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TITLE

A scoping review of variations among psychedelic interventions for psychological suffering associated with the end of life

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ABSTRACT

Background: Psychedelic substances are recognized for their potential to ease psychological suffering linked to end-of-life issues, yet policy remains restrictive. The wide range of both substances and therapeutic approaches used in end-of-life populations has not been adequately covered by reviews to date.

Aim: To identify and learn from the variety that exists within the research on therapeutic psychedelic interventions reported in populations coping with psychological suffering associated with life-threatening illness and the end of life itself.

Methods: Following Arksey and O'Malley's (2005) framework for scoping reviews, updated methodological guidance, and the Preferred Reporting Items for Systematic Review and Meta-Analyses extension for scoping reviews guideline, data extracted from selected studies covered intervention details, substances used, participant characteristics, measured outcomes, and theorized mechanisms.

Results: Fifty-nine studies on six types of psychedelic substances for end-of-life issues were identified, with case study designs most common. Interventions were categorized into dosing alone, preparation/dosing/integration, and dosing with any psychotherapeutic support not provided within the tripartite model. Most studies reported challenging experiences, with a large proportion considering them therapeutic. Outcome measures spanned biopsychosocial-spiritual domains, with affective and cognitive-affective sub-domains most often assessed; neurobiological mechanisms were reported in 54% of studies, psychological in 51%, and spiritual in 44%, indicating diverse therapeutic processes.

Conclusion: There is extraordinary variety in how psychedelics are studied to address the experience of psychological suffering associated with end-of-life concerns. The variability in psychedelic research reflects an early and exploratory phase, differences in beliefs about how therapeutic psychedelic interventions effect change, and the genuine richness in possibilities for therapeutic psychedelic intervention.

INTRODUCTION

After a gap of decades, scientific and clinical interest has been renewed in the healing potential of therapeutic psychedelic interventions (TPIs), especially to alleviate psychological suffering in populations coping with life-threatening illness and the end of life.[1] Certain psychedelics, specifically, lysergic acid diethylamide (LSD) and mescaline, were initially studied to treat alcoholism and neuroses beginning in the 1950s, and as tools to better understand the causes and treatment of schizophrenia.[2-5] Psychedelics gained recognition for their potential to ease end-of-life distress in the early 1950s, with writer and philosopher Aldous Huxley considered one of the first to explore this connection. He famously administered mescaline to his wife Maria as she suffered through the late stages of cancer, and was known later for his own use of LSD while he was on his deathbed.[6,7] Initial research on LSD in the context of terminal illnesses began in the early 1960s paving the way for studies on other psychedelics in populations with broad end-of-life concerns.[8] A general moratorium on research since the 1980s was reversed in the early 2000s, fueled by a series of pivotal open-label studies or randomized controlled trials with methylenedioxymethamphetamine- (MDMA)-, psilocybin-, and LSD-assisted therapy, and intranasal ketamine without concurrent psychotherapy for anxiety and/or depression.[9-15] This momentum has been bolstered by policy shifts and drug approvals, notably Health Canada's and the US Food and Drug Administration's approval of intranasal esketamine (Spravato®) for depressive disorders.[16,17]

Although the field is still early in its development, there has emerged a substantial body of work reporting on TPIs to address psychological distress associated with end-of-life concerns, encompassing various substances and therapeutic modalities. However, a paucity of research has been undertaken to learn from this variety; indeed, the landscape of these interventions and their individual components remains inadequately assessed. Understanding these factors is essential to improving clinical protocols and future research, and to inform policies that can judiciously implement TPIs in the context of life-threatening illness.[18]

The term psychedelics broadly refers to psychoactive substances whose effects are "mind revealing" or consciousness expanding;[19] it does not denote specific drug classes. There is general consensus that psychedelics include the following list: N,N-dimethyltryptamine

(DMT), ayahuasca, ketamine; psilocybin, 3,4-methylenedioxymethamphetamine (MDMA), LSD, ibogaine, peyote, and mescaline.[20] Although some research has noted the psychedelic effects of cannabis[21] and certain clinical approaches incorporate cannabis-assisted therapy in a manner similar to that of classic psychedelics,[22] controlled studies have not documented sufficient mind revealing effects[21] that would indicate its use for end-of-life distress. Moreover, cannabis has not been studied or categorized as a psychedelic for addressing end-of-life distress, reinforcing its distinction in this context.

Psychological suffering, as used here, refers to the complex experience of distress arising from confronting mortality.[1] This multifaceted condition encompasses physical, cognitive, affective, social, and spiritual dimensions and includes elements such as existential distress, death anxiety, hopelessness, perceived loss of dignity, and diminished spiritual well-being. Although the construct of end-of-life psychological suffering does not align neatly with traditional psychiatric nosology, it represents a condition long recognized by palliative care clinicians—evidenced by the historical use of palliative sedation as a last resort. This operational definition aligns our study's objectives, inclusion criteria, and synthesis of findings, ensuring a clear and focused framework for evaluating therapeutic psychedelic interventions in the context of end-of-life care.

The purpose of this review is to scope the variation in TPIs addressing psychological suffering associated with end-of-life concerns. This kind of distress arises from coping with a foreshortened future in response to a life-threatening illness. Typically, the literature considers a life-threatening illness to be a terminal disease, such as advanced cancer. However, a life-threatening illness need not be in the terminal stages to activate concerns about mortality and the end of life. For example, patients with long-term HIV/AIDS may experience distress from a psychologically foreshortened future.[8] Further, this distress need not only be in response to physical disease but can include mental illness in which survival is poor, such as with patients with life-threatening suicidality.[23-25]

Knowledge to Date: Prior Reviews of TPIs

To set the context, research on non-TPI treatments has identified meaning-centered psychotherapies for those with cancer-related psychological distress[26-29] with a small to moderate effect size[30] and psychodynamic therapies for those with co-morbid mood or anxiety disorders and serious physical illness.[31] Currently, antidepressants and benzodiazepines have been used to treat co-occurring depression and anxiety disorders, or depression and anxiety symptoms as manifestations of distress in oncology care.[32]

Prior reviews of TPIs to address end-of-life concerns have tended to focus on the effectiveness of treatment using meta-analysis, traditional systematic review, and narrative approaches.[33-38] In general, meta-analyses across clinical populations have found that medium to large effects on psychological outcomes are possible.[39,40] Sicignano et al. (2023) reported significant reductions in anxiety and depression among patients with advanced cancer or life-threatening diseases who received psychedelics (psilocybin, LSD, or MDMA) compared to control therapies.[41] A meta-analysis focusing solely on psilocybin showed significant improvements in anxiety and depression symptoms in life-threatening disease patients.[42] Another meta-analysis indicated lasting reductions in trait anxiety following psilocybin therapy, evident from one day to six months post-treatment, despite significant heterogeneity.[43]

Other systematic reviews have examined safety, mechanisms of action, and long-term effects,[44-51] and have found that significant reductions in anxiety and depression may occur with TPIs in an end-of-life context and effects may be sustained with overall safety. Across reviews, agreement exists that the progress of research has been restricted by stringent governmental regulations on controlled substances, among other factors.[45,49] Researchers advocate for more rigorous studies backed by government funding and more extensive study of non-cancer populations.[35]

Extending the Scope: Addressing Gaps and Clarifying Contexts

A shortcoming across this literature is that many authors draw conclusions that typically ignore variation in the clinical samples under study and the interventional approaches taken. Additionally, recent research has indicated that these existing reviews often do not adequately

characterize psychosocial components.[52] They overlook key factors such as the type and extent of accompanying psychotherapy, the qualifications of the therapist or guide, and the therapy setting. Aesthetic elements like music, eyeshades, or art are important aspects often insufficiently described in the literature.[38] The present review comprehensively scopes these interventional components, research study characteristics, choice of outcome measures, and postulated mechanisms in the end-of-life TPI literature. Its purpose is to characterize the range of interventional approaches, in order to learn from this variety. The identification and analysis of patterns that occur in therapeutic contexts, practices and settings can provide valuable insights into how the field of psychedelic medicine is evolving, where its limitations and pressing issues warrant future investigation.

METHODS

This scoping review was based on Arksey and O'Malley's scoping review framework[53] with updated methodological guidance.[54,55] The five key stages are described below. An optional sixth stage involving consultation[56] was not included in this study. The Preferred Reporting Items for Systematic Review and Meta-Analyses extension for scoping reviews (PRISMA-ScR) guideline was used.[57]

Stage 1: Identifying the Research Questions

The overarching question is: What is known about how empirical studies vary in the TPI literature in populations coping with life-threatening illness? This question was examined focusing on four aspects of variation: (1) study characteristics (e.g. design, inclusion/exclusion criteria); (2) intervention characteristics (e.g. type of psychedelic, setting); (3) outcome measures; and (4) postulated mechanisms by which TPIs were thought to achieve their effects. The major components of the research question were organized according to the PCC mnemonic: Population, Concepts, Context mnemonic (see Table 1).

Stage 2: Identifying Relevant Studies

Medline, Embase, APA PsychINFO, and CINAHL was searched from inception to October 27th, 2023, for the following concepts in combination: "end-of-life," "psychedelics," and "psychological suffering." See Table 2 for related search terms that were included (e.g. "life-

threatening illness" and "existential distress"). Backward citation searching using reference lists and forward citation searching using Google Scholar from included publications was conducted.

Stage 3: Study Selection: Inclusion and Exclusion Criteria

Types of Participants

Adult participants (age ≥ 18 years) who provided informed consent to participate in studies of TPIs to address psychological suffering associated with end-of-life issues, including depression, anxiety, and hopelessness.

Types of Interventions

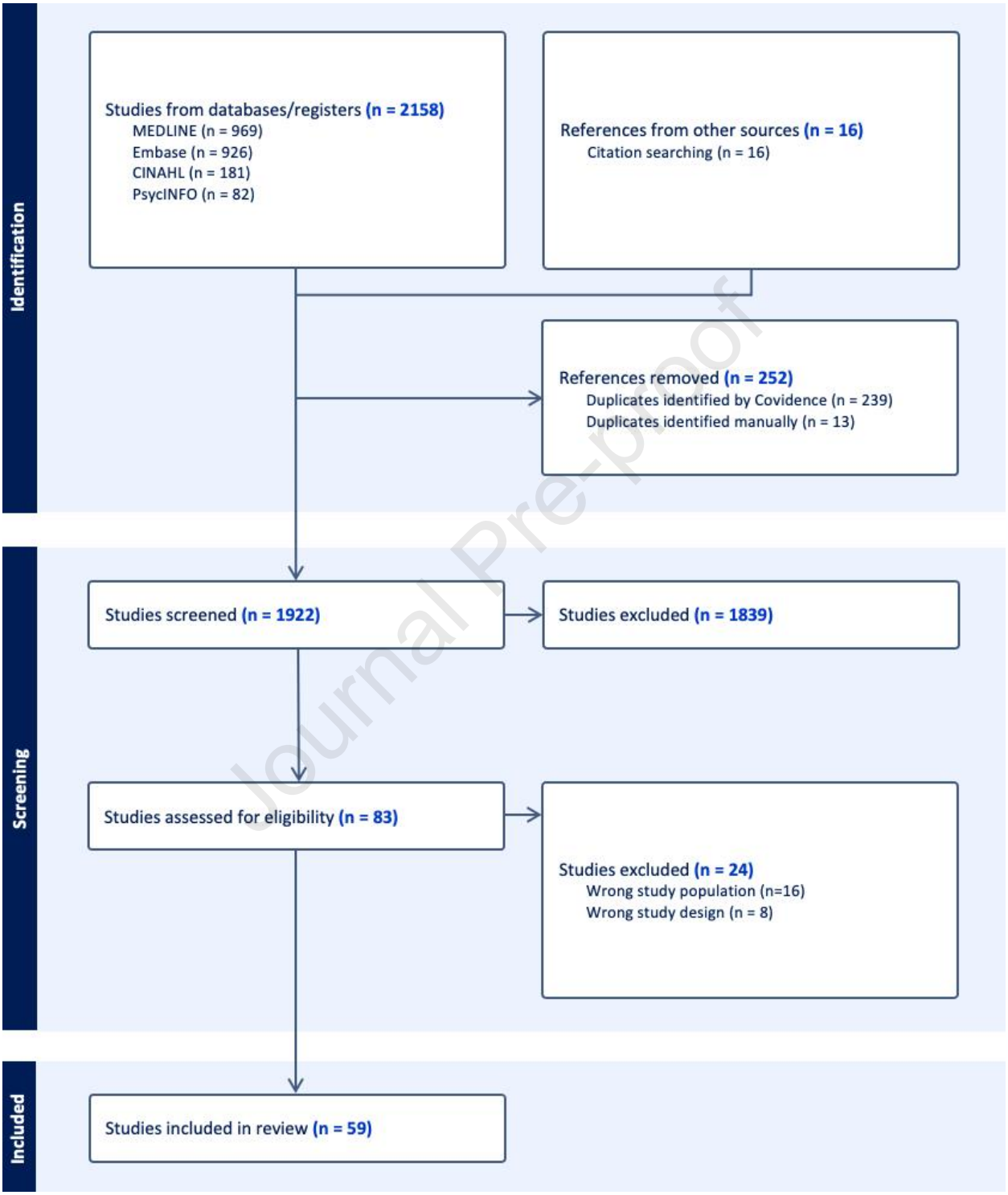
TPIs that used any of the following: ketamine; psilocybin; ayahuasca; MDMA; N,N-Dipropyltryptamine (DPT); LSD; ibogaine; peyote; and mescaline—at any dosage and with any type of therapy, such as psychotherapy, music therapy or other similar therapeutic modalities.

Types of Data Sources

Primary empirical studies published in peer-reviewed research journals with any data type—quantitative, qualitative, and mixed methods—and design, including clinical trials, observational studies, and case studies. Languages were restricted to (a) English and French, Canada's official languages, and (b) Spanish and Portuguese, due to Central and South American contributions to the study of psychedelics within Indigenous populations. Full-text empirical publications were included. Abstracts, poster presentations and dissertations were excluded. We chose to focus on studies meeting established scientific standards with the aim of providing findings that are most likely to inform future research, policy and practice, therefore excluding grey literature.

Screening for eligibility of retrieved publications including resolving deduplication was done using Covidence software.[58] Two reviewers (S.K., A.N.) independently screened and assessed the eligibility of retrieved publications. Discrepancies were resolved by consulting with the supervisory team (C.L., B.R.), who made the final decision regarding inclusion. The search strategy yielded 2158 citations from January 1964 to October 2023, which was reduced to 59 publications for this review (see Figure 1).

209 *Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analysis Extension*
210 *Modified for Scoping Reviews (PRISMA-ScR) Diagram of the Search Strategy*



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Stage 4: Charting the Data

Data extraction was conducted using a structured form according to guidelines.[59] Three team members (S.K., S.J., A.N.) independently charted data from the first five publications to pilot-test the data extraction form. The team members compared and discussed the extracted data, made relevant changes, and proceeded to chart all data. Data was recorded in a Google Drive Excel sheet. As standard for scoping reviews, quality of evidence was not appraised.

Stage 5: Collating, Summarizing and Reporting the Results

An initial raw data extraction was performed related to each of the Population, Concepts and Context fields from eligible articles. Using thematic analysis, data were coded according to emergent data categories (see Table 3 for data categories). Subsequently, evidence was summarised using quantitative descriptors and narratively synthesized in the results. When the same interventional approach was described in multiple studies and the focus of synthesis was on the number of interventional approaches, then only the most representative study was cited to avoid overcounting and ensure clarity in referencing.

Categorisation of Data

We categorised the interventional approach based on the type of intervention administered. These approaches fit into three categories: (1) dosing alone, (2) dosing with some form of psychotherapeutic approach, and (3) the tripartite model. The tripartite model[60] refers to an established structured approach to psychedelic-assisted psychotherapy that consists of three key phases: (1) Preparation, which involves developing a therapeutic alliance and preparing the client for the psychedelic experience; (2) dosing, of the psychedelic substance; and (3) integration, which involves supporting the client to process and make sense of any insights gained during the psychedelic experience.

Outcome measures refer to key dependent variables that were assessed in studies, some of which may be intermediate outcomes. The term does not indicate any specific time course and could capture measures collected mid-intervention, shortly post-intervention, or after a lengthier follow-up. This applies equally to measures of adverse mental health effects and other clinical indicators, for example. The review of outcome measures was focused on formally validated measures as evidenced by a published psychometric validation of the tool.

The exception was for clinical indicators which consisted of physiological measurements and symptom assessments (single item or checklists) for which there is clinical acceptance of validity.

Outcome measures were categorized into four main domains: (1) clinical indicators of health, e.g. vital signs; (2) psychological measures, e.g. depression, demoralization; (3) spiritual measures of transcendental experiences, e.g. dissolution of ego boundaries, sense of connectedness to the universe; (4) holistic measures which refer to comprehensive assessments of physical, emotional, social and spiritual well-being.

Clinical indicators were further distinguished into two sub-domains: (1) indicators of general physical health, e.g. sleep, pain; and (2) adverse mental health effects in response to the psychedelic intervention, e.g. nausea, dizziness. The psychological domain was further distinguished into four sub-domains: (1) affective measures, e.g. anxiety; (2) cognitive-affective measures, which refer to assessment of cognitive-emotional states and beliefs, e.g. death attitudes; (3) psychiatric measures assessing mental or behavioural disorder, e.g., hallucinations, addictions; and (4) personality measures, e.g. personality traits.

RESULTS

Study Characteristics

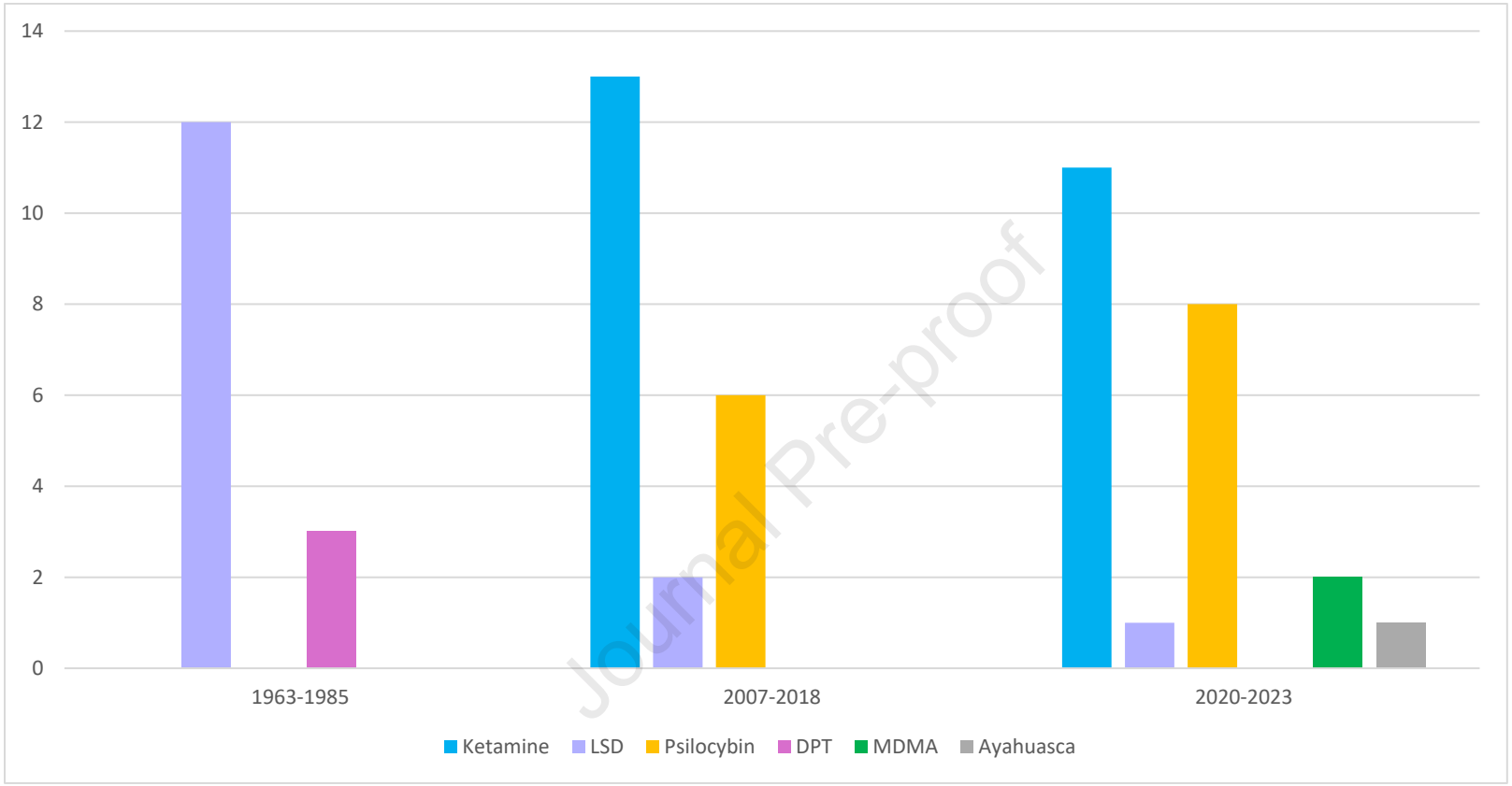
Type of Psychedelic

Six substances were studied, including ketamine (41%; n=24/59),[15,77-89,95,97,100-106,113] LSD (25%; n=15/59),[11,14,62-73,98] psilocybin (24%; n=14/59),[8,10,12,13,90-92,96,107-112] DPT (5%; n=3/59),[74-76] MDMA (3%; n=2/59)[9,93] and ayahuasca (2%; n=1/59).[94]

Year of Publication and Type of Psychedelic

There were three waves of psychedelic studies (see Figure 2). The earliest wave spanned 22 years and only involved LSD (80%; n=12/15)[62-73] and its structurally similar relative, DPT (20%; n=3/15).[74-76] The second wave spanned eleven years and was dominated by ketamine (62%; n=13/21)[77-89] followed by psilocybin (29%; n=6/21)[10,12,13,19-21] studies. The third wave, spanning only 4 years, followed a similar pattern but saw the introduction of MDMA (9%; n=2/23)[9,93] and ayahuasca (4%; n=1/23).[94]

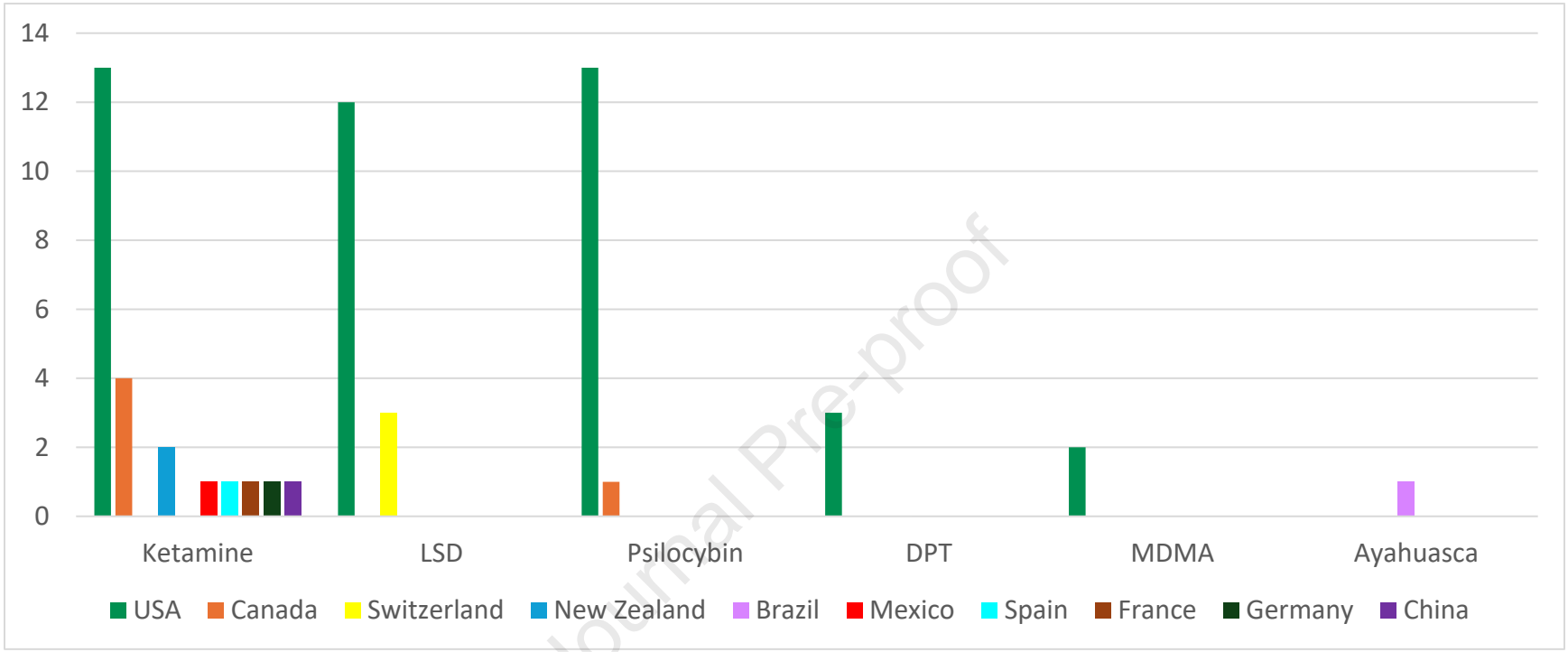
Figure 2. Types of Psychedelic Substances Published Across Time: Counts



Country of Publication and Type of Psychedelic

Researchers from the United States dominated psychedelics research, publishing studies on all psychedelics except ayahuasca (see Figure 3). Ketamine was the most studied internationally. Canadian researchers have only studied ketamine and psilocybin.[15,22-25] Although the US was the only nation to study LSD in the first wave, it is interesting to note that only three studies have been conducted on LSD since the 2000s and they were all done in Switzerland,[11,14,26] the birthplace of LSD.[99]

Figure 3. Comparative Counts of Country of Publication by Type of Psychedelic



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283 *Type of Study Design and Type of Psychedelic*

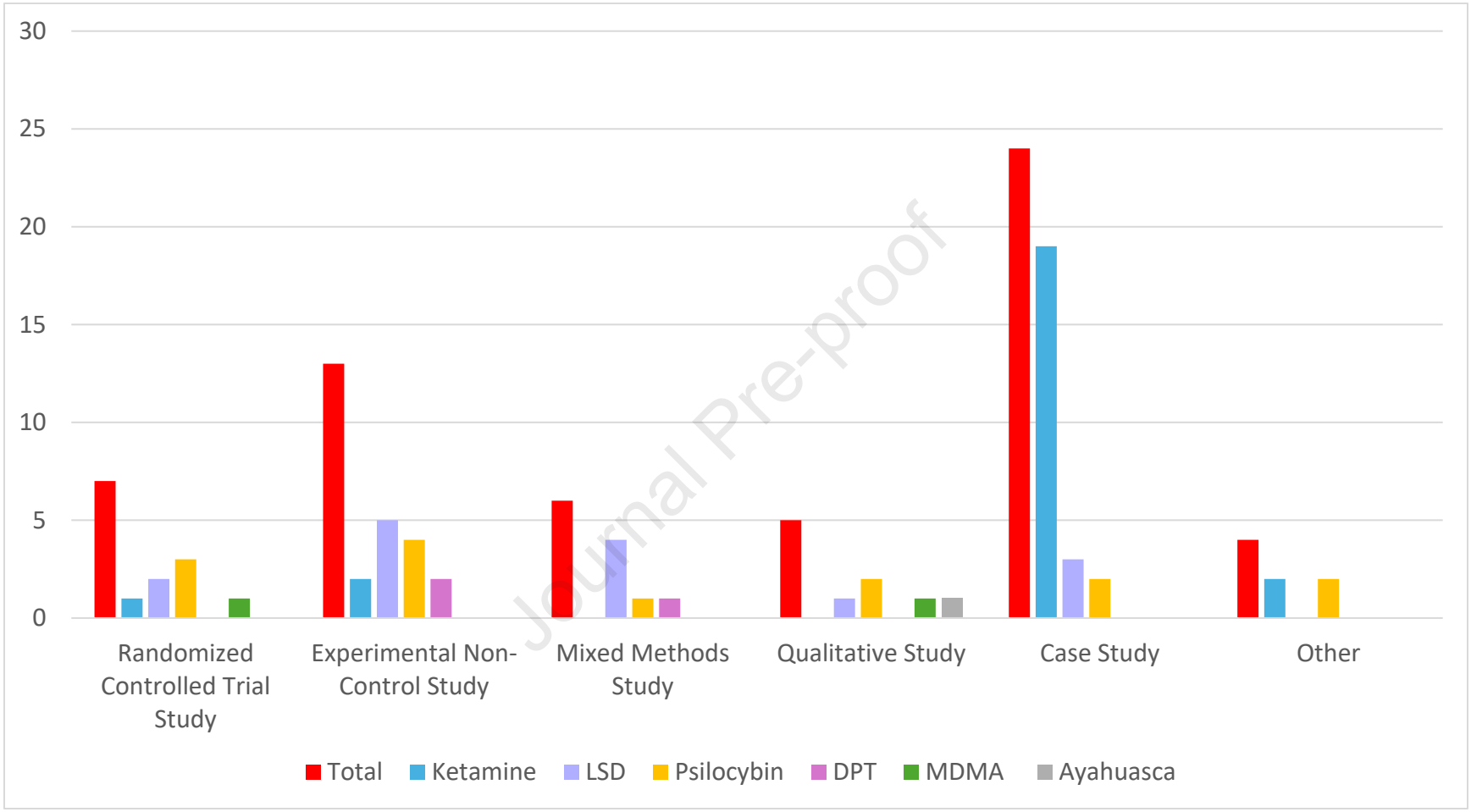
284 The case study was the most frequent design (n=24/59; 41%)[67,69,73,77-82,85-87,89,95-97,100-107]
285 (see Figure 4). Most case studies were ketamine studies (n=19/24, 79%).[77-82,85-87,89,95,97,100-106]

286 Second to the case study design, experimental non-control studies were most often
287 used to study psychedelics at the end of life (22%; n=13/59).[8,15,62-65,72,75,76,83,110-112] The
288 psychedelic most often studied using an experimental non-control design was LSD (38%;
289 n=5/13).[62-65,72]

290 For RCTs psilocybin was most often researched with this study design (43%;
291 n=3/7).[10,12,13] Although there have been only two studies on MDMA, one was an RCT design.[9]

292

293 *Figure 4. Psychedelic Substances Studied by Research Design: Counts*



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297 *Inclusion Criteria Related to a Life-Threatening Disease*

298 The majority of studies (70%; n= 41/59) included patients with cancer,[10,12,13,15,63-77,80-
299 82,85,86,88-92,95,96,100-102,104,107-112] although 14 studies (24%) included a mix of life-threatening
300 conditions.[9,11,14,62,78,79,83,84,87,93,94,98,103,113] In contrast, four studies included participants with
301 only one specific non-cancer life-threatening condition. These conditions were HIV,[8] severe
302 suicidality,[105] end-stage heart failure,[106] and a patient actively requesting Medical Assistance in
303 Dying (MAID) due to severe and prolonged treatment-resistant depression.[97]

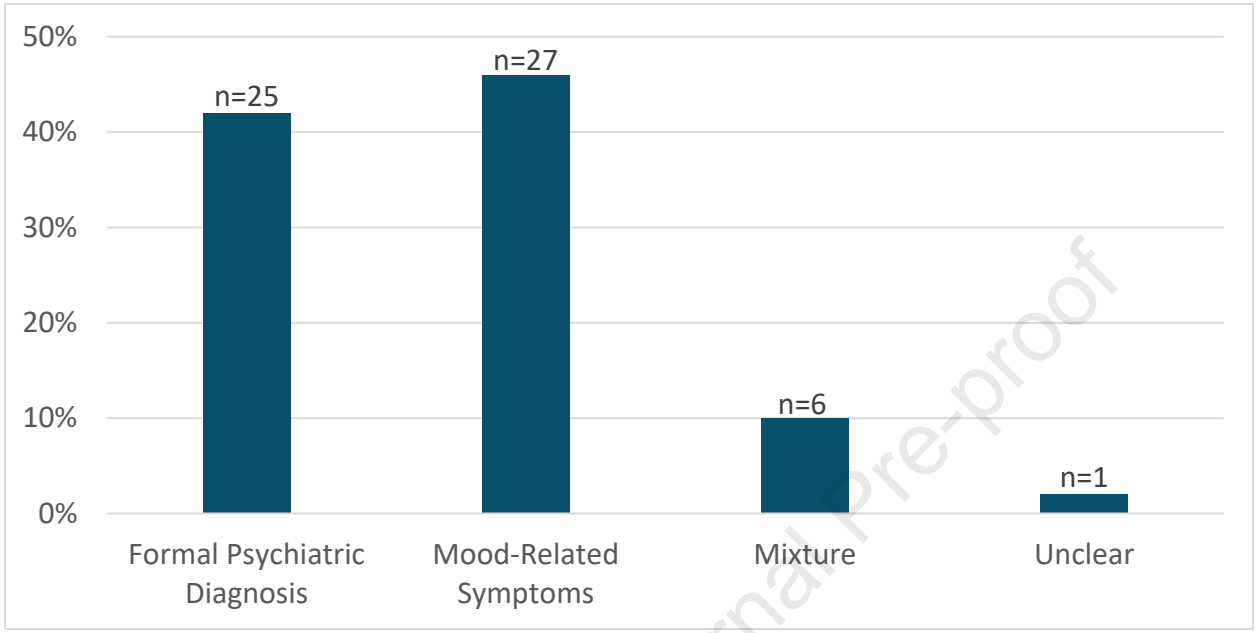
304 Although suicidality was not an explicit focus of our keyword search, it emerged as a
305 relevant topic because of its severity and risk to life, despite the absence of physical illness. Two
306 such case studies without physical illness were found: one involved a case with life-threatening
307 severe suicidal ideation,[105] and the other had a participant with severe depression, anxiety,
308 near-constant suicidal ideation, two documented requests for MAID requests, and no hope for
309 recovery.[97]

310 *Psychiatric Diagnosis Versus Mood Symptoms Inclusion Criteria*

311 As shown in Figure 5, nearly half of studies (n=25/59; 42%) included participants with
312 mood-related symptoms like anxiety and depression.[8,62-76,78,86,88,94,96,102,104,107,113] Nearly half of
313 studies (n=27/49; 46%).[10-13,15,77,79,80-83,85,89-92,95,97,98,100,101,105,106,109-112] included participants with
314 a formal psychiatric diagnosis, such as major depressive disorder. Six studies (10%) included
315 participants who had either a formal diagnosis or mood symptoms, or both.[9,14,87,93,103,108]

316

317 *Figure 5. Percentage of Studies Using Formal Psychiatric Diagnosis or Mood-Related Symptoms for Inclusion Criteria*



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Psychiatric Exclusion Criteria

Among the 19 studies that specified exclusion criteria, 17 studies (89%) excluded participants with specific psychiatric issues, including suicidal ideation.[9-15,24,27-35] The most common psychiatric exclusions were a personal or family history of psychosis or psychotic disturbances (79%; n=15/19).[9-15,24,27,28,30-34] Eight studies (42%) excluded participants with bipolar disorder,[9-12,14,15,110,111] and five studies (26%) excluded those with a substance use disorder.[9,10,11,15,110] One study used a broader criterion, excluding individuals with personal and family history of psychiatric disorders.[88]

Notably, two studies excluded individuals with suicidal ideation or attempts, either before cancer diagnosis,[88] or in those with anxiety or affective disorders within a year of their cancer diagnosis.[12] This exclusion suggests that researchers focused on understanding the impact of a life threatening diagnosis on the development of suicidal ideation and mood disorder symptoms, without the influence of pre-existing mental health conditions.

Sample Size and Diversity

Of the 59 studies, most had small sample sizes at baseline: 61% (n=36) included between two and 50 participants,[8-12,14,15,62,65-68,72,73,75,76,78,83,84,86-88,90-95,98,103,108-113] and 29% (n=17) were single-participant case studies.[69,77,79-82,85,89,96,97,100-102,104-107] The largest study was conducted in 1967 and involved 128 participants administered LSD.[64]

All studies reported participants' biological sex in binary terms. Notably 34% (n=20/60) of studies had a majority female sample[9,10,12,15,64,65,68,70-72,75,76,83,84,88,95,108,109,111,112] and 24% percent (n=14/59) included female participants only.[67,69,73,80-82,85,93,96,97,101,104,105,107] No studies reported gender identity.

The majority (59%; n=35/59) of studies did not report the racial characteristics of their participants.[10-12,14,15,62-65,67,70,74,77,80-82,84-89,94,95-98,100-102,104,106,107,110,113] Among the 24 studies that did report race;[8,9,13,66,68,69,71-73,75,76,78,79,83,90-93,103,105,108,109,111,112] 14 had a majority of White participants;[8,9,13,68,70,71,75,83,90,92,93,108,109,111]; and five included White participants only.[73,78,79,91,103]

Intervention Characteristics

Interventional Approach

Among the 59 studies, 45 interventional approaches were reported. Half of these used a dosing-only model (n=23/45), administering the substance alone without psychotherapeutic intervention (see Figure 6).[15,62-64,77-85,87-89,100-104,106,113] Of these dosing-only interventions, most administered ketamine (87%; n=20/23).[15,77-85,87-89,100-104,106,113]

Of the 21 interventions that provided some form of psychotherapeutic approach, 17 (81%) followed a tripartite model as the sole therapeutic framework, and of these 12 employed an individual therapy format.[9-14,71,74-76,86,96] Four administered psilocybin,[10,12,13,96] four administered LSD,[11,14,70,71] three administered DPT,[74-76] one administered ketamine,[86] and one administered MDMA[9] within the tripartite approach.

Group psychotherapy was used in four tripartite interventions, and they all administered psilocybin.[8,110-112] One of these studies had modified brief supportive-expressive group therapy for use in people living with HIV.[8]

One interventional approach used a tripartite model and four grams of Psilocybe cubensis with assisted sensory deprivation as a complementary therapy. They also administered additional intermittent microdosing of psilocybin throughout nearly three years without psychotherapy.[107]

Among the 21 studies that included psychotherapy, the use of standardised modalities was rare. Two used a structured form of psychotherapy: meaning-centred psychotherapy[105] and brief supportive expressive group therapy modified for people living with HIV.[8] A third study used a manualized approach to MDMA-assisted psychotherapy according to the Multidisciplinary Association for Psychedelic Studies (MAPS) treatment manual.[9]

The one ayahuasca study included a sample of participants who had taken ayahuasca within various ritual contexts and was categorised as broadly psychotherapeutic although this may not fit the typical definition.[94]

Setting and Aesthetic Elements

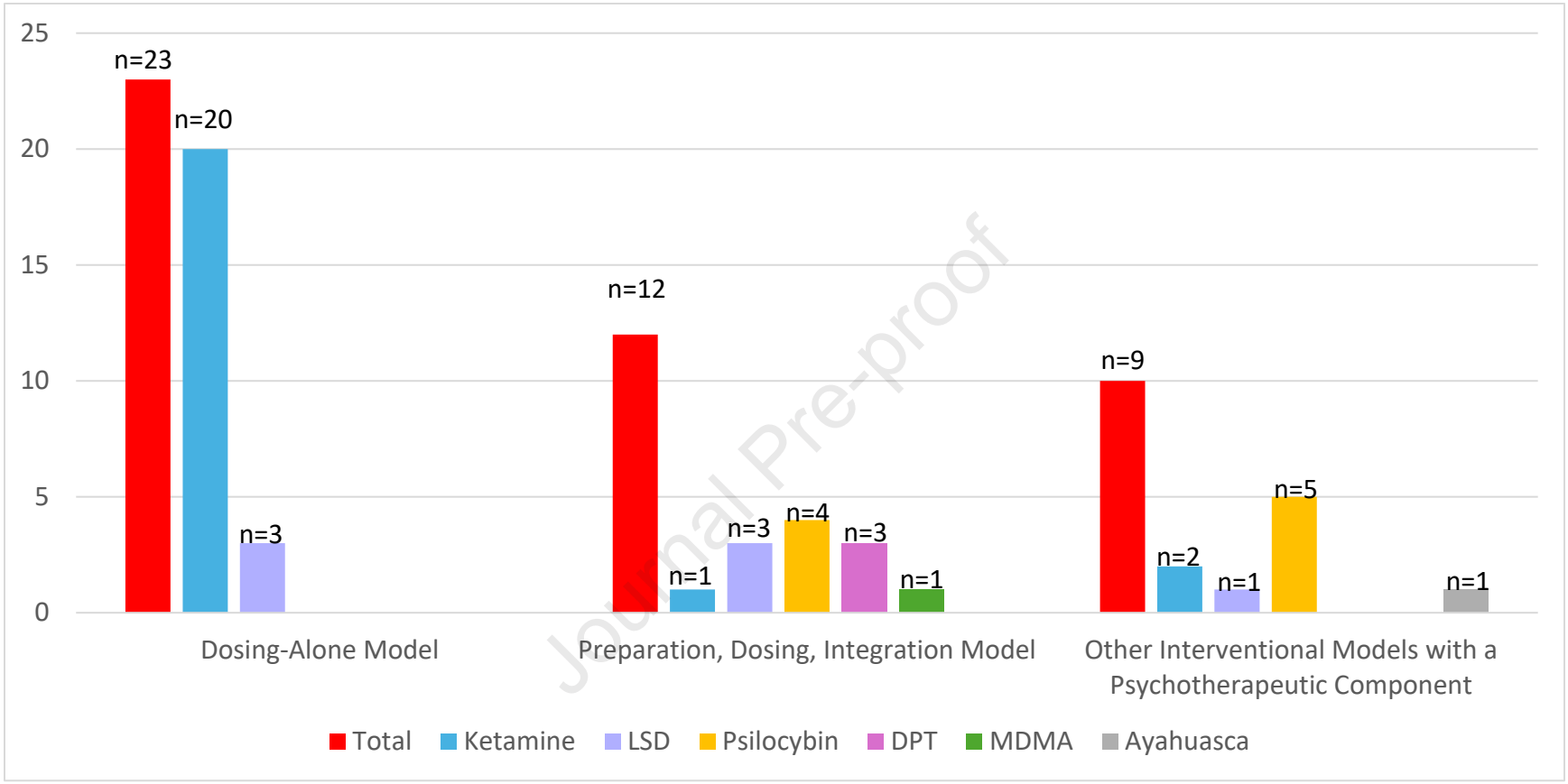
Intervention settings varied widely, with hospital settings most common (51%; n=23/45).[15,66-73,77,80,81,85,87,88,95,97,100-102,104,105,113] Other settings included cancer institutes,

research centres, hospices, community cancer settings, and private practice offices. The ayahuasca report described contexts ranging from personal at-home neo-shamanic use to administration within institutionalised religious group settings, including within the Santo Daime syncretic religious ceremony.[94]

Of 45 interventions, 73% (n=33) did not report on the aesthetic elements of the room used for drug administration.[8,15,62-64,67,74,76-89,94,97,100-107,111,113] The remaining 12 (27%) interventions mentioned features like artwork, family photos, fresh flowers and fruit, with some describing the dosing room as living-room-like or calm and comfortably furnished.[9-14,66,71,75,96,110,112]

Sixty-two percent (n=28/45) did not include music during dosing sessions,[15,62-64,74,77-85,87-89,94,97,100-107,113] and 26% (n=12/46) incorporated the use of eyeshades.[9-13,66,75,76,96,110-112]

387 *Figure 6. Psychedelics Administered by Type of Interventional Approach: Counts*



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Psychotherapeutics

Psychotherapeutics were identified based on author descriptions of the therapeutic components comprising the overall interventional approach. While this section is organized into preparation, dosing, and integration phases, not all interventions applied the full tripartite approach.

Preparatory Support

Preparatory support was used in 44% (n=20/45) of interventions, prior to dosing.[8-14,64,67,71,74-76,86,96,105,107,110-112] Preparation centered mainly on developing trust and rapport through meetings with study personnel, during which participants discussed various aspects of their lives, developed an intention for the psychedelic dosing session and cultivated an open mindset regarding their expectations. The preparatory phase averaged about 6–12 hours. Only early studies from the 1970s to 1980s using LSD or DPT involved family members in preparatory work.[66,68,70-72,75,76]

Support During Dosing Session(s)

Various kinds of therapeutic support were provided during the dosing session in 44% (n=20/45) of interventions.[8-14,62-64,67,71,74-76,86,96,110-112] A typical approach incorporated non-directive therapy, regular physiological and emotional monitoring, and the strategic use of music to facilitate introspection. Sessions typically occurred in controlled settings, incorporating ritualistic or ceremonial elements (e.g., setting intentions, listening to or chanting mantras, grounding or breathing exercises), or tools used by some protocols to help shape the sensory environment and support inward focus (e.g., wearing eyeshades and/or headphones). Therapist involvement varied, but generally included active listening, reassurance and emotional support. Some studies employed a group format for the dosing session.

Integration Support

Integration support was part of 49% (n=22/45) of interventions.[8-14,63,64,67,71,74-76,86,96,97,105,107,110-112] This could involve supportive psychotherapy using existential and psychodynamic methods. These sessions emphasized applying insights from the psychedelic experience, resolving interpersonal conflicts, and promoting self-actualization. Integration

strategies were reported as crucial to sustaining therapeutic benefits and were delivered in both group or individual formats, sometimes as part of the same intervention.[113] At the very least participants integration support included daily follow-up for about three weeks.[63,64]

The number of sessions ranged from a single follow-up, daily meetings for three weeks, to six hours over six weeks. Duration of sessions ranged from 45 minutes to 75 minutes. Apart from the 18 studies that included integrative support, three studies provided additional supportive measures that were not classified as integration per se. Specifically two studies conducted daily interviews for three weeks post-LSD dosing;[63,64] another provided eight meaning-centered psychotherapy sessions that were interspersed with three ketamine dosing infusions;[107] while the another study provided six ketamine infusions over four weeks accompanied by weekly supportive psychotherapy.[99] Only early studies from the 1970s-1980s using LSD or DPT interventions incorporated family members in integration.

Challenging and/or Adverse Experiences

Of the 59 studies, 66% (n=39) reported on the presence of challenging and/or adverse experiences.[8-15,62,64,66-73,77,80,82,84,86,90-96,98,100,102,103,108-112] These experiences were diverse and ranged from emotional numbness, detachment from one's external world, detachment from one's body or self, vomiting and dizziness, although these were often not permanent and did not require intervention to resolve.[71,72] Participants experienced fears, traumatic memories, and existential concerns, leading to intense emotions like grief and anxiety, which usually resolved within the dosing session or during integration sessions.[69,109]

Despite these symptoms, 41% (n=24/59) of studies reported that challenging experiences were part of the therapeutic process.[8,10,66-76,90-94,96,98,108,110-112] Working through cancer-related fears, emotionally charged experiences, and experiences of catharses were a significant part of the therapeutic process for some.[66,73,90] After processing these experiences, some participants reported feeling joy, peace, lightness and an "unburdening".[96,98]

Not all participants successfully resolved the psychological difficulties that emerged during the TPI. One participant experienced intense fear and a sense of fading from existence.[86] This individual, after completing an integration session, declined further treatment, and died less than two weeks later from a suspected accidental overdose.[86] In another instance, a

psilocybin group therapy study for men living with HIV identified two participants who experienced persistent intervention effects, including trauma flashbacks and severe anxiety leading to drug relapse.[8] One psilocybin study reduced the dose when two of the first three participants were removed from the study after indicating a preference to reduce the chance of a challenging experience.[13] Early LSD studies with terminally ill cancer patients noted the dosing experience as psychologically demanding, leading in some cases to the early stoppage of treatment with chlorpromazine.[62,70]

Dosing by Type of Psychedelic

Ketamine Dosing

The ketamine interventions showed the most variety in dosing methods and administration routes, with oral, intravenous, intramuscular, subcutaneous, and intranasal approaches. Of 45 interventions, eight interventions (18%) administered a single dose,[86-88,100,101,113,104,106] with seven using intravenous[87,88,100,101,104,106,113] and one using intramuscular.[86] Most interventions used multiple doses over varying time frames, such as nightly oral doses for 28 days[83] or weekly injections for ten months.[82] Some interventions used multiple routes of administration in a sequential manner, where different routes were employed at different stages of the overall interventional approach like oral and subcutaneous doses,[84] or a single subcutaneous dose followed by daily oral therapy for 135 days.[103] Two interventions (4%) used continuous intravenous infusion.[85,89] The ketamine doses varied based on the route of administration; for example, intravenous ketamine, the most common route of administration, was often given at a dose of 0.5 mg/kg.[106,97,100,77,88,101]

LSD Dosing

LSD has been given orally, intramuscularly, intravenously, or subcutaneously. Of 45 interventions, 9% (n=4/45) used LSD in a single dosing session.[62,64,67,72] The two RCTs (4%) administered LSD orally in two sessions.[11,14] One intervention (2%) did not specify the number of dosing sessions,[63] although the study specified that LSD was administered subcutaneously.[63] In studies published from the 1960s to 1980s, dosing varied per client, with options for

repeated sessions. For instance, in one case, the participant received four LSD dosing sessions.[69] LSD doses ranged from 100 mcg to 500 mcg.

DPT Dosing

In the three DPT interventions reviewed, this psychedelic was administered in a single dose.[74-76] Two studies used the intramuscular route, while the third did not specify the route. Since DPT is inactive when taken orally, it can be inferred that a parenteral route was used. DPT doses ranged from 75 mg/kg to 127.5 mg/kg.

Psilocybin Dosing

Eight psilocybin interventions (18%; n=8/45) involved a single dosing session.[8,10,12,13,24,30,33,36] One intervention administered both a high dose of psilocybin mushrooms (4 g) and microdoses (10–20 mg) over nearly three years, with the high dose given four times.[107] Six interventions reported administering psilocybin orally, while three did not specify the route.[8,10,12,13,96,102] A dose of 25 mg of psilocybin was administered in three interventions.[110-112] Otherwise, various doses were noted in the studies, such as 30 mg/70 kg or 22 mg/70kg.[13] Another intervention administered a single high dose of 5 g of psilocybin mushroom.[96]

MDMA and Ayahuasca Dosing

In the single MDMA RCT, participants received oral MDMA (125 mg) over three sessions, with an optional supplementary dose (62.5 mg) in each session.[9] The qualitative ayahuasca study did not specify doses but reported varied session frequencies, ranging from weekly, biweekly, and monthly, to sporadic and variable patterns.[93]

Dosing in Control Group

Of 45 interventions, 20% (n=9) included a control group.[9-14,81,88,113] Three of these studies used active controls of lower doses or alternative medications, such as 20 mcg of LSD,[4] 0.05 mg/kg of midazolam,[88] and 1 or 3 mg/70 kg of psilocybin.[13] The remaining six studies employed inactive controls (e.g. normal saline, 250 mg of niacin, lactose capsules)[9,10-12,81] or a comparison group that received standard palliative care treatment.[37]

Outcome Measures

Table 4 lists the clinical indicator assessment tools and validated measures of other domains that were reviewed and tallies the frequency of their administration across studies. In terms of frequency of administration, the domains most often assessed were affective (n=56 measures), cognitive affective (n=29 measures), spiritual (n=15 measures), holistic (n=12 measures), adverse mental health effects (n=10 measures), and physical (n=10 measures). The least assessed domains were personality (n=8 measures), psychiatric (n=4 measures).

A total of 29 studies measured the affective domain.[9-15,77,78,80-83,87-89,91,95-98,101-104,108,109,112,113] Eleven studies measured the cognitive-affective domain. [8-10,13,81,83,88,97,105,108,109 14] Ten studies measured the holistic domain.[9,10,13-15,77,83,84,96,109] Eight studies measured the spiritual domain,[10-13,96,108,109,111] and seven studies measured the adverse mental health effects domain.[8,12,75,78,83,102,113] Seven measured the physical domain.[9,78,80,83,93,102,112] Six studies measured the personality domain.[68,70,73,74,75,76] Four studies measured the psychiatric domain.[8,11,13,14]

Only one study included two measures of substance use: the Alcohol Use Disorder Identification Test (AUDIT) and Drug Use Disorders Identification Test (DUDIT).[8] Rationale for the inclusion of these two psychiatric measures was not included in the study.

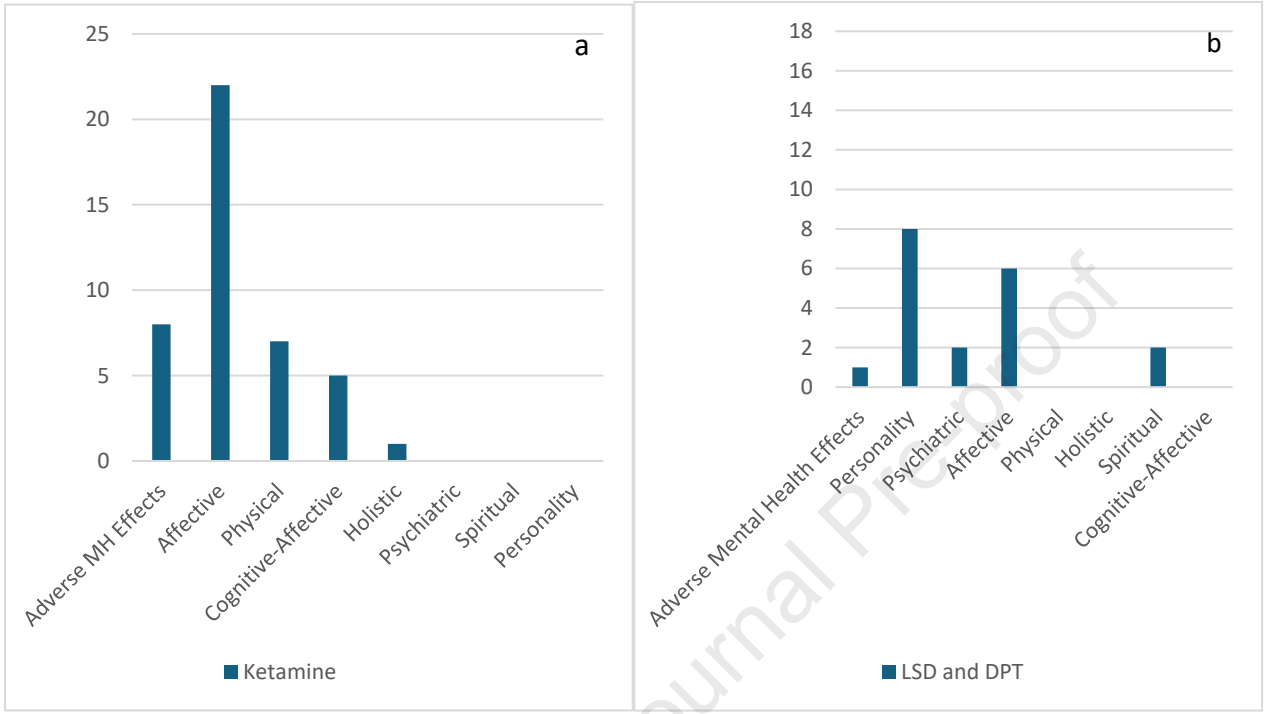
Outcome Measures by Psychedelic

Figure 7 shows the assessment of domains by psychedelic, excluding ayahuasca. A study could assess more than one domain and therefore contribute to the count in several domains.

Ketamine studies (n=24) most frequently assessed were affective (92%; n=22/24), adverse mental health effects (33%; n=8/24), physical (29%; n=7/24), and cognitive-affective (21%; n=5/24) domains. Most LSD or DPT studies (n=18) assessed personality (44%; n=8/18), and affective (33%; n=6/18) domains. Psilocybin (n=14) studies provided the most comprehensive assessment of domains. The most frequently assessed domain was affective (;n=24/14), followed by cognitive-affective (n=22/14), spiritual (n=12/14), and measured adverse and psychiatric at the same level (n=3/14). The assessment pattern for MDMA studies is shown in Figure 7 for completeness, but it is difficult to offer an interpretation with only two studies.

The one ayahuasca study was qualitative and involved semi-structured interviews that included questions addressing the subjective impact of diagnosis, the effects of ayahuasca ritual experiences on the understanding of illness, and subsequent behavioural changes.[97]

533 *Figure 7. Count of Studies Assessing Each Domain by Psychedelic, excluding Ayahuasca*



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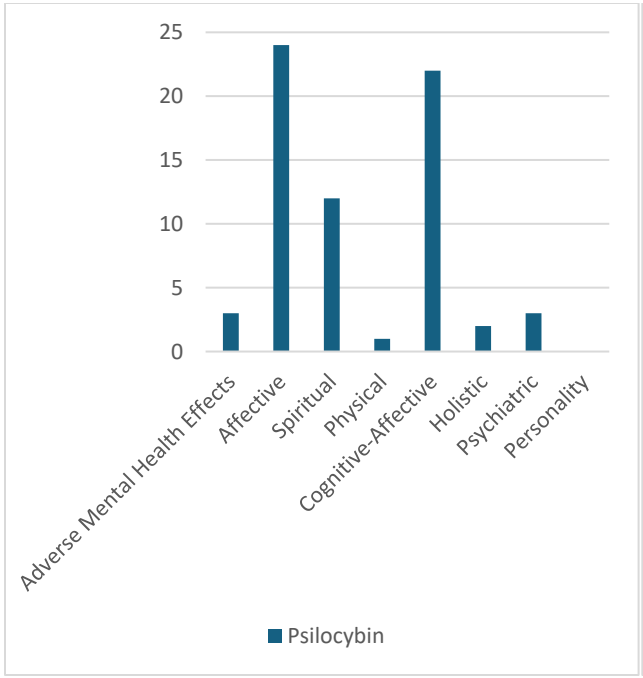

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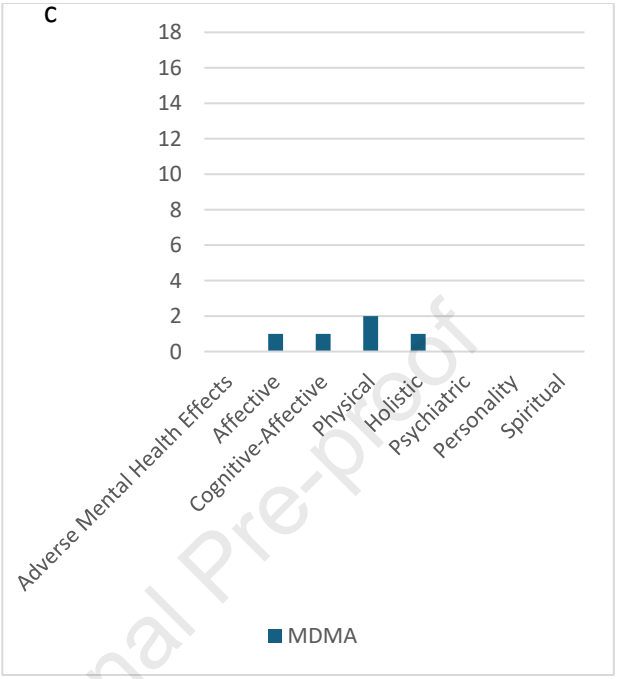

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Postulated Mechanisms by Type of Psychedelic

Theorized intervention mechanisms were identified based on author descriptions of the underlying processes or systems by which psychedelics exert their effects—whether that be on a neurobiological, psychological, or spiritual level.

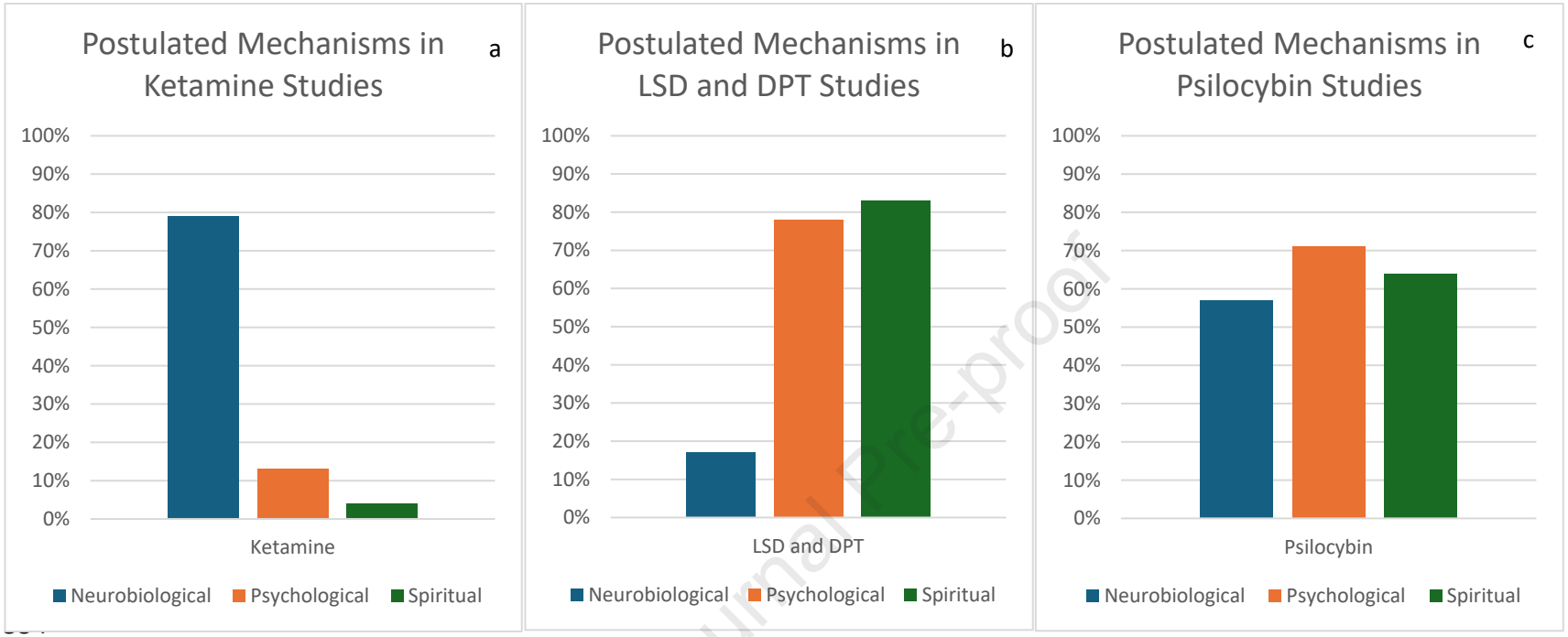
Postulated Neurobiological Mechanisms

Neurobiological mechanisms focused on altered brain activity at the structural or molecular levels, exploring how psychedelics interact with specific neurotransmitters, receptors and neural pathways. This type of mechanism was reported by 54% of studies (n=32/59).

As shown in Figure 8, 79% (n=19/24) of ketamine studies postulated neurobiological mechanisms. [15,77-81,83-89,100-103,106,113] This compared to 57% (n=8/14) of psilocybin studies, [8,10,12,13,107-109,112] and only 15% (n=3/20) of LSD/DPT studies.[11,14,98]

Both MDMA studies highlighted neurobiological mechanisms, suggesting MDMA therapy reduces amygdala activity to decrease fear and anxiety, enhanced frontal lobe activity for better emotional regulation, and elevated oxytocin and serotonin levels to enhance empathy and introspection.[9,93]

553 *Figure 8. Postulated Mechanisms by Psychedelic (Excluding MDMA and Ayahuasca)*



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Postulated Psychological Mechanisms

Psychological mechanisms, reported by 51% (n=30/59) of studies,[9-13,65-76,86,90-96,98,105,108,109,111] refer to mental, emotional, and psychosocial processes that can be influenced by TPIs. In the context of TPIs, these mechanisms involve profound mental and emotional effects, ranging from the resurfacing of repressed memories, emotional catharsis from confronting these memories, or cognitive breakthroughs in understanding behaviours, thought patterns, and ways of relating. They accelerated or intensified standard psychotherapeutic processes like transference and cognitive restructuring, often accelerating and intensifying these experiences, leading to insight and emotional healing, and improved social functioning.

Of 20 LSD/DPT studies, 70% (n=14) discussed psychological mechanisms.[11,65-76,98] Of 14 psilocybin studies, 71% (n=10) discussed psychological mechanisms.[10,12,13,90-92,96,108,109,111] Only three (13%) of 24 ketamine studies postulated a psychological mechanism.[86,95,105]

The two MDMA studies postulated that the creation of a psychologically safe space for trauma processing and broad existential exploration may have led to improvements in psychological suffering associated with end-of-life issues.[9,38]

The one study on the ritual use of ayahuasca discussed psychological mechanisms.[94] Ayahuasca was seen to alter perspectives and affect the process of illness resignification in the context of severe physical illnesses. The study notes that the exact psychological mechanisms through which ayahuasca exerts these effects are not fully understood and therefore warrant further research.

Postulated Spiritual Mechanisms

Spiritual mechanisms refer to the processes by which psychedelics induce experiences that are deeply meaningful in relation to self, others, and the universe. These can include feelings of interconnectedness with the universe, dissolution of ego boundaries, or a profound sense of sacredness. Such experiences often lead to a reconfiguration of personal beliefs, values and understanding of existence.

This type of mechanism was reported by 44% (n=26/59) of studies.[8,14,62,63,64,66-74,76,90-93,98,105,107-111] Of 18 LSD/DPT studies, 83% (n=15) discussed spiritual mechanisms.[14,62-64,66-74,76,98]

Of 14 psilocybin studies, 64% (n=9) discussed spiritual mechanisms.[8,90-92,107-111] Only one of 24 ketamine studies postulated a spiritual mechanism.[105]

A follow-up qualitative interview study on MDMA,[93] involving participants from an MDMA RCT,[9] postulated a spiritual mechanism that was not discussed in the trial. The ayahuasca study did not touch on spiritual outcomes.

DISCUSSION

This is the first scoping review aimed at mapping the empirical literature on the range of TPIs in populations coping with end-of-life issues. We found that tremendous variety exists and discuss the implications.

State of the Art

TPI research remains at an early stage of development, with researchers testing an extraordinary range of interventional approaches in an end-of-life context. At this time, the cultivation of a range of approaches may be appropriate and desirable given the variety of options regarding dosing substances and strategies and the possibility of interactions with individual and contextual factors. As the field progresses and mechanisms of action become clearer, we can expect that each approach will develop and refine and that patients will be able to choose in which theoretical frame they want to receive psychedelics as a treatment for their condition. For palliative populations especially, TPIs will need to demonstrate evidence of real-world effectiveness and tolerability that can meet the nature and scope of patient needs at the end of life.

Case studies were by far the most common research design, followed by experimental non-controlled studies. The high proportion of case studies compared to the other study designs, may be due to several factors, including interest in providing a comprehensive account of clinical processes, exploratory testing of safety and efficacy, and the relative affordability and feasibility of these designs. While the case study design provided valuable insights into understanding specific instances of TPI use, there is a need for more rigorous designs, namely RCTs, to establish causal inferences and enhance generalizability. It is also important to include research designs that provide contextual insights, such as naturalistic outcome studies. These

studies provide real-world data on effectiveness, capturing how TPIs operate in healthcare settings, which is needed to understand issues with their implementation.

RCTs are more complex and costly endeavours that comprise 11% of studies in this review—but they offer the best evidence of a causal relationship between psychedelic-assisted therapy and outcomes. However, there are some methodological challenges to overcome related to this design related to functional unmasking.[114] Selecting an adequate placebo poses challenges, particularly for substances like psilocybin and LSD. Using a lower dose as an active control maintains blinding but complicates dose-effect analysis. Conversely, MDMA studies benefit from easier control selection, such as using a stimulant (e.g., methamphetamine) as a comparison drug to better distinguish the effects of MDMA from a stimulant,[115] but this method has yet to become standard.

There is a need for more RCTs with active controls to generate best evidence for large-scale approval in end-of-life populations. More comparative experimentation is required to identify optimal combinations of components and contexts that will contribute to efficacy. However, naturalistic studies using programme evaluation methods that track patient outcomes in clinical settings will also remain valuable to clarify real-world effectiveness and implementation issues.

TPI studies using an RCT design most often explore psilocybin, perhaps because interest in this substance for end-of-life distress has gained traction in recent times,[10,13,14,37-43] and because its illicit status means that it can only be made accessible in a controlled research context. Ketamine, in comparison, is available for medical use and therefore easier to investigate, which helps to explain the many case studies focused on this substance. MDMA and ayahuasca appear left behind on the research landscape, with few research efforts examining their safety and effectiveness at end-of-life. It is worth further exploring how MDMA, an empathogen, known to enhance connectedness to self, others, and the world,[9,38] may be an effective psychedelic for alleviating end-of-life distress. MDMA may be particularly well-suited to end-of-life applications where the resolution of relationships is often a focus. At this time, there is not enough evidence supporting psilocybin as best suited or most effective for end-of-life compared MDMA, LSD, and ketamine.

We noted substantial under-reporting of participant race across studies; when this was reported, most participants were identified as White. More inclusive recruitment is needed to test effectiveness and to improve the generalisability of effects. Cultural differences may affect treatment acceptability in real world implementation.

Outcome Measures

Outcome measures were grouped across several domains, reflecting a convergence among researchers around the biopsychosocial-spiritual model for studying the effects of TPIs as part of end-of-life care,[119] although individual studies still reflect authors' preferred inclusion and labelling of these domains. Early LSD or DPT publications found that participants reported feelings of connection to loved ones, ascertained through qualitative patient accounts that quantitative measures often failed to capture.[66,67,75] Based on these findings, an opportunity exists to further develop validated measures for the impacts of TPIs on social interactions. Personality measures were included in early studies and dropped in recent research.[70,73-76] There may be less interest in personality changes following intervention given the foreshortened life expectancy in an end-of-life context. However, not all populations coping with end-of-life issues may be facing imminent death and treatment interactions with personality factors may warrant further investigation.

The results suggest that studies of different psychedelic substances focus on distinct outcome domains, which may reflect underlying assumptions held by researchers about their effects. Ketamine research focused heavily on physical and affective outcomes, likely due to its established use in clinical settings for these purposes. LSD and DPT studies emphasized personality and psychiatric outcomes. Psilocybin studies were comprehensive and focused on most domains, suggesting a potential for holistic therapeutic applications. This differentiation may imply that investigators tailor their outcome measurements based on beliefs about each substance's scope of impact and hypothesized efficacy, ultimately affecting study design and interpretation. Understanding these patterns can help improve future research to ensure a more balanced evaluation of a psychedelic intervention's therapeutic potential across domains.

The diversity of outcome measures in psychedelic research makes synthesis across studies a challenge. There is growing recognition of the need to standardize outcome measures.[126] The findings of this review highlight the importance of consistently assessing key outcome domains—physical, psychological (including affective, cognitive-affective, psychiatric, and personality aspects), social, holistic, and spiritual—using validated instruments across various TPIs. This comprehensive approach will enhance comparability of results, crucial in an emerging field where mechanisms and outcomes are not yet fully understood.

Psychological Suffering of Study Participants

Researchers and clinicians are improving their understanding of enduring and intolerable psychological suffering that exists in an end-of-life context,[127,128] and have found that the construct spans the biopsychosocial-spiritual domains, aligning with the breadth of outcomes employed in the TPI field of research. To date, assessment instruments deployed in studies have not adequately assessed the effects of interventions on psychological suffering at end-of-life. Most studies operationalised psychological suffering in terms of the syndromes of depression and anxiety but how such reductionism affects clinical inferences or generalizability of effects is unclear. These studies recruited participants with mood-related symptoms of anxiety and depression or those with a formal psychiatric diagnosis, such as Generalized Anxiety Disorder or Major Depressive Disorder—although a small percentage of studies included participants from both of these groups. However, as each of these criteria are distinct, it can be difficult to interpret the effectiveness of TPIs in addressing the psychological distress arising from life-threatening conditions, as opposed to treating longstanding diagnoses of anxiety and depression. Subgroup analyses in future are recommended to address this question.

Nonetheless, given that psychiatric co-morbidity in this population is common,[129,130] future research should also explore how these co-occurring conditions interact and affect the effectiveness of TPIs. Studying heterogeneous samples may provide more clinically relevant insights than focusing on narrowly selected diagnostic subgroups. Studies aimed at clarifying the relationships between mood-related symptoms (e.g., self-reported) and diagnosis criteria

within the end-of-life context would add to our understanding and development of TPI treatment protocols. Analyses of subgroups scoring above recognised thresholds on mood-related symptoms or showing minimal clinically important differences can also be recommended.

Enduring and intolerable psychological suffering at the end of life is typically conceptualised in response to a life-foreshortening physical illness. However in this review, we found two relevant case studies of participants with intractable life-threatening suicidal ideation in the absence of physical disease.[97,105] Even though the physical indication was absent, their mental disorder was so severe that premature death was an imminent threat and justified the use of TPI. These studies further open the doorway to a conversation about what constitutes an end-of-life condition and the relationship between mental disorders and the experience of enduring and intolerable suffering.[131,132]

Postulated Mechanisms

We found relationships between the postulated mechanisms of action (neurobiological, psychological, and spiritual) and characteristics of the TPI (substance and approach) under investigation. The psychological and spiritual emphasis in LSD research may be influenced by its past clinical use in psychotherapy, along with early research informed by a more spiritual perspective.[133-135] Psilocybin has been consistently used in a holistic fashion, favouring a tripartite model and discussion of spiritual and psychological mechanisms. It is quite possible that the spiritual focus in psilocybin studies stems from its historical use in Indigenous rituals.[136] The two MDMA studies both postulated neurobiological mechanisms, with the qualitative study also discussing psychological and spiritual mechanisms. MDMA is not typically thought of as a classic psychedelic that can induce mystical experiences[137,138] relevant to coping with the end of life, nor are mystical experiences as prevalent with MDMA. However, nearly all participants in a qualitative follow-up study of MDMA-assisted therapy for end-of-life-related anxiety reported experiencing a beneficial mystical experience.[93] MDMA-induced mystical experiences deserve further study as a potential mechanism in this context.

The focus of ketamine research on a dosing-alone approach and neurobiological mechanisms reflects the broader psychiatric trend towards biological explanations for mental health issues,[139,140] exemplified by theories like the monoamine hypothesis of depression.[141,142] However, the ongoing debate over the etiology of mental health concerns—whether they are neurobiological or influenced by broader psychological and social factors[143-146]—suggests that a more holistic approach incorporating spiritual and psychological aspects into the intervention could enrich our understanding of ketamine's therapeutic potential.

Such a holistic approach not only aligns with the growing interest in TPIs for a variety of conditions, but also challenges the existing biomedical paradigm.[147,148] The biomedical paradigm features prominently in psychedelic research, in particular ketamine research, and privileges neurobiological mechanisms. This paradigm typically positions physicians as the preferred prescribers and interventionists, and often marginalizes other healthcare professionals who may seek to address the psychosocial-spiritual domains of healing. There is a concern among some stakeholders[149] that psychedelic-assisted therapies may become reduced to psychedelic therapies, stripped of their holistic components, consistent with general trends in healthcare to deprioritise social and psychological supports.[150,151] Such a development may limit the potential effectiveness of the psychedelic modality, which may benefit from a more holistic approach within an end-of-life care context. Research in palliative and supportive care has consistently supported an integrative view that considers the interplay of neurobiological, psychological and spiritual mechanisms underlying treatment.[119]

In light of this, researchers must report whether they consider all three postulated mechanisms to be involved in the TPI experience. The discussion of researcher stances on biopsychosocial-spiritual processes would lay a foundation on which to further elucidate the action of psychedelic substances. It may also foster a more inclusive agenda that values the contributions of various healthcare professionals, including psychologists, social workers, and spiritual care providers, alongside physicians.

From Challenging to Adverse Experiences

All healthcare interventions carry a potential risk for negative outcomes, ranging from minor to severe. The lack of uniform terminology in the psychedelic research publications that is used to describe adverse outcomes poses significant difficulties for those conducting reviews and developing clinical protocols and policies.[152] Terms such as "adverse event," "adverse effect," "adverse drug reaction," "side effect," and "harms," among others, are often used interchangeably.[153] They refer to undesirable or harmful results arising during or following the administration of a medical intervention. Within psychedelic studies, the terms "adverse effect" or "side effect," along with "challenging experience," have been used to capture various states of experience ranging from mild and transient adverse physical effects like nausea and vomiting[71,76,96] to distressing psychological episodes, such as derealization and dissociation.

Although the distinction is not always consistent or clear, the term challenging experience has the connotation that it can contribute to the therapeutic process, unlike an adverse effect, which is clinically undesirable. It may be useful to consider that when a challenging experience exceeds a certain threshold of severity, that it be considered an adverse effect. Pragmatically, therapists attempt to manage the psychedelic encounter such that clients can pass through challenging experiences feeling supported and preventing its escalation to the level of trauma. Subsequent care entails integrating challenging experiences to further promote healing and change. However, where this threshold lies for each person, and how it may be affected by such set and setting, including preparatory work and clinician factors, requires substantial work to clarify. The spectrum of challenging experiences raises ethical concerns about risk assessment and informed consent in psychedelic interventions, suggesting that TPIs may require different risk assessment criteria compared to more conventional medical procedures, where risks and benefits are more clearly defined in advance.[154]

How integral are challenging experiences to the therapeutic outcome, if at all? We do not yet know based on the findings in the studies reviewed. Given this uncertainty, it is crucial to identify and report the range of such challenging to adverse experiences, especially given a clinical legacy where these experiences were once historically intentionally induced, resulting in a mix of therapeutic and harmful outcomes.[155,156] This need is heightened by the broader issue

783 of their underreporting, partly due to systematic assessment gaps.[157-160] Developing a
784 standardized framework for understanding and managing these experiences could enhance the
785 consistency, effectiveness, and overall conceptualization of psychedelic-assisted therapy.[161]
786 This framework could include defining what constitutes an adverse and/or challenging
787 experience in both physical (e.g., nausea) and psychological (e.g., panic) domains and to what
788 extent. This would pave the way for clearer guidelines on how to handle such events and
789 integrate them into treatment, or not, contributing to the improved safety and efficacy of TPIs.
790
791 ***Summary Implications***
792 We have described the variability of TPIs and laid the foundation for a much-needed
793 step toward more rigorous research in this field. When considering what a TPI is and how it can
794 be best applied within the end-of-life context, it is crucial to consider and ensure the reporting
795 of four key aspects: (1) The researcher's choice of outcome measures while also reflecting on
796 and considering assessment based on the full biopsychosocial-spiritual model; (2) the
797 discussion of postulated mechanisms, as this, in turn shapes (3) the interventional approach,
798 such as the type of substance chosen, and whether psychotherapy, music, and so forth are
799 included in the treatment. Additionally, (4) aligning the approach to identifying adverse and/or
800 challenging experiences in TPIs could clarify their therapeutic role, improve treatment
801 consistency and safety, and offer clearer guidelines for practitioners, enabling further progress
802 in this field of research. These four aspects should serve as a starting point for developing
803 greater rigour in design and reporting of future psychedelics research. At this exploratory stage,
804 rigid standardization of interventional approaches may not be appropriate. Cultivating a range
805 of therapeutic options may be valuable given the richness of this renewed frontier for
806 psychiatric medicine and the diversity of patient populations.

LIMITATIONS

Although a comprehensive search was conducted, some studies may have been overlooked. The inclusion criteria limited studies to those published in English, Spanish, Portuguese, and French, to the exclusion of other languages. Database coverage did not consult additional health-related databases such as Scopus and Web of Science, which may have limited the comprehensiveness of our search. The exclusion of the grey literature may have omitted important non-peer-reviewed sources. The heterogeneity in types of TPIs, study designs, methodologies, and outcome measures across the included studies could have led to overly generalized findings. These limitations underscore the need for continued review efforts on the emerging TPIs that are being studied and comparisons of their interventional approaches and outcome data in the end-of-life context.

CONCLUSION

The contribution of this scoping review is its unveiling of the extraordinary variation, previously unidentified, in how TPIs are studied to address the experience of psychological suffering associated with end-of-life concerns. This analysis of this variety revealed how research conceptualization and progress can be influenced by sociohistorical factors and assumptions about the mechanisms of action for psychoactive substances. Some of the variation observed can be attributed to the early stage of development in psychedelic medicine, which is still grappling with defining and measuring the main indication for its use in an end-of-life setting. As the field progresses, we can expect greater consensus about best practices and that further variation will be more intentional in the development of therapeutic modalities to address different population needs. Overall, the findings offer a unique demonstration of the social science of medicine in the evolution of TPIs as part of palliative care.

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1287 *Table 1. The Population, Concepts, Context Framework*

Population	**Concepts**		**Context**
End of Life	Indication: Psychological Suffering	Intervention: Psychedelics	Setting
People coping with life-threatening illness and the end of life.	*A multifaceted experience of psychological suffering associated with confronting end-of-life issues.*	*Therapeutic psychedelic interventions encompass psychedelics that may be applied alone or as an adjunct to psychotherapy.*	*Contextual factors related to when, where, and under what conditions studies were conducted, shaping how TPIs are implemented and understood.*
Physical illness type	Psychiatric diagnoses	Intervention characteristics (e.g., clinical approach, aesthetic elements)	Year of publication
Biological sex	Symptoms of anxiety and depression	Psychotherapeutics (e.g., type of supports provided, approach to challenging experiences)	Country of publication
Race	Outcome measures	Postulated mechanisms	Study setting

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1289 *Table 2. Example Search Terms Used in the Search Strategy*

Example Search Terms		
Population	**Concepts**	
End-of-Life	**Indication: Psychological Suffering**	**Intervention: Psychedelics**
People coping with life-threatening illness and the end of life.	*A multifaceted experience of psychological suffering associated with end-of-life issues.*	*Therapeutic psychedelic interventions encompass psychedelics that are an adjunct to psychotherapy.*
palliative care	anxiety	ketamine
hospice	demoralization	psilocybin
terminally ill	psychological suffering	mescaline
life-threatening illness	existential distress	peyote
	depression	MDMA
		LSD
		DPT
		psychedelic-assisted therapy
		ayahuasca
		ibogaine

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1291 *Table 3. Extracted Data Variables*

Overarching Domain	Data Variables
Study Characteristics	Author
	Year of publication
	Country of publication
	Study design
	Setting
Sample Details	Sample size
	Biological sex
	Race
	Psychiatric indication
	Physical indication
	Psychiatric exclusion criteria
Intervention Details	Type of psychedelic
	Dosage
	Route of administration
	Interventional approach
	Aesthetic elements
	Preparatory sessions
	Dosing sessions
	Integration experiences
	Challenging and/or adverse experiences
Outcome Measures	Clinical indications (physical health, adverse mental health effects)
	Psychological measures (affective measures, cognitive-affective measures, psychiatric measures, personality measures)
	Spiritual measures
	Holistic measures
	Cognitive impairment measures
Postulated Mechanisms	Neurobiological mechanisms
	Psychological mechanisms
	Spiritual mechanisms

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1294 *Table 4. Validated Outcome Measures by Domain of Assessment*

Domains	Subdomains	Validated Measurement Tools	Frequency
Clinical Indicators	Physical (No. of administrations=10)	Pain Visual Analogue Scale	6
		Functional Status Karnofsky Performance Status Scale (KPSS)	1
		Medical Outcomes Study Sleep Scale (MOS-Sleep)	1
		Pain Visual Analogue Scale derived from the Brief Pain Inventory Short Form (BPI-SF)	1
		Pittsburgh Sleep Quality Index (PSQI)	1
	Adverse Mental Health Effects (No. of administrations=10)	Brief Psychiatric Rating Scale (BPRS)	3
		Mini-Mental State Exam (MMSE)	2
		Dissociative Symptoms Scale (DSS)	1
		Frequency, Intensity, Burden of Side Effects Rating (FIBSER)	1
		Young Mania Rating Scale (YMRS)	1
		Montreal Cognitive Assessment (MoCA)	1
		Restlessness and anxiety from the Palliative Symptom Burden Score (PSBS) considered a measure of persistent psychotomimetic side effects	1
Psychological	Affective (No. of administrations=56)	Beck Depression Inventory (BDI)/(BDI-II)	10
		Hamilton Anxiety and Depression Scale (HADS)	9
		Montgomery Asberg Depression Rating Scale (MADRS)	9
		State Trait Anxiety Inventory (STAI) (Form X/Y/Global)	9
		Hamilton Depression Rating Scale (HDRS)/HRSD/GRID-HAMD	5
		Patient Health Questionnaire–9 (PHQ-9)	3
		Generalized Anxiety Disorder-7 (GAD-7)	2
		Profile of Mood States (POMS)	2
		Brief Edinburgh Depression Scale (BEDS)	1
		Hamilton Anxiety Rating Scale (HAM-A)	1
		Maudsley Visual Analogue Scale	1
		Patient Health Questionaire-4 (PHQ-4)	1

		Quick Inventory of Depressive Symptomatology–Self-Report (QIDS-SR)	1
		Self-Compassion Scale (SCS)	1
		State Trait Anxiety Depression Inventory (STADI)	1
	Cognitive-Affective (No. of administrations=29)	Demoralization Scale (DS/DS-II)	5
		Beck Scale for Suicidal Ideation (BSI-I/BSI-II)	4
		Hopelessness Assessment in Illness (HAI) Questionnaire	3
		Death Anxiety Scale (DAS)	2
		Brief Symptom Inventory (BSI)	1
		Challenging Experiences Questionnaire (CEQ)	1
		Columbia Suicidality Severity Rating Scale (C-SSRS)	1
		Composite score representing Suicidal Ideation (from BDI-II and BSI)	1
		Death Attitude Profile (DAP)	1
		Death Transcendence Scale (DTS)	1
		Five Facet Mindfulness Questionnaire (FFMQ-15)	1
		Inventory of Complicated Grief-Revised (ICG-R)	1
		Life Attitude Profile (LAP/LAP-R)	1
		Life Orientation Test-Revised (LOT-R)	1
		Post Traumatic Stress Disorder Checklist-5 (PCL-5)	1
		Purpose in Life Test (PIL)	1
		Schedule of Attitudes toward Hastened Death (SAHD)	1
		Mini International Neuropsychiatric Interview (M.I.N.I. PLUS / Suicide Risk Assessment)	1
		Complex Assessment and Management of Suicidality (CAMS)	1
	Psychiatric (No. of administrations=5)	Symptom Checklist-90-Revised instrument (SCL-90-R)	2
		Alcohol Use Disorder Identification Test (AUDIT)	1
		Drug Use Disorders Identification Test (DUDIT)	1
		Hallucinogen Rating Scale (HRS)	1
	Personality (No. of administrations=8)	Personal Orientation Inventory (POI)	4
		Minnesota Multiphasic Personality Inventory (MMPI) and the Mini-Mult: A short form of the Minnesota Multiphasic Personality Inventory	4

Spiritual (No. of administrations =15)		Mystical Experience Questionnaire (MEQ 30)	5
		Functional Assessment of Chronic Illness Therapy-Spiritual Well-Being (FACIT-Sp-12)	4
		5-Dimensional Altered States of Consciousness Rating Scale (5D-ASC)	3
		Mysticism Scale (Experience-specific 9-point scale)	1
		Faith Maturity Scale (FMS)	1
		Healing Experience of All Life Stressors (NIH-HEALS)	1
Holistic (No. of administrations =12)		McGill Quality of Life Questionnaire (MQOL)/(MQOL-R)	3
		World Health Organization Quality of Life scale, Brief Version (WHOQOL-Bref)	2
		Edmonton Symptom Assessment Scale (ESAS/ESAS-r)	2
		Functional Assessment of Chronic Illness Therapy (FACIT) (physical well-being, social/family well-being, emotional well-being, functional well-being, additional concerns)	1
		EORTC QLG Core Questionnaire (EORTC QLQ-C30)	1
		Global Assessment of Functioning (GAF)	1
		Posttraumatic Growth Inventory (PTGI)–Posttraumatic Growth	1
		National Institute of Health, Healing Experiences in All Life Stressors (NIH-HEALS)	1

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HIGHLIGHTS

- Research on psychedelic interventions for end-of-life distress is highly diverse
- Ketamine was uniquely linked to the biomedical model unlike other substances
- Measures of psychological suffering spanned biopsychosocial-spiritual domains
- The therapeutic value of challenging experiences remains uncertain
- Exploring treatment diversity is key but standardised reporting would enhance rigor

Ethics approval was not needed for this scoping review.