b]	Groups (participants), No.	Follow-up, median (range), wk	Outcomes, No. (%)[b]	Groups (participants), No.	Follow-up, median (range), wk	Outcomes, No. (%)[b]
Outcome: other NSAEs[c]										
Healthy	Early	17 (297)	NA	0	27 (630)	NA	0	14 (139)	NA	2 (1.4)
	Delayed	7 (234)	13 (1-52)	0	14 (379)	13 (1-60)	1 (0.3)	12 (109)	4 (1-52)	2 (1.8)
Outpatient	Early	6 (128)	NA	3 (2.3)	25 (618)	NA	14 (2.3)	1 (6)	NA	0
	Delayed	5 (118)	52 (1-52)	0	22 (573)	14 (6-52)	22 (3.8)	1 (6)	1 (1-1)	0
Inpatient	Early	8 (466)	NA	11 (2.4)	NA	NA	NA	NA	NA	NA
	Delayed	6 (278)	10 (1-52)	3 (1.1)	NA	NA	NA	NA	NA	NA

Abbreviations: DMT, dimethyltryptamine; HPPD, hallucinogen persisting perception disorder; LSD, lysergic acid diethylamide; NA, data not available (ie, no relevant studies found); NSAE, nonserious adverse event; SAE, serious adverse event.

[a] Phase was dichotomized as early (ie, acute and subacute, up to 48 hours) or delayed (any period of observation or follow-up beyond 48 hours).

[b] Adverse event rates are presented descriptively as simple outcome percentages of exposed population size for each combination of study drug, population type, and phase.

[c] NSAEs clearly requiring or entailing a known medical or psychiatric intervention that did not fall into 1 of the prespecified outcome categories (ie, suicidality, psychotic disorder, manic symptoms, cardiac events, and HPPD) were classified as other events.

In high-dose psilocybin studies, 23 of 584 outpatient participants (3.9%) experienced delayed SAEs. Eleven of these 23 (47.8%) had treatment-resistant depression and experienced a total of 17 SAEs over 12 weeks of follow-up, including suicidal ideation (5 events), suicidal behavior (3 events), nonsuicidal intentional self-injury (4 events), adjustment disorder (2 events), worsening depression (1 event), codeine withdrawal syndrome (1 event), and hospitalization (1 event).[28] All 3 participants exhibiting suicidal behavior were nonresponders per Montgomery-Åsberg Depression Rating Scale scores. One participant with major depressive disorder was hospitalized for worsening depression and suicidal ideation.[29] A participant with history of stimulant-induced psychosis relapsed and used methamphetamine and cocaine, after which he experienced a brief psychotic episode and a nonlethal suicide attempt.[30] One participant in a study for alcohol use disorder was admitted to an inpatient alcohol detoxification program.[31] A participant in a study of psilocybin for depression in cancer was diagnosed with a *Helicobacter pylori* infection during follow-up and was prescribed standard quadruple therapy.[32] The remaining SAEs following psilocybin therapy included 6 deaths of progression of preexisting cancers,[33-35] 1 episode of acute cholecystitis, and a pneumothorax during biopsy for metastatic disease.[30]

In studies enrolling participants with life-threatening illnesses, deaths occurring during follow-up are described above. Several studies disclosed deaths occurring after study completion; this practice is atypical, and as such, they are not tabulated in Table 1. However, for completeness, these deaths included: 3 deaths in a study of LSD for anxiety[27] and 30 deaths across 3 studies of psilocybin for anxiety and mood disorders in participants with life-threatening cancer diagnoses during a period of up to approximately 5 years of postdosing follow-up.[33-35]

Nine of 611 inpatient participants (1.5%) given LSD experienced delayed SAEs. In the aforementioned study involving repeated doses of LSD, up to 2000 µg, there was 1 suicide death and 1 unexplained death in the weeks following LSD treatment.[22] Another study that administered LSD, up to 1000 µg, to 162 inpatient participants with neurotic and personality disorders between 1 and 50 times recorded 3 suicide attempts and 1 death from alcohol or barbiturate exposure in the 18 months following discharge.[36] The remaining 3 LSD inpatient participant SAEs were continuations of the early-phase manic episodes experienced by inpatient participants with preexisting affective psychoses.[25]

NSAEs Requiring Medical Intervention

Rates of NSAEs for which medical or psychiatric intervention was described or clearly indicated are presented in Table 1. Due to spatial constraints, only those events pertaining to suicidality are presented in narrative form here. Descriptions of all other significant NSAEs are provided in Supplement 1.

Suicidality

We identified no published NSAEs involving suicidal ideation or behavior requiring medical or psychiatric attention among healthy participants administered a classic psychedelic. Studies of LSD in psychiatric inpatient participants also did not describe any such events.

Among outpatient participants administered psilocybin, 3 of 553 participants (0.5%) experienced worsening suicidal ideation, with 1 such episode starting on the day of dosing.[28] One suicide death occurred in a participant with life-threatening cancer and significant comorbid anxiety and depression who had received a placebolike dose of psilocybin, 1 mg per 70 kg, after which they "reported feeling bored and was discontinued from the study after insisting upon leaving this study session early."[33] Under the study design described in the informed consent document, the participant was told that they would receive a dose of psilocybin in a second session. Prior to dying by suicide, the participant demonstrated "no behavioral impairment and no adverse sequelae on follow-up later that day and over the subsequent several days." This event was

not included in our analysis because the participant had not received a dose with psychoactive effects (although the dose of 1 mg/70 kg could be considered a nonpsychoactive microdose).

Common Acute and Subacute AEs: Meta-Analyses of Proportion

For each AE reported by at least 3 independent studies, we generated meta-analytic estimates of frequency with 95% CIs (**Table 2**). Given the exploratory nature of the analysis, these data are presented descriptively, without attempts to test for statistically significant differences. As expected, most AEs exhibit at least moderate heterogeneity (ie, $I^2 \geq 50\%$). We generated forest plots of common AEs for which the most data were available, specifically headache, anxiety, nausea, fatigue, and dizziness (eFigures 1-5 in Supplement 1). We considered that certain common AEs may be influenced by the presence of preexisting neuropsychiatric disorders and therefore produced a stratified analysis for LSD and psilocybin, which had sufficient data for this purpose (eTables 3 and 4 in Supplement 1).

Risk of Bias Assessment

Risk of bias scores were collected using a modified Newcastle-Ottawa scale (eMethods in Supplement 1) for biases that could affect AE outcome detection and reporting. Scores for included articles are presented in eTable 5 in Supplement 1. These scores were used to test whether there were differences between contemporary and first-wave psychedelic research with respect to the frequency of biases that could affect AE outcome detection and reporting (**Table 3**). χ^2 Tests were used to compare early (pre-2005) to current (2005-February 2024) studies with respect to the frequencies at which they controlled for biases that may have reduced detection or communication of adverse events (ascertainment bias). Only 16 of 68 studies published since 2005 (23.5%) clearly described a systematic approach to assessing AEs, which is not significantly increased compared with earlier studies, of which 17% included a systematic approach ($\chi^2 = 0.3$; $df = 1$; $P = .58$). There were statistically significant increases in the rates at which contemporary studies addressed other domains of ascertainment bias compared with older studies, including attribution of event causality (29% in recent studies vs 0% in early studies), documentation of severity (28% vs 2.1%), duration of follow-up (84% vs 35%), and adequacy of follow-up (79% vs 22%).

Discussion

In supportive clinical or research settings, AEs with plausible relatedness to a classic psychedelic experience requiring medical or psychiatric attention are relatively rare, but do occur. No cases of sustained psychosis were reported in participants without preexisting psychotic illness; benign flashback experiences have been reported, but no cases of hallucinogen persisting perception disorder were identified, despite the estimated prevalence of 4.2% among recreational users.[37] Similarly, only participants with a preexisting depressive disorder developed suicidality requiring psychiatric attention, and we identified no suicides following high-dose classic psychedelic administration in published studies. This is reassuring, given the 0.1% to 0.2% absolute risk for suicide deaths in placebo conditions of antidepressant trials.[38-40] One suicide death was observed following a low, placebolike, nonpsychoactive psilocybin dose, 1 mg/70 kg. This death may have been causally related to the psilocybin exposure, although indirect explanations, such as disappointment or demoralization, were deemed more plausible.

Critically, we believe the assessment and reporting of AEs in classic psychedelic research should be improved. We found that 114 of 214 studies meeting inclusion criteria (53.3%) reported at least some AE data, and while this is above the median of 46% among clinical trials of health interventions, there is room for improvement in this field and others.[41] Approximately 70% of contemporary studies reported only suspected adverse drug reactions (ie, those deemed possibly attributable to the investigational product) rather than AEs properly understood (ie, any undesirable event, regardless of causality assessment). Therefore, we can neither exclude the possibility that the studies reporting AEs did so incompletely nor speculate on the possibility of serious or medically significant AEs in the 47% of studies without AE data.

The 2023 US Food and Drug Administration (FDA) draft guidance for psychedelic drug research recommends using validated scales as part of AE monitoring, tabulating several psychedelic phenomena (eg, emotional lability, euphoria, and hallucinations) among AEs, and providing narrative descriptions of AEs in detail, including phenomena theorized to be linked to therapeutic efficacy (eg, euphoric or blissful states).[42] Targeted questions or questionnaires could also mitigate well-characterized biases affecting both investigators (eg, ascertainment and confirmation biases) and participants (eg, response bias) and are increasingly called for, particularly in psychiatric medication trials.[43] Only 16 of 68 post-2005 studies (23.5%) described clear and systematic methods for ascertaining AEs and describing their severity, suggesting the possibility of systematic AE underdetection. This methodological variation likely explains some heterogeneity in our meta-analysis, as well as the lower-than-expected rates of certain events (eg, visual illusions). Existing scales, such as the 5-Dimensional Altered States of Consciousness rating scale and the Challenging Experiences Questionnaire, may be complementary in this endeavor, but we believe they should not substitute for dedicated AE monitoring.

Acutely challenging or unpleasant experiences can be highly meaningful and potentially therapeutic, as is frequently the case in psychotherapy,[44] but recording aversive experiences as AEs is pragmatic and necessary. In particular, the presence (and absence) of any AEs deemed relevant to serious theoretical complications of psychedelic use, such as precipitation of an affective or psychotic illness, persisting perceptual disturbances, and cardiac toxicity, should be clearly reported. Documenting anomalous reactions and behaviors during sessions and the steps taken to maintain participant and staff safety[44] could inform contingency planning. Data on perisession use of professional medical services may also inform postsession practices. More broadly, the work reported herein

Table 2. Meta-Analysis of Common Adverse Events in Psychedelic Trials[a]

Event	Psilocybin			LSD			DMT		
	Groups (participants), No.	Proportion affected, % (95% CI)	I^2	Groups (participants), No.	Proportion affected, % (95% CI)	I^2	Groups (participants), No.	Proportion affected, % (95% CI)	I^2
Abdominal discomfort	9 (273)	7.6 (4.2-13.2)	24.3	NA	NA	NA	NA	NA	NA
Abnormal bodily sensations	10 (279)	24.5 (10.8-46.7)	81.9	10 (219)	45.2 (29-62.4)	74.6	NA	NA	NA
Abnormal taste in mouth	NA	NA	NA	3 (57)	31.2 (11.8-60.6)	70.9	NA	NA	NA
Agitation or restlessness	9 (301)	9.2 (3.8-20.7)	67.4	16 (279)	36.9 (24.9-50.7)	63.7	NA	NA	NA
Anxiety	26 (803)	22.3 (15.8-30.4)	73.8	16 (281)	29.5 (22.1-38.3)	38.6	11 (88)	16.3 (9.7-26.0)	0
Appetite change	5 (201)	20.9 (6.4-50.5)	88.3	9 (208)	45 (34.8-55.7)	50.9	NA	NA	NA
Blurred or unfocused vision	5 (141)	11.4 (2.9-35.1)	84.2	4 (79)	34.7 (18.3-55.7)	60.3	NA	NA	NA
Bruxism	NA	NA	NA	4 (128)	41.5 (33.2-50.2)	0	NA	NA	NA
Change in speed of thoughts	NA	NA	NA	5 (67)	37.7 (10.6-75.6)	79.7	NA	NA	NA
Chest pain or pressure	3 (71)	19.7 (2.2-72.7)	89.5	NA	NA	NA	NA	NA	NA
Concentration or memory difficulty	7 (226)	37.7 (14.0-69.2)	88	16 (299)	52.7 (34.0-70.7)	70.8	NA	NA	NA
Delusional thoughts	NA	NA	NA	10 (179)	12.1 (5.6-24.3)	34.5	NA	NA	NA
Depersonalization	NA	NA	NA	5 (69)	31 (9.8-64.8)	67.6	NA	NA	NA
Derealization, dissociation, or sense of surrealness	5 (108)	27.3 (9.6-57.0)	76	7 (118)	33.5 (19.2-51.6)	64	NA	NA	NA
Despair, distress, or fear	5 (113)	38.1 (25.3-52.9)	59.4	NA	NA	NA	NA	NA	NA
Diarrhea	4 (138)	3.3 (1.1-9.0)	0	NA	NA	NA	NA	NA	NA
Difficulty sleeping	10 (404)	6.6 (3.9-10.8)	6.1	3 (140)	2 (0.6-6.8)	0	NA	NA	NA
Disorientation or confusion	10 (321)	11.3 (3.9-28.4)	81.4	10 (125)	18.7 (6.8-42.0)	73.3	NA	NA	NA
Dizziness	13 (449)	17.1 (7.7-33.8)	81.5	8 (187)	46.7 (23.0-72.1)	82.1	11 (92)	12.5 (6.9-21.6)	0
Dull feeling	NA	NA	NA	4 (128)	36 (28.1-44.6)	0	NA	NA	NA
Fatigue or weakness	17 (581)	26.6 (11.9-49.2)	87.8	19 (308)	55.9 (40.0-70.8)	63.4	7 (67)	38.8 (11.7-75.2)	52.4
Feeling cold	3 (90)	6.1 (2.6-13.9)	0	8 (129)	38.3 (20.5-59.8)	74.4	NA	NA	NA
Hallucination, nonvisual	5 (147)	9.4 (3.2-24.7)	55.9	8 (123)	17.9 (9.9-30.2)	37.7	NA	NA	NA
Hallucination, visual	5 (111)	46.6 (13.3-83.2)	78	12 (171)	28.6 (18.1-42)	54	NA	NA	NA
Headache	28 (820)	39.9 (30.8-49.7)	78.5	17 (305)	33.9 (19.1-52.6)	67.3	11 (92)	25.5 (10.5-49.9)	43
Hearing change or tinnitus	5 (106)	17.8 (4.8-48.2)	76.9	5 (95)	32 (23.4-42.2)	0	NA	NA	NA
Hypertension	12 (302)	19.1 (9.9-33.6)	70.5	NA	NA	NA	4 (37)	10.5 (3.6-26.8)	0
Illusion, nonvisual	6 (202)	20.7 (5.8-52.4)	85.5	NA	NA	NA	NA	NA	NA
Illusion, visual	4 (58)	58.2 (23.2-86.5)	69.6	9 (158)	39.9 (23.0-59.6)	69.2	NA	NA	NA
Incoordination	5 (112)	42.5 (19.3-69.6)	79.5	16 (246)	42.5 (33.5-52.1)	41.4	NA	NA	NA
Laughter	NA	NA	NA	5 (70)	34.9 (15.7-60.7)	46.7	NA	NA	NA
Migrainoid headache	6 (157)	11.6 (4.8-25.3)	58.7	NA	NA	NA	NA	NA	NA
Mood depression	12 (375)	19.2 (8.0-39.3)	83.9	10 (164)	18.8 (7.6-39.5)	72	5 (61)	11 (5.2-21.8)	0
Mood elevation	7 (277)	31.4 (11.1-62.6)	87.3	16 (224)	37.3 (23.7-53.3)	57.3	NA	NA	NA

(continued)

Table 2. Meta-Analysis of Common Adverse Events in Psychedelic Trials[a] (continued)

Event	Psilocybin			LSD			DMT		
	Groups (participants), No.	Proportion affected, % (95% CI)	I^2	Groups (participants), No.	Proportion affected, % (95% CI)	I^2	Groups (participants), No.	Proportion affected, % (95% CI)	I^2
Mood lability or change	5 (244)	20.1 (4.4-57.7)	89.8	NA	NA	NA	NA	NA	NA
Musculoskeletal pain	8 (255)	9.6 (4.8-18.4)	55.5	NA	NA	NA	NA	NA	NA
Mydriasis	NA	NA	NA	7 (76)	72.6 (30.6-94.1)	58.4	NA	NA	NA
Nausea	25 (718)	24.2 (17.9-31.8)	69.5	21 (337)	32.1 (23.4-42.3)	48.3	12 (103)	11.7 (6.7-19.8)	0
Odor sensitivity	3 (132)	17.8 (6.1-42.1)	80.9	5 (149)	29.9 (22.8-38.1)	30.9	NA	NA	NA
Palpitations	5 (164)	10.8 (2.0-42.1)	89.6	NA	NA	NA	10 (77)	18.4 (11.0-29.1)	0
Panic or flashbacks	3 (98)	11.5 (1.6-50.8)	88.5	4 (104)	7.8 (4.0-14.9)	0	NA	NA	NA
Paranoia	14 (330)	12.2 (6.9-20.9)	56.7	10 (135)	17.2 (8.3-32.2)	59.4	NA	NA	NA
Paresthesias or numbness	9 (300)	12.7 (5.4-27.1)	76.8	10 (132)	43.6 (18.9-72.0)	58	9 (85)	21.7 (10.2-40.4)	4.6
Salivation change	6 (191)	17.5 (9.9-29.0)	57	12 (265)	40.9 (29.7-53.1)	61.5	NA	NA	NA
Shortness of breath	3 (112)	7.9 (1.3-35.9)	64.1	3 (59)	36.7 (4.5-87.6)	76.8	NA	NA	NA
Somnolence	6 (231)	12.6 (3.0-39.7)	85.8	8 (119)	31.8 (23.8-41.1)	0	NA	NA	NA
Synesthesia	3 (43)	18.9 (7.3-40.7)	33.9	3 (75)	27.3 (9.3-57.8)	82.8	NA	NA	NA
Tachycardia	4 (68)	8.9 (4.1-18.5)	0	NA	NA	NA	NA	NA	NA
Tearfulness	4 (154)	41.6 (5.6-89.6)	88.7	NA	NA	NA	NA	NA	NA
Time distortion	7 (154)	30.8 (12.6-57.9)	79	11 (170)	42.3 (25.5-61.1)	67.4	NA	NA	NA
Tremulousness	4 (103)	34.5 (14.6-62.0)	83.8	8 (156)	37.2 (22.5-54.6)	65.7	NA	NA	NA
Urinary symptoms	5 (181)	5.8 (1.8-16.9)	64.4	5 (123)	18.5 (12.3-27)	27.8	NA	NA	NA
Vivid dreams	4 (110)	3.4 (1.2-9.2)	0	3 (36)	13.9 (2.6-49.3)	46.6	NA	NA	NA
Vomiting	9 (271)	4.8 (2.6-8.8)	0	NA	NA	NA	NA	NA	NA
Warmth or flushing	6 (215)	12.4 (4.2-31.3)	75.7	14 (251)	35.4 (29.5-41.8)	13.8	8 (68)	16.3 (7.8-30.8)	0
Yawning	3 (94)	11.4 (3.3-32.6)	60.2	NA	NA	NA	NA	NA	NA

Abbreviations: DMT, dimethyltryptamine; LSD, lysergic acid diethylamide; NA, data not available (ie, no relevant events found among analyzed studies).

[a] Adverse events of all severity reported by at least 3 independent studies reported were analyzed with meta-analysis of proportions to generate estimates of adverse event frequency (proportion), with 95% CIs and conventional heterogeneity statistics (I^2).

Table 3. Methods to Address Risk of Bias in Adverse Event (AE) Monitoring and Reporting by Era

Method[a]	Studies demonstrating method by period, No. (%)		χ^2	*P* value
	1951-2004 (n = 46)	2005-2024 (n = 68)		
Systematic AE assessment	8 (17)	16 (24)	0.3	.58
All AEs reported	0	20 (29)	14.4	<.001
Severity framework	1 (2)	19 (28)	10.9	<.001
Adequate follow-up duration	16 (35)	57 (84)	26.6	<.001
Adequate follow-up retention	10 (22)	54 (79)	34.8	<.001

[a] A modified version of the Newcastle-Ottawa scale (eTable 1 in the Supplement) was used to assess for biases that could affect AE outcome detection and reporting. The number and proportion of studies that described an approach for minimizing the impact of each bias is provided. χ^2 Tests were used to test whether there were statistically significant differences between early (pre-2005) and contemporary (post-2005) psychedelic studies. Bonferroni-corrected significance cutoff for the 5 tests performed was $P < .01$.

may be situated alongside calls for investigators to attend to broader forms of harm associated with psychedelic-assisted therapy study procedures.[1]

We are developing generalizable templates for detecting and characterizing AEs that can be incorporated into existing protocols to account for FDA recommendations. Since AEs may

be subjectively or functionally impactful but not hazardous to participant health (eg, a debilitating headache), we recommend adopting ICH language to differentiate intensity (severity) from medical significance and intervention. Alternatively, investigators may modify frameworks integrating intensity and medical significance, such as the Common Terminology Criteria for Adverse Events ratings, supplemented with narrative description. Frequently, articles reported only that no SAEs were recorded; we advocate tabulating, describing, and reporting all AEs and their frequency.

Our analysis was also not restricted to studies with placebo comparisons and did not estimate relative risk of AEs. Valid placebo comparisons are challenging in psychedelic work given their psychologically salient psychoactive nature, though a recent targeted meta-analysis of psilocybin trials[45] suggested that headache, nausea, dizziness, and blood pressure elevations were significantly more likely following psilocybin than placebo. Another meta-analysis[46] found that heart rate and blood pressure, but not anxiety or headache, increased in a dose-dependent manner in trials of ayahuasca, LSD, and psilocybin.

Limitations

As previously noted, the current work was not limited to placebo-controlled comparisons and therefore cannot estimate AE risks compared with placebo. The study design emphasized characterization of serious or medically significant AEs and provided less insight into the dose dependence of routinely encountered AEs. Furthermore, methodological heterogeneity limits population comparisons. Well-funded trials with intensive pharmacovigilance among participants with psychiatric conditions will detect more AEs. Overall, current screening is stricter than earlier work; most participants in contemporary studies have no personal or even family history of psychotic or manic illness. Furthermore, some studies selectively recruit participants with prior psychedelic experience (and exclude those with a history of adverse reactions); such studies may be less likely to encounter significant acute or delayed AEs, thus reducing their generalizability. Finally, only 1% to 2% of psychedelic trial participants are over the age of 65 years due to active exclusion or underrecruitment, limiting the generalizability of safety findings to older populations with higher rates of preexisting conditions (eg, cardiovascular disease).[47]

Conclusions

Uncertainty remains about the characterization and quantification of risks associated with clinical use of high-dose classic psychedelics. Our results broadly indicate that while medically or psychiatrically significant AEs (eg, psychosis, suicidality) are relatively rare, these events are often serious when they occur. The present systematic review and meta-analysis can only be as accurate as the source material, and more systematic detection and transparent reporting of AEs going forward will provide more precise estimates of risks, thereby helping to inform and safeguard future participants. The reality of risks associated with classic psychedelics, as well as their prevalence and severity, should be communicated to potential participants during the informed consent process and to the public in general. Finally, the data reported herein cannot be meaningfully generalized to unsupervised psychedelic use in nonclinical settings.

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