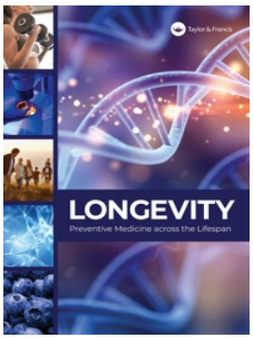


Longevity

ISSN: 3065-3495 (Online) Journal homepage: www.tandfonline.com/journals/tpml20

# Psychedelics and longevity: implications for lifespan, healthspan and functional aging

Mark Haden, Birgitta Woods, Tina Woods & Kenneth W. Tupper

**To cite this article:** Mark Haden, Birgitta Woods, Tina Woods & Kenneth W. Tupper (2026) Psychedelics and longevity: implications for lifespan, healthspan and functional aging, Longevity, 7:1, 2696224, DOI: 10.1080/30653495.2026.2696224

**To link to this article:** https://doi.org/10.1080/30653495.2026.2696224

LONGEVITY
https://doi.org/10.1080/30653495.2026.2696224

RESEARCH ARTICLE

OPEN ACCESS Check for updates

# Psychedelics and longevity: implications for lifespan, healthspan and functional aging

Mark Haden[a], Birgitta Woods[b], Tina Woods[c] and Kenneth W. Tupper[a,d]

[a]University of British Columbia, School of Population and Public Health, Vancouver, British Columbia, Canada; [b]Vancouver Coastal Health, Vancouver, British Columbia, Canada; [c]Collider Health, International Institute of Longevity, London, UK; [d]Canadian Institute of Substance Use Research, University of Victoria, Victoria, British Columbia, Canada

**ABSTRACT**

Longevity science has increasingly shifted its focus from extending lifespan to improving healthspan, the years lived in good physical, cognitive, and social health. While much research targets biological hallmarks of aging, emerging frameworks emphasize upstream psychosocial drivers such as chronic stress, trauma, social isolation, and health behavior. In parallel, research on psychedelic compounds (e.g., psilocybin, LSD, MDMA, and ayahuasca) suggests they can produce durable changes in mental health, behavior, and social functioning, with downstream physiological implications. Multiple mechanisms implicated in psychedelic effects, (e.g., enhanced neuroplasticity, modulation of immune and inflammatory signaling, stress-response recalibration, and sustained improvements in psychological well-being and social connectedness), overlap with pathways influencing biological aging. This narrative review examines the convergence of psychedelic research and longevity science, exploring how psychedelic-assisted interventions may influence aging trajectories through both direct biological and indirect psychosocial pathways. We also discuss safety issues and research priorities, including integrating biomarkers, functional outcomes, and longitudinal study designs, and consider whether psychedelic interventions may function as systems-level catalysts for healthier aging.

**ARTICLE HISTORY**
Received 30 April 2026
Accepted 17 June 2026

**KEYWORDS**
Psychedelics; longevity; psilocybin; LSD; lifespan; healthspan

## Introduction

Population aging is one of the defining global challenges of the 21st century, marked by rising rates of chronic disease, disability, healthcare utilization, and health system costs. While advances in medicine have significantly extended lifespan, they have also increased the number of years many individuals live with chronic disease, disability, or functional impairment. For many this translates into years or even decades of ill health, diminished quality of life, and increased healthcare expenses.

As a result, longevity research has shifted from the single focus of extending the number of years lived toward improving the portion of life spent in good physical, mental, and social health, free from serious disease or disability. Throughout this review, we distinguish several related but conceptually distinct constructs. Lifespan refers to total years lived; healthspan refers to years lived in good physical, cognitive, and social functioning, biological aging refers to the physiological processes that contribute to age-related decline, and psychosocial flourishing refers to positive psychological well-being and social functioning, that may contribute to healthspan but is not itself equivalent to slowed biological aging. Similarly, reductions in disease burden may improve healthspan without necessarily altering underlying biological aging processes.

At the biological level, longevity research is grounded in a growing understanding of the 'hallmarks of aging', which a recent geroscience framework described a set of interconnected processes, that included cellular senescence, altered intercellular communication, and chronic inflammation, that drive age-related decline [1]. Interventions that target these mechanisms have been shown to extend both lifespan and healthspan in model organisms, highlighting their potential relevance for human aging.

Longevity science increasingly recognizes that aging and disease arise not only from isolated molecular damage, but also from interactions among biological, psychological, and social systems that shape resilience, disease risk, and functional decline over time [1,2]. While early longevity research emphasized direct molecular interventions, more recent reviews of observational and epidemiological

**CONTACT** Mark Haden mark@markhaden.com

evidence identify upstream regulators of aging, including chronic stress, inflammation, behavioral patterns, and social integration [2–4].

In parallel, over the past two decades there has been a resurgence of scientific research on psychedelic compounds, including classic serotonergic psychedelics such as lysergic acid diethylamide (LSD), mescaline, psilocybin, *N*,*N*-dimethyltryptamine (DMT) and DMT-containing preparations such as ayahuasca, the atypical psychoactive alkaloid ibogaine, the empathogen-entactogen MDMA, and the dissociative anesthetic ketamine. While these compounds can produce overlapping therapeutic and psychological effects, hence their categorization as 'psychedelic' substances, they differ substantially in pharmacology, mechanisms of action, and evidence base. Despite important differences in pharmacology and mechanism of action, growing clinical and observational literatures suggest that several psychedelic compounds may improve outcomes across a range of psychiatric and behavioral conditions. These include numerous mental and substance use disorders [5,6], traumatic brain injuries [7,8], and catalyzing behavioural change in both the pro-health [9] and prosocial domains [10,11].

With respect to the classic serotonergic psychedelics, in particular the prototypical compound psilocybin, there is evidence emerging from in vitro aging models and mouse survival studies suggesting direct effects on hallmarks of aging, including extension of cellular lifespan and improved survival in aged mice following psilocybin exposure [12]. Notably, the work by Kato et al. provides preliminary empirical support for the 'psilocybin-telomere hypothesis' [13] as telomere length was preserved in psilocin-treated age-matched cells and reduction in telomere length is a hallmark of cellular aging.

Positive correlates of psychedelic use with physical, psychological and social health have been observed in both the clinical trial research and 'naturalistic use' evidence which examines observational data collected outside of clinical trials [14]. Both clinical trials and naturalistic use studies consistently suggest that psychedelics can produce profound durable changes in mental health, stress regulation, emotional flexibility, social functioning and chronic dependent substance use [6,14,15], all of which are independently associated with biological aging trajectories and mortality risk [2,4]. Although psychedelics have not typically been conceived as longevity interventions, emerging scientific evidence regarding their effects on stress, behavior, and social functioning suggests potential relevance to healthspan science. Within this broader systems view, psychedelic research intersects with longevity science both as a direct life-extension strategy, and more importantly as a potential modulator of healthspan-relevant behaviours.

An emerging framework that integrates the biopsychosocial determinants of aging is the exposome, defined as the cumulative set of environmental, behavioral, and psychosocial exposures experienced across the life course along with their biological responses [16]. While early exposome research focused largely on chemical and physical exposures, contemporary formulations explicitly include psychosocial, socioeconomic, and lifestyle exposures as critical components shaping health trajectories. Within this framework, factors such as chronic stress, trauma, social isolation, socioeconomic adversity, sleep disruption, diet, and other health behaviors constitute a *psychosocial exposome* that interacts with biological systems to influence aging processes [17].

Importantly, these exposures rarely occur in isolation. Instead, they accumulate and interact over time, producing cumulative biological effects through neuroendocrine, immune, metabolic, and epigenetic pathways. This perspective aligns with life-course models of aging that emphasize how repeated social and psychological experiences become biologically embedded. Framing psychosocial influences within an exposome model therefore provides a systems-level perspective for understanding how complex experiential environments shape the biological processes underlying longevity and age-related disease.

It is important to note that much of the evidence linking psychedelic exposure with positive health outcomes derives from observational, naturalistic, and population-based studies. Such studies are vulnerable to selection effects, expectancy influences, confounding variables, publication bias, inaccurate recall, and uncertainty regarding compound identity, dose, and context of use.

To date, the intersection between longevity biology and psychedelic research has received limited systematic attention. Yet multiple mechanisms implicated in psychedelic effects (e.g., enhanced neuroplasticity, modulation of immune and inflammatory signaling, stress-response recalibration, and sustained changes in psychological well-being and social connectedness) overlap with biological pathways known to influence aging trajectories.

This narrative review paper examines the convergence between longevity science and psychedelic research by identifying areas of overlap across both literatures. It explores how psychedelic-assisted interventions may plausibly influence aging trajectories, either directly through biological mechanisms associated with aging [12] or indirectly through sustained improvements in mental health, social functioning, and health-promoting behaviours.

## Neuroplasticity, neurogenesis, and brain aging

Brain aging is characterized by progressive reductions in synaptic density, neurogenesis, and network flexibility, alongside increased neuroinflammation and vulnerability to neurodegenerative disease [18]. Age-related cognitive decline is driven in part by reductions in neuroplasticity and network flexibility. Preservation of neuroplasticity is increasingly viewed as an important determinant of cognitive healthspan, contributing to resilience against dementia, depression, and functional decline. Interventions that enhance neural plasticity, have been associated in systematic reviews and meta-analyses with delayed cognitive aging and a reduced risk of dementia, including physical exercise [19] and cognitive enrichment [20].

Psychedelic compounds have emerged as potent modulators of structural and functional neuroplasticity and may facilitate large-scale neural circuit reorganization. Neuroplasticity encompasses several related processes, including neurogenesis (generation of new neurons), neuritogenesis (growth of the axons and dendrites), synaptogenesis (formation of synaptic connections among neurons), and spinogenesis (fine-tuning of those connections). Both preclinical and clinical studies provide converging evidence for these effects. In a series of cellular and animal-model experiments Ly and colleagues [21] demonstrated that classic psychedelics including LSD, DMT, and 2,5-dimethoxy-4-iodoamphetamine (DOI), increase neuritogenesis and spinogenesis in cellular and animal models, with subsequent cellular neuroplasticity experiments showing that brief exposures (15 minutes to 6 hours) were sufficient to initiate downstream neuronal growth processes [22]. These structural changes were accompanied by increases in synapse number and function and persisted well beyond acute drug exposure, suggesting durable remodeling of neural circuits relevant to learning and adaptability. Consistent with this, a rodent neuroplasticity study using psilocybin demonstrated increases dendritic spine density in the frontal cortex of mice for weeks following a single administration, with corresponding antidepressant-like effects [23]. Similarly, animal and cellular studies of DMT in ayahuasca have been shown to regulate neural stem cell proliferation and enhance neurogenesis, with associated improvements in spatial learning and memory tasks [24]. Multiple open-label neuroimaging studies in humans have demonstrated increased global connectivity, neurodynamic complexity and reduced dominance of the default mode network after psilocybin administration, reflecting a transient loosening of rigid neural hierarchies [25,26]. Psilocybin induced neuroplasticity may explain the dramatic improvement in the symptoms of Alzheimer's disease reported in a single case study [27]. A systematic review of 20 research papers observed that a single administration of a psychedelic produced rapid changes in brain plasticity mechanisms on a molecular, neuronal, synaptic and dendritic level, providing a robust explanatory mechanism for the clinical effects of psychedelic based treatments [28].

While most psychedelic clinical trials have focused on psychiatric outcomes in midlife adults, the capacity to transiently reopen windows of plasticity suggests potential relevance for cognitive reserve, a key determinant of dementia risk and late-life functional independence [18]. Longevity research increasingly values interventions that preserve adaptability rather than simply prevent damage. In this context, a review of the evidence on the ability of psychedelics to rapidly and intensely promote plasticity in adult brains [29] suggests a plausible mechanism for counteracting age-related neural rigidity. Preliminary empirical observations further support this possibility, including reports of improved neuropsychological functioning following ibogaine treatment in veterans with traumatic brain injury [7]. From a longevity perspective, psychedelic-induced plasticity may represent a novel approach to counteracting age-related rigidity in neural and behavioral systems.

Although direct evidence linking psychedelic exposure to preserved cognition in older adults is lacking, these findings raise the hypothesis that psychedelic-induced plasticity, if safely harnessed, could support cognitive resilience and slow aspects of brain aging. Testing this hypothesis will require longitudinal neuroimaging studies and cognitive outcome trials specifically designed for older adult populations.

### *Inflammation and psychedelics*

Chronic low-grade inflammation, or 'inflammaging', is a central feature of biological aging and a major contributor to cardiovascular disease, neurodegeneration, cancer, and frailty [30]. Inflammaging contributes both to systemic physiological changes, and to local pathological processes, including arteriosclerosis, neuroinflammation, osteoarthritis, and intervertebral disc degeneration [1], and is a common feature of an aging brain [18]. Because persistent low-grade inflammation contributes to multiple age-related diseases, interventions that reduce chronic inflammation may influence long-term disease risk and subsequent functional decline.

Emerging evidence suggests that psychedelics may influence immune signaling pathways relevant to inflammation. A review of pre-clinical immunology studies suggests that serotonergic psychedelics can modulate immune responses and reduce pro-inflammatory cytokine signaling under certain conditions [31]. Much of the effect appears to be mediated through the activation of the 5-$HT_{2A}$ receptor, which is expressed not only in the central nervous system but also on immune cells. A review by Flanagan and Nichols [32] reported that several serotonergic psychedelics exert potent anti-inflammatory effects in cellular and animal models via 5-$HT_{2A}$ signaling, often at doses too low to cause psychedelic effects. These authors observed that the synthetic psychedelic DOI had powerful anti-inflammatory activity, and that LSD was less potent but still similarly active. They concluded that 'overall, psychedelics regulate inflammatory pathways via novel mechanisms and may represent a new and exciting treatment strategy for several inflammatory disorders' (Flanagan and Nichols [32], p. 363)

Interestingly, the immunological effects of psychedelic compounds appear to differ from those produced by endogenous serotonin at the same receptor. While serotonin signaling at the 5-$HT_{2A}$ receptor can promote inflammatory responses in some immune contexts, activation of this receptor by psychedelic agonists may paradoxically produce anti-inflammatory effects based on a recent review of findings from cellular and animal models [33].

Clinical research also suggests that psychedelics may influence inflammatory processes in humans. In a small open-label study, ayahuasca was associated with reductions in inflammatory biomarkers and improvements in depressive symptoms in patients with treatment resistant depression [34]. According to a systematic review of ketamine and inflammatory biomarkers, reductions in these markers (particularly TNF-α, a potent pro-inflammatory cytokine) may be associated with an antidepressant response [35]. In a placebo-controlled human experimental study, a single dose of psilocybin produced acute alterations in immune signaling followed by reductions in inflammatory markers, including C-reactive protein (CRP) and interleukin-6 (IL-6), seven days after administration in healthy volunteers [36]. These findings suggest that psychedelic administration may induce short-term immune activation followed by longer-term modulation of inflammatory pathways.

Preclinical evidence further supports the immunomodulatory properties of psychedelics. A systematic review of animal and cellular studies found that 'classical' psychedelics (i.e., psychedelics that interact with the 5-$HT_{2A}$ receptor) exert context-dependent effects on immune function, with anti-inflammatory responses most evident under preexisting inflammatory conditions [37]. Similarly, Inserra et al. [38], reviewed evidence suggesting that psychedelic compounds influence interconnected systems involving neurotransmission, neuroplasticity, and immune signaling, suggesting important implications for treating psychiatric disorders. Patients with major depressive disorder, posttraumatic stress disorder (PTSD), anxiety and bipolar disorder typically exhibit elevated pro-inflammatory markers such as IL-1β, IL-6, TNF-α, and C-reactive protein, and dysregulated immune signaling has been proposed to contribute to depressive symptomatology (Inserra et al. [38], p. 228). The authors note that many psychedelics (i.e., DMT, 5-MeO-DMT, LSD, MDMA, and ketamine) demonstrate immune modulating properties and speculate that these effects may contribute to psychedelics' therapeutic benefits by restoring immune system balance. Similar conclusions have been reached in other reviews of DMT, 5-MeO-DMT, and related compounds [39].

Many psychosocial exposures strongly associated with accelerated aging, including trauma, chronic stress, depression, and substance use, converge on inflammatory pathways, suggesting that immune signaling may serve as a central biological mediator linking life-course experience to healthspan.

However, the extent to which these effects are direct, versus secondary to neuroendocrine changes, psychological stress reduction or improvement in mental health remains uncertain. Disentangling direct immunological effects of psychedelics from secondary systemic changes remains an important area for future research.

## Psychosocial risks of aging

### *Trauma, depression, substance use, and stress*

Although stress and adversity are common human experiences, greater exposure to trauma and chronic hardship is associated with increased risk of adverse physical and mental health consequences. Recent studies identify accelerated biological aging as a key mechanism explaining how trauma and adversity contribute to poor health. Traumatic events are particularly harmful and can cause posttraumatic stress disorder (PTSD), characterized by reexperiencing trauma, avoidance behaviors, and changes in cognition and mood. Also, the hyperarousal symptoms associated with PTSD correlate with physiological dysregulation, including cardiovascular dysfunction which are linked to poor health outcomes. Recent work demonstrates that both trauma exposure and PTSD development are associated with accelerated

biological aging. For example, in a sample of 339 trauma-exposed veterans, greater PTSD hyperarousal symptom severity was associated with accelerated DNA methylation–based biological aging [40] and this association between accelerated aging and PTSD was further supported in two systematic literature reviews [41,42].

Depression and anxiety disorders are also associated with accelerated epigenetic aging and increased disease risk in a theoretical review analysis [43] and therefore may be associated with reduced lifespan. A meta-analysis of 293 studies [44] found a significant association between depression and excess mortality. Depression can be conceptualized as a state of 'accelerated aging' at the cellular level and depressed individuals have a higher incidence of various diseases of aging, such as cardiovascular and cerebrovascular diseases, metabolic syndrome, and dementia [43].

In an examination of postmortem brain tissue across individuals with varying levels of substance use disorders (SUDs), greater SUD severity was associated with accelerated biological aging, suggesting that chronic substance use may contribute to physiological damage and accelerated 'biological weathering' [45]. Tobacco smoking has been identified as a major contributor to premature mortality in analyses of World Health Organization data [46], while a meta-analysis of observational studies found that alcohol use disorder is associated with substantially reduced life expectancy [47]. Individuals with substance use disorders often exhibit biological ages that exceed their chronological ages and experience elevated rates of age-related disease and premature mortality. As a result, substance use disorders represent one of the strongest behavioral predictors of diminished healthspan and shortened lifespan, highlighting a critical intersection between addiction, biological aging, and longevity outcomes.

Again, these two bodies of literature are linked as psychedelics have been shown to be a very promising option in the treatment of PTSD, depression, and substance use disorders. Stage two and stage three clinical trial research indicates that psychedelic-assisted therapies, most notably using MDMA as an adjunct to psychotherapy, represent a promising new paradigm for treating PTSD, particularly for individuals who have not responded to conventional treatments [48,49]. While MDMA is currently the most advanced in clinical trials, other substances are also under investigation, although at different stages of evidence development. Psilocybin-assisted therapy has demonstrated efficacy in several controlled clinical trials for depression and is being studied for substance use disorders and cancer-related distress. Ketamine is used clinically for treatment-resistant depression in some jurisdictions, although its pharmacology differs substantially from classic psychedelics. Ibogaine remains investigational, with most evidence derived from observational studies and open-label cohorts focused on substance use disorders. Ayahuasca research consists primarily of small clinical studies, observational investigations, and naturalistic research.

A systematic review of 15 studies reported beneficial effects of psychedelic-assisted interventions for Major Depressive Disorder (MDD) and Treatment-Resistant Depression (TRD) [50]. Unlike conventional antidepressant medications that require daily administration, psychedelic treatments typically involve only one to three dosing sessions conducted within a structured framework of psychological preparation and integration [51]. Treatment of depression with psychedelic assisted therapies has been observed to be effective and durable at the 12 month follow-up in a randomized controlled study [52].

Psychedelics were researched as a potential treatment for alcoholism in the 1950-1970s [53], which focused largely on the clinical use of LSD [54]. Currently, psilocybin is showing encouraging preliminary clinical findings for treatment of substance use disorders [54–57]. This has been demonstrated in a "proof of concept" clinical study [59]. Psychedelics have been shown to assist with tobacco cessation in an online survey [60] and a clinical study [61] which demonstrated durability at the 12 month follow-up [62]. Two narrative reviews observe the potential for ibogaine [63] and psilocybin [64] in the treatment of substance use disorders and this effect has been observed to be durable in an online survey [65]. Cocaine use disorder was shown to be reduced with psilocybin assisted treatment in a randomized clinical trial [66]. Population-level studies also show lower prevalence of substance use disorders among individuals with psychedelic exposure [66–68].

Irrespective of mental health and substance use, psychological stress has been associated with accelerated biological aging via telomere shortening, inflammation, and dysregulated neuroendocrine signaling [70,71]. Conversely, psychological well-being and sense of purpose are associated with longer healthspan and lifespan [72,73]. Psychedelic-assisted therapies showed sustained improvements in existential well-being in a clinical study comparing psilocybin with escitalopram [48,74] and improvements in cognition and affect in older adults has been noted in a review article [75]. These effects are frequently mediated by insight, meaning-making, and psychological flexibility, mechanisms that differ fundamentally from traditional pharmacotherapies.

While mental health conditions and substance use disorders represent psychosocial risk states associated with accelerated aging, they also identify potentially modifiable domains through which resilience and healthspan may be enhanced.

## Psychosocial protectors of aging

In addition to mitigating psychosocial risk factors, longevity research increasingly emphasizes the role of positive social and psychological experiences in promoting resilience, buffering stress-related physiology and supporting healthy aging.

### *Social connection and empathy community cohesion*

Social connection is among the strongest non-genetic predictors of longevity, with effect sizes larger than smoking cessation and physical activity according to a meta-analytic review of 148 longevity studies [76]. How social cohesion exerts biological effects, such as through stress buffering, immune modulation, and behavioral reinforcement [77,78], remains a key question for longevity science.

Again, psychedelic science plausibly links with longevity science, as psychedelics are theorized to facilitate a fundamental shift from a state of disconnection to one of profound connectedness, which encompasses an improved relationship with the self, other people, and the broader social and natural environment. Some researchers believe that the experience of connectedness is fundamental to the healing process observed in psychedelic assisted therapies [79]. Additional support comes from clinical studies showing that psychedelic-assisted interventions reliably enhance social connectedness, empathy, and perceived meaning in life [80,81].

Clinical studies suggest that psychedelic experiences may be associated with increases in prosocial behaviour and positive social attitudes [82,83] while improved cooperative behaviour has been observed in naturalistic research settings [84]. Psychedelic use has also been associated with reductions in neuroticism [85], and individuals treated with psilocybin for depression have reported more positive worldviews following treatment [81].

The association between psychedelics and enhanced social connection is also evident in clinical research on MDMA-assisted psychotherapy, which may facilitate trauma processing through increases in interpersonal trust and emotional openness [86]. Also, ceremonial use of ayahuasca has been associated with increased perceptions of community cohesion [87].

### *Meaning and purpose*

The experience of *meaning* (i.e., here and now is valuable) and *purpose* (i.e., positive future goals) are also increasingly understood to be important psychological factors contributing to longevity. A meta-analysis of 10 prospective studies on longevity found that a higher sense of *purpose in life* was associated with a reduced risk of mortality [72]. In an analysis of 5 studies it was observed that having *purpose in life* through a sense of progress toward meaningful goals contributes to a purposeful life and this is correlated with self-protection, disease avoidance, affiliation, mate retention, and family care motives [88]. *Purpose in life* is also associated with reduced risks of Alzheimer's disease and cognitive impairment [89,90].

Again, the psychedelic literature and longevity research intriguingly coincide, as psychedelic experiences are frequently rated as among the most meaningful events in individuals' lives. Across multiple controlled studies psychedelic experiences have been frequently rated among the most meaningful events of the participants lives. Specifically subjects commonly report substantial increases in spiritual significance, purpose and existential well-being with effects persisting for months or years after administration [62,80,90–96].

*Meaning* and *purpose*, which can be central outcomes of psychedelic experiences, are increasingly recognized as determinants of healthy aging, influencing stress resilience, behavior, and immune function. Psychedelic research therefore offers a unique model for studying how profound subjective experiences can translate into durable psychosocial and physiological changes with direct relevance to aging and longevity. However, while increases in social connectedness, meaning, and psychological well-being are among the most replicated findings in psychedelic research, these outcomes should not be interpreted as direct evidence of slowed biological aging. Rather, they represent psychosocial factors that may plausibly influence healthspan through behavioral, neuroendocrine, immune, and social pathways.

## Psychological health and positive health behaviors

While longevity pursuits may be enhanced by the reduction of problematic or risky behaviours, it is advantageous to consider a converse approach of how healthspan can be maximized through the adoption of positive, health promoting behaviours that are correlated with long-term health benefits. In this regard, the current narrow research agenda for much of today's psychedelic science, investigating these substances as

medications to treat specific illnesses, may be foreclosing broader inquiry into their potential as tools for health promotion and illness prevention.

Emerging evidence suggests that psychedelic experiences may be associated with sustained improvements in holistic well-being and health-promoting behaviours. One useful framework for understanding well-being is Seligman's PERMA model, which conceptualizes well-being as comprising positive emotion, engagement in activities, relationships, meaning and accomplishment ([9899]. When individuals are doing well across several (ideally all) domains, they are "flourishing". A systematic review found that psychedelic use was associated with enhancements across all PERMA domains, with studies including substances such as LSD, 5-MeO-DMT, ayahuasca, and psilocybin [100]. Similar findings have been reported in a review paper, with psychedelics associated with increased well-being, flourishing, and positive behavioural change [9].

From a longevity perspective, these domains are not merely subjective outcomes but are closely linked to health behaviours, stress regulation, and social integration. Improvements across PERMA domains may therefore represent a mechanism through which psychedelic interventions may reshape the psychosocial exposome, reducing cumulative allostatic load and promoting sustained engagement in health supporting behaviours. In this way, increased engagement in positive health behaviors represents a plausible pathway through which psychedelic-assisted interventions could influence longevity outcomes.

While psychedelics are rightly understood to be important potential tools in the clinical treatment of mental health and substance use disorders, there is growing evidence to suggest that when used skillfully and with intention, they may also function as catalysts for well-being in the broader population. Their greatest population-level impact may ultimately lie in their capacity to promote flourishing, resilience, and sustained behavioural change, thereby contributing to increased healthspan and longevity, even among otherwise healthy people.

This perspective is consistent with population health frameworks that recognize mental well-being, social connection, purpose, and health behaviours as important mediators between social determinants of health and long-term health outcomes. While psychedelic interventions should not be viewed as substitutes for addressing structural socio-economic inequities, future research may usefully explore whether they can help mitigate some downstream consequences of adverse social and environmental conditions that contribute to health disparities and accelerated aging.

## Implications for exposome-oriented aging research

A psychosocial exposome framework may provide a useful organizing model for future research examining potential relationships between psychedelic interventions and longevity-related outcomes. The exposome refers to the cumulative environmental, behavioral, social, and biological exposures experienced across the lifespan and their interactions with underlying biological systems. Future studies could incorporate longitudinal assessments of psychosocial exposures (e.g., stress, trauma history, social connectedness, sleep, and health behaviors) alongside biological markers associated with inflammaging and immune aging. Integrating exposome-informed measures with biological endpoints may provide a more comprehensive understanding of how experiential, behavioral, and biological pathways interact to influence aging trajectories. Such approaches would allow investigators to evaluate whether psychedelic-induced changes in psychological and behavioral domains mediate downstream effects on inflammatory signaling, metabolic regulation, and biological aging biomarkers.

## Safety considerations

While psychedelics may hold promise as interventions that influence factors associated with healthy aging, their application in older adults and medically complex populations requires careful consideration of safety. Much of the contemporary clinical research has been conducted in relatively healthy participants under controlled conditions, limiting the generalizability of findings to populations most relevant to longevity and healthspan research.

Cardiovascular safety is likely to be a primary consideration when evaluating psychedelic interventions in older populations. Classic psychedelics such as psilocybin and LSD can produce transient increases in blood pressure and heart rate. Although these changes are generally well tolerated in healthy individuals, they may pose greater risks in older adults with cardiovascular disease, uncontrolled hypertension, arrhythmias, or a history of stroke. Special consideration is warranted for ibogaine, which differs from other psychedelic compounds in having a well-documented risk of QT interval prolongation and potentially serious cardiac arrhythmias, making cardiovascular screening particularly important in older adults and individuals with pre-existing cardiac disease. As the prevalence of cardiovascular conditions increases with age, future studies should more systematically evaluate cardiovascular

outcomes and identify appropriate screening and monitoring protocols for older participants.

Polypharmacy presents another important challenge. Older adults frequently take multiple medications, increasing the potential for drug-drug interactions. Age-related changes in pharmacokinetics and pharmacodynamics may further influence both therapeutic response and adverse-event profiles. Attention should be paid to serotonergic medications, including selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and monoamine oxidase inhibitors (MAOIs), as well as cardiovascular, anticoagulant, and centrally acting medications. Although serious adverse interactions appear uncommon in controlled clinical settings, the interaction profiles of psychedelics in aging populations remain incompletely understood.

Frailty and reduced physiological reserve may also influence both the risks and benefits of psychedelic interventions. Future studies should incorporate frailty measures and functional outcomes to better characterize risk-benefit profiles.

Psychiatric contraindications warrant particular attention. Current clinical trials generally exclude individuals with psychotic disorders, bipolar I disorder, or a strong personal or family history of psychosis due to concerns regarding symptom exacerbation. Careful psychiatric screening remains essential, especially given the increased prevalence of neurocognitive disorders and complex psychiatric presentations in older populations. Additional research is needed to determine the safety, tolerability and efficacy of psychedelic-assisted interventions in individuals with mild cognitive impairment, dementia, and other age-related neurological conditions.

Importantly, safety should be evaluated not only in terms of acute adverse events but also through a healthspan lens that considers long-term functional outcomes, quality of life, independence, cognitive function, social engagement, and healthcare utilization. As psychedelic research expands beyond psychiatric indications and increasingly intersects with longevity science, establishing evidence-based safety frameworks for older and medically complex populations will be critical for responsible clinical implementation.

## Conclusion: integrated interpretation and implications for longevity research

The intersection of longevity science and psychedelic research remains largely underexplored, yet it is biologically plausible and increasingly relevant as longevity frameworks expand beyond isolated molecular targets to include upstream psychological, behavioural and social determinants of aging trajectories. Across the domains reviewed here (i.e., neuroplasticity, inflammation, immune signaling, stress physiology, social connection, meaning and purpose, and health behavior change) psychedelic interventions appear capable of producing durable changes in factors associated with morbidity, functional decline, and mortality. Although scientific research on psychedelics has not yet focused directly on their potential as longevity therapies, the capacity of this class of substances to produce sustained shifts after limited dosing sessions raises a distinctive question for healthspan science: whether brief, well-supported psychedelic experiences or interventions can create lasting improvements in resilience-related systems that accumulate benefit over time.

A key challenge for the field is distinguishing between evidence supporting improved psychosocial functioning, evidence supporting reductions in disease burden, evidence supporting improvements in healthspan-related outcomes, and evidence supporting direct modification of biological aging processes. Although these domains may overlap, they represent distinct levels of inference and currently rest on substantially different evidentiary foundations.

From a mechanistic perspective, psychedelic effects relevant to healthspan likely operate through two interacting pathways. First, there may be direct biological effects (e.g., transient enhancement of neuroplasticity, modulation of inflammatory signaling, and downstream impacts on neuroendocrine function) that overlap with hallmarks of aging such as altered intercellular communication and chronic inflammation. Second, psychedelics may act indirectly through behavior and psychosocial change, including reductions in chronic dependent substance use, improvements in mood and trauma-related symptoms, enhanced psychological flexibility, and increases in social connectedness and meaning and purpose. These shifts, which can be understood as modifications of the psychosocial exposome, plausibly reduce cumulative allostatic load and support healthier long-term behavioral trajectories.

In this context, psychedelic interventions may be conceptualized less as anti-aging therapies and more as systems-level catalysts, capable of shifting patterns of stress regulation, behaviour, and social engagement in ways that accumulate health benefits over time. At the same time, substantial uncertainties remain. While findings from cellular and animal models suggest potential effects on aging-related biological processes [12] current evidence does not establish that psychedelics slow biological aging in humans.

Also, much of the immunology and neuroplasticity literature is preclinical or derived from non-aging populations. Important questions also remain regarding durability, dose–response relationships, individual differences in benefit and risk, and the extent to which immune changes reflect direct pharmacologic effects versus secondary consequences of neuroendocrine shifts and improved psychological well-being. In addition, any longevity-relevant framing of psychedelic research must be paired with careful attention to physical and psychological safety, medical contraindications, and real-world implementation constraints, particularly for older adults and medically complex populations.

These limitations help define the research agenda. Future psychedelic trials, especially those targeting conditions that strongly shape healthspan, such as depression, trauma-related disorders, and substance use, could be strengthened by incorporating aging-relevant outcomes alongside symptom measures. This includes (i) biological aging biomarkers, potentially including epigenetic clocks, telomere length, and related biomarkers of aging; (ii) functional and behavioural endpoints (i.e., sleep, nutrition, physical activity, cardiometabolic markers, cognitive performance, frailty proxies); (iii) longitudinal follow-up sufficient to assess sustained behavioral change and downstream health effects; and (iv) designs capable of testing mediation (e.g., whether improvements in stress regulation, social connectedness, or health behaviors account for changes in inflammatory tone or biological aging markers). Comparative work across molecules, routes of administration, and treatment models, including psychotherapy-supported dosing paradigms versus other delivery frameworks, will be essential to identify which components contribute most substantially to durable healthspan-relevant outcomes.

Future research should also distinguish between findings derived from naturalistic studies of whole-psilocybin-mushroom use and those obtained from clinical studies employing pharmaceutical-grade psilocybin. While both approaches involve psilocybin exposure, whole mushrooms contain other alkaloids, which may contribute to biological and clinical effects. This distinction could prove important when evaluating specific mechanisms and biological outcomes relevant to aging and longevity.

More broadly, future studies should clearly distinguish among mechanistic laboratory findings, animal-model outcomes, controlled clinical trial results, naturalistic use studies, and population-level observational associations. These evidence streams differ substantially in their capacity to support causal inference. While observational and naturalistic studies have identified intriguing associations between psychedelic exposure and a range of favorable health outcomes, such findings remain vulnerable to confounding, selection effects, expectancy influences, publication bias, and other methodological limitations [100]. As a result, current observational evidence should be interpreted as hypothesis-generating rather than definitive evidence of longevity-related benefit. Such distinctions are essential for accurately evaluating the strength of evidence supporting potential longevity-related effects and for avoiding overinterpretation of preliminary findings.

In summary, while psychedelics are currently being investigated primarily as adjuncts in the treatment of mental health and substance use disorders, the converging evidence reviewed here suggests a credible rationale for studying them within a lifespan and healthspan framework. Psychedelic-assisted interventions may offer an opportunity to promote sustained changes in behavior, stress physiology, and immune signaling—pathways that shape aging trajectories over decades. Rigorous interdisciplinary research integrating geroscience, psychiatry, immunology, behavioral science and population health is now needed to determine whether these effects can be safely and effectively harnessed to promote longer, healthier lives.

## Author contributions

CRediT: **Mark Haden**: Writing – original draft; **Birgitta Woods**: Writing – review & editing; **Tina Woods**: Writing – review & editing; **Kenneth W. Tupper**: Writing – review & editing.

## Disclosure statement

No potential conflict of interest was reported by the author(s).

## ORCID

Mark Haden http://orcid.org/0000-0001-6549-5639
Birgitta Woods http://orcid.org/0009-0005-1189-1456
Tina Woods http://orcid.org/0009-0008-4950-9488

## References

[1] López-Otín C, Blasco MA, Partridge L, et al. Hallmarks of aging: an expanding universe. Cell. 2023;186(2):243–278. doi: 10.1016/j.cell.2022.11.001
[2] Kim ES, Tkatch R, Martin D, et al. Resilient aging: psychological well-being and social well-being as targets for the promotion of healthy aging. Gerontol Geriatr Med. 2021;7:23337214211002951. doi: 10.1177/23337214211002951
[3] Franck M, Daunizeau C, Aronoff JE, et al. Inflamm-aging as a diverse and context-dependent process: from species and population differences to

individual trajectories. Ageing Res Rev. 2026;113:102880. doi: 10.1016/j.arr.2025.102880

[4] Ong AD, Mann FD, Kubzansky LD. Cumulative social advantage is associated with slower epigenetic aging and lower systemic inflammation. Brain Behav Immun Health. 2025;48:101096. doi: 10.1016/j.bbih.2025.101096

[5] Carhart-Harris RL, Goodwin GM. The therapeutic potential of psychedelic drugs: past, present, and future. Neuropsychopharmacology. 2017;42(11):2105–2113. doi: 10.1038/npp.2017.84

[6] Siegel JS, Liston C, Nicol GE, et al. The science of psychedelic medicine. Nat Med. 2026;32(2):449–462. doi: 10.1038/s41591-025-04194-5

[7] Cherian KN, Keynan JN, Anker L, et al. Magnesium–ibogaine therapy in veterans with traumatic brain injuries. Nat Med. 2024;30(2):373–381. doi: 10.1038/s41591-023-02705-w

[8] Palmer C, Ferber AT, Greenwald BD. The potential role of psilocybin in traumatic brain injury recovery: a narrative review. Brain Sci. 2025;15(6):572. doi: 10.3390/brainsci15060572

[9] Teixeira PJ, Johnson MW, Timmermann C, et al. Psychedelics and health behaviour change. J Psychopharmacol. 2022;36(1):12–19. doi: 10.1177/02698811211008554

[10] Bhatt KV, Weissman CR. The effect of psilocybin on empathy and prosocial behavior: a proposed mechanism for enduring antidepressant effects. Npj Ment Health Res. 2024;3(1):7. doi: 10.1038/s44184-023-00053-8

[11] Schmid Y, Bershad AK. Altered states and social bonds: effects of MDMA and serotonergic psychedelics on social behavior as a mechanism underlying substance-assisted therapy. Biol Psychiatry Cogn Neurosci Neuroimaging. 2024;9(5):490–499. doi: 10.1016/j.bpsc.2024.02.001

[12] Kato K, Kleinhenz JM, Shin YJ, et al. Psilocybin treatment extends cellular lifespan and improves survival of aged mice. NPJ Aging. 2025;11(1):55. doi: 10.1038/s41514-025-00244-x

[13] Germann CB. The psilocybin-telomere hypothesis: an empirically falsifiable prediction concerning the beneficial neuropsychopharmacological effects of psilocybin on genetic aging. Med Hypotheses. 2020;134:109406. doi: 10.1016/j.mehy.2019.109406

[14] Haden M, Paschall SA, Woods B. Beyond prohibition: a public health analysis of naturalistic psychedelic use. J Psychedelic Stud. 2026;10(1):45–58. doi: 10.1556/2054.2025.00450

[15] Kramer HM, Hibicke M, Middleton J, et al. Psychedelics produce enduring behavioral effects and functional plasticity through mechanisms independent of structural plasticity. Neuropsychopharmacology. 2026;51(3):641–649. doi: 10.1038/s41386-025-02272-3

[16] Wild CP. Complementing the genome with an "exposome": the outstanding challenge of environmental exposure measurement in molecular epidemiology. Cancer Epidemiol Biomarkers Prev. 2005;14(8):1847–1850. doi: 10.1158/1055-9965.EPI-05-0456

[17] Woods T, Palmarini N, Corner L, et al. New frontier of longevity-through the framework of the 'exposome', healthy longevity: policies and practices. In: Stambler I, editor. Healthy longevity: policies and practices. Vol. 23. Cham: Springer; 2026. doi: 10.1007/978-3-032-20006-8_18

[18] Mattson MP, Arumugam TV. Hallmarks of brain aging: adaptive and pathological modification by metabolic states. Cell Metab. 2018;27(6):1176–1199. doi: 10.1016/j.cmet.2018.05.011

[19] Iso-Markku P, Kujala UM, Knittle K, et al. Physical activity as a protective factor for dementia and Alzheimer's disease: systematic review, meta-analysis and quality assessment of cohort and case-control studies. Br J Sports Med. 2022;56(12):701–709. doi: 10.1136/bjsports-2021-104981

[20] Liu Y, Lu G, Liu L, et al. Cognitive reserve over the life course and risk of dementia: a systematic review and meta-analysis. Front Aging Neurosci. 2024;16:1358992. doi: 10.3389/fnagi.2024.1358992

[21] Ly C, Greb AC, Cameron LP, et al. Psychedelics promote structural and functional neural plasticity. Cell Rep. 2018;23(11):3170–3182. doi: 10.1016/j.celrep.2018.05.022

[22] Ly CC, Greb AC, Vargas MV, et al. Transient stimulation with psychoplastogens is sufficient to initiate neuronal growth. ACS Pharmacol Transl Sci. 2021;4(2):452–460. doi: 10.1021/acsptsci.0c00065

[23] Shao LX, Liao C, Gregg I, et al. Psilocybin induces rapid and persistent growth of dendritic spines in frontal cortex in vivo. Neuron. 2021;109(16):2535–2544.e4. doi: 10.1016/j.neuron.2021.06.008

[24] Morales-Garcia JA, Calleja-Conde J, Lopez-Moreno JA, et al. N,N-dimethyltryptamine compound found in the hallucinogenic tea ayahuasca, regulates adult neurogenesis in vitro and in vivo. Transl Psychiatry. 2020;10(1):331. doi: 10.1038/s41398-020-01011-0

[25] Carhart-Harris RL. The entropic brain – revisited. Neuropharmacology. 2018;142:167–178. doi: 10.1016/j.neuropharm.2018.03.010

[26] Carhart-Harris R, Leech R, Hellyer P, et al. The entropic brain: a theory of conscious states informed by neuroimaging research with psychedelic drugs. Front Hum Neurosci. 2014;8:20. doi: 10.3389/fnhum.2014.00020

[27] Lago M, Cerveira M., & Simonet, J. X. (2026). Transient multidomain functional improvement in advanced Alzheimer's disease following high-dose psilocybin-containing mushroom administration: a case report. Front Neurosci, 20, 1813281. doi: 10.3389/fnins.2026.1813281

[28] de Vos CMH, Mason NL, Kuypers KPC. Psychedelics and neuroplasticity: a systematic review unraveling the biological underpinnings of psychedelics. Front Psychiatry. 2021;12:724606. doi: 10.3389/fpsyt.2021.724606

[29] Dölen G, Wilkinson ML. The emerging neurobiology of psychedelics: critical periods, metaplasticity, and extracellular matrix remodeling. Annu Rev Neurosci. 2026. doi: 10.1146/annurev-neuro-112723-045129

[30] Franceschi C, Garagnani P, Parini P, et al. Inflammaging: a new immune-metabolic viewpoint for age-related diseases. Nat Rev Endocrinol. 2018;14(10):576–590. doi: 10.1038/s41574-018-0059-4

[31] Qureshi O, Cowley J, Pegg A, et al. Are we hallucinating or can psychedelic drugs modulate the immune system to control inflammation? Br J

Pharmacol. 2026;183(14):4006–4021. doi: 10.1111/bph.70138
[32] Flanagan TW, Nichols CD. Psychedelics as anti-inflammatory agents. Int Rev Psychiatry. 2018;30(4):363–375. doi: 10.1080/09540261.2018.1481827
[33] Nichols CD, Foster TP. Serotonin, immune function, and psychedelics as potent anti-inflammatories. Int Rev Neurobiol. 2025;181:45–76. doi: 10.1016/bs.irn.2025.04.011
[34] Galvão-Coelho NL, de Menezes Galvão AC, de Almeida RN, et al. Changes in inflammatory biomarkers are related to the antidepressant effects of Ayahuasca. J Psychopharmacol. 2020;34(10):1125–1133. doi: 10.1177/0269881120936486
[35] Sukhram SD, Yilmaz G, Gu J. Antidepressant effect of ketamine on inflammation-mediated cytokine dysregulation in adults with treatment-resistant depression: rapid systematic review. Oxid Med Cell Longev. 2022;2022(1):1061274. doi: 10.1155/2022/1061274
[36] Mason NL, Szabo A, Kuypers KPC, et al. Psilocybin induces acute and persisting alterations in immune status in healthy volunteers: an experimental, placebo-controlled study. Brain Behav Immun. 2023;114:299–310. doi: 10.1016/j.bbi.2023.09.004
[37] Low ZXB, Ng WS, Lim ESY, et al. The immunomodulatory effects of classical psychedelics: a systematic review of preclinical studies. Prog Neuropsychopharmacol Biol Psychiatry. 2025;136:111139. doi: 10.1016/j.pnpbp.2024.111139
[38] Inserra A, De Gregorio D, Gobbi G. Psychedelics in psychiatry: neuroplastic, immunomodulatory, and neurotransmitter mechanisms. Pharmacol Rev. 2021;73(1):202–277. doi: 10.1124/pharmrev.120.000056
[39] Szabo A. Psychedelics and immunomodulation: novel approaches and therapeutic opportunities. Front Immunol. 2015;6:358. doi: 10.3389/fimmu.2015.00358
[40] Wolf EJ, Logue MW, Stoop TB, et al. Accelerated DNA methylation age: associations with posttraumatic stress disorder and mortality. Psychosom Med. 2018;80(1):42–48. doi: 10.1097/PSY.0000000000000506
[41] Li X, Wang J, Zhou J, et al. The association between post-traumatic stress disorder and shorter telomere length: a systematic review and meta-analysis. J Affect Disord. 2017;218:322–326. doi: 10.1016/j.jad.2017.03.048
[42] Wolf EJ, Maniates H, Nugent N, et al. Traumatic stress and accelerated DNA methylation age: a meta-analysis. Psychoneuroendocrinology. 2018;92:123–134. doi: 10.1016/j.psyneuen.2017.12.007
[43] Wolkowitz OM, Epel ES, Reus VI, et al. Depression gets old fast: do stress and depression accelerate cell aging? Depress Anxiety. 2010;27(4):327–338. doi: 10.1002/da.20686
[44] Cuijpers P, Vogelzangs N, Twisk J, et al. Comprehensive meta-analysis of excess mortality in depression in the general community versus patients with specific illnesses. Am J Psychiatry. 2014;171(4):453–462. doi: 10.1176/appi.ajp.2013.13030325
[45] Bruno Kluwe-Schiavon LS, Barichello T, Meyer TD, et al. Deciphering the molecular basis of accelerated biological aging in substance use disorder: Integrative transcriptomic analysis. Genomic Psychiatry. 2025;1(3):44–52. doi: 10.61373/gp025a.0029
[46] Rentería E, Jha P, Forman D, et al. The impact of cigarette smoking on life expectancy between 1980 and 2010: a global perspective. Tob Control. 2016;25(5):551–557. doi: 10.1136/tobaccocontrol-2015-052265
[47] Roerecke M, Rehm J. Alcohol use disorders and mortality: a systematic review and meta-analysis. Addiction. 2013;108(9):1562–1578. doi: 10.1111/add.12231
[48] Mitchell JM, Bogenschutz M, Lilienstein A, et al. MDMA-assisted therapy for severe PTSD: a randomized, double-blind, placebo-controlled phase 3 study. Nat Med. 2021;27(6):1025–1033. doi: 10.1038/s41591-021-01336-3
[49] Mitchell JM, Ot'alora GM, van der Kolk B, et al. MDMA-assisted therapy for moderate to severe PTSD: a randomized, placebo-controlled phase 3 trial. Nat Med. 2023;29(10):2473–2480. doi: 10.1038/s41591-023-02565-4
[50] Horato N, Dalvi-Garcia F, Dutra PEP, et al. The therapeutic potential of psychedelics for treatment-resistant depression: reality or hallucination? A systematic review. J Clin Psychopharmacol. 2026;46(2):195–206. doi: 10.1097/JCP.0000000000002122
[51] Aday JS, Mitzkovitz CM, Bloesch EK, et al. Long-term effects of psychedelic drugs: a systematic review. Neurosci Biobehav Rev. 2020;113:179–189. doi: 10.1016/j.neubiorev.2020.03.017
[52] Gukasyan N, Davis AK, Barrett FS, et al. Efficacy and safety of psilocybin-assisted treatment for major depressive disorder: 12-month follow-up. J Psychopharmacol. 2022;36(2):151–158. doi: 10.1177/02698811211073759
[53] Dyck E. 'Hitting highs at rock bottom': LSD treatment for alcoholism, 1950-1970. Soc Hist Med. 2006;19:313–329. doi: 10.1093/shm/hkl039
[54] Krebs TS, Johansen PØ. Lysergic acid diethylamide (LSD) for alcoholism: meta-analysis of randomized controlled trials. J Psychopharmacol. 2012;26(7):994–1002. doi: 10.1177/0269881112439253
[55] Bogenschutz MP. It's time to take psilocybin seriously as a possible treatment for substance use disorders. Am J Drug Alcohol Abuse. 2017;43(1):4–6. doi: 10.1080/00952990.2016.1200060
[56] Bogenschutz MP, Johnson MW. Classic hallucinogens in the treatment of addictions. Prog Neuropsychopharmacol Biol Psychiatry. 2016;64:250–258. doi: 10.1016/j.pnpbp.2015.03.002
[57] Garcia-Romeu A, Davis AK, Erowid E, et al. Persisting reductions in cannabis, opioid, and stimulant misuse after naturalistic psychedelic use: an online survey. Front Psychiatry. 2019;10:955. doi: 10.3389/fpsyt.2019.00955
[58] Meshkat S, Malik G, Zeifman RJ, et al. Efficacy and safety of psilocybin for the treatment of substance use disorders: a systematic review. Neurosci Biobehav Rev. 2025;173:106163. doi: 10.1016/j.neubiorev.2025.106163
[59] Bogenschutz MP, Forcehimes AA, Pommy JA, et al. Psilocybin-assisted treatment for alcohol dependence: a proof-of-concept study. J Psychopharmacol. 2015;29(3):289–299. doi: 10.1177/0269881114565144
[60] Johnson MW, Garcia-Romeu A, Johnson PS, et al. An online survey of tobacco smoking cessation associated with naturalistic psychedelic use. J Psychopharmacol. 2017;31(7):841–850. doi: 10.1177/0269881116684335

[61] Johnson MW, Garcia-Romeu A, Cosimano MP, et al. Pilot study of the 5-HT2AR agonist psilocybin in the treatment of tobacco addiction. J Psychopharmacol. 2014;28(11):983–992. doi: 10.1177/0269881114548296

[62] Johnson MW, Garcia-Romeu A, Griffiths RR. Long-term follow-up of psilocybin-facilitated smoking cessation. Am J Drug Alcohol Abuse. 2017;43(1):55–60. doi: 10.3109/00952990.2016.1170135

[63] Luz M, Mash DC. Evaluating the toxicity and therapeutic potential of ibogaine in the treatment of chronic opioid abuse. Expert Opin Drug Metab Toxicol. 2021;17(9):1019–1022. doi: 10.1080/17425255.2021.1944099

[64] de Veen BT, Schellekens AF, Verheij MM, et al. Psilocybin for treating substance use disorders? Expert Rev Neurother. 2017;17(2):203–212. doi: 10.1080/14737175.2016.1220834

[65] Garcia-Romeu A, Davis AK, Erowid F, et al. Cessation and reduction in alcohol consumption and misuse after psychedelic use. J Psychopharmacol. 2019;33(9):1088–1101. doi: 10.1177/0269881119845793

[66] Hendricks PS, Lappan SN, Shelton RC, et al. Psilocybin in the treatment of cocaine use disorder: a randomized clinical trial. JAMA Netw Open. 2026;9(5):e2611029. doi: 10.1001/jamanetworkopen.2026.11029

[67] Jones G, Ricard JA, Lipson J, et al. Associations between classic psychedelics and opioid use disorder in a nationally-representative U.S. adult sample. Sci Rep. 2022;12(1):4099. doi: 10.1038/s41598-022-08085-4

[68] Jones GM, Nock MK. Exploring protective associations between the use of classic psychedelics and cocaine use disorder: a population-based survey study. Sci Rep. 2022;12(1):2574. doi: 10.1038/s41598-022-06580-2

[69] Lake S, Lucas PG. The Canadian psychedelic survey: characteristics, patterns of use, and access in a large sample of people who use psychedelic drugs. Psychedelic Medicine. 2023;1(2):98–110. doi: 10.1089/psymed.2023.0002

[70] Alhazzaa OA, Abahussin HM, Majrashi MA, et al. Molecular pathways linking chronic psychological stress to accelerated aging: mechanisms and interventions. Front Aging. 2026;7:1743142. doi: 10.3389/fragi.2026.1743142

[71] Polsky LR, Rentscher KE, Carroll JE. Stress-induced biological aging: a review and guide for research priorities. Brain Behav Immun. 2022;104:97–109. doi: 10.1016/j.bbi.2022.05.016

[72] Cohen R, Bavishi C, Rozanski A. Purpose in life and its relationship to all-cause mortality and cardiovascular events: a meta-analysis. Psychosom Med. 2016;78(2):122–133. doi: 10.1097/PSY.0000000000000274

[73] Martín-María N, Miret M, Caballero FF, et al. The impact of subjective well-being on mortality: a meta-analysis of longitudinal studies in the general population. Psychosom Med. 2017;79(5):565–575. doi: 10.1097/PSY.0000000000000444

[74] Carhart-Harris R, Giribaldi B, Watts R, et al. Trial of psilocybin versus escitalopram for depression. N Engl J Med. 2021;384(15):1402–1411. doi: 10.1056/NEJMoa2032994

[75] Aday JS, Bloesch EK, Davoli CC. Can psychedelic drugs attenuate age-related changes in cognition and affect? J Cogn Enhanc. 2020;4(2):219–227. doi: 10.1007/s41465-019-00151-6

[76] Holt-Lunstad J, Smith TB, Layton JB. Social relationships and mortality risk: a meta-analytic review. PLoS Med. 2010;7(7):e1000316. doi: 10.1371/journal.pmed.1000316

[77] Birmingham WC, Holt-Lunstad J. Social aggravation: understanding the complex role of social relationships on stress and health-relevant physiology. Int J Psychophysiol. 2018;131:13–23. doi: 10.1016/j.ijpsycho.2018.03.023

[78] Holt-Lunstad J. Why social relationships are important for physical health: a systems approach to understanding and modifying risk and protection. Annu Rev Psychol. 2018;69(1):437–458. doi: 10.1146/annurev-psych-122216-011902

[79] Carhart-Harris RL, Erritzoe D, Haijen E, et al. Psychedelics and connectedness. Psychopharmacology (Berl). 2018;235(2):547–550. doi: 10.1007/s00213-017-4701-y

[80] Griffiths R, Johnson MW, Richards WA, et al. Psilocybin occasioned mystical-type experiences: Immediate and persisting dose-related effects. Psychopharmacology (Berl). 2011;218(4):649–665. doi: 10.1007/s00213-011-2358-5

[81] Lyons T, Carhart-Harris RL. More realistic forecasting of future life events after psilocybin for treatment-resistant depression. Front Psychol. 2018;9:1721. doi: 10.3389/fpsyg.2018.01721

[82] Baggott MJ, Coyle JR, Siegrist JD, et al. Effects of 3,4-methylenedioxymethamphetamine on socioemotional feelings, authenticity, and autobiographical disclosure in healthy volunteers in a controlled setting. J Psychopharmacol. 2016;30(4):378–387. doi: 10.1177/0269881115626348

[83] Borissova A, Ferguson B, Wall MB, et al. Acute effects of MDMA on trust, cooperative behaviour and empathy: a double-blind, placebo-controlled experiment. J Psychopharmacol. 2021;35(5):547–555. doi: 10.1177/0269881120926673

[84] Stewart LH, Ferguson B, Morgan CJ, et al. Effects of ecstasy on cooperative behaviour and perception of trustworthiness: a naturalistic study. J Psychopharmacol. 2014;28(11):1001–1008. doi: 10.1177/0269881114544775

[85] Weiss B, Nygart V, Pommerencke LM, et al. Examining psychedelic-induced changes in social functioning and connectedness in a naturalistic online sample using the five-factor model of personality. Front Psychol. 2021;12:749788. doi: 10.3389/fpsyg.2021.749788

[86] Mithoefer MC, Mithoefer AT, Feduccia AA, et al. 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy for post-traumatic stress disorder in military veterans, firefighters, and police officers: a randomised, double-blind, dose-response, phase 2 clinical trial. Lancet Psychiatry. 2018;5(6):486–497. doi: 10.1016/S2215-0366(18)30135-4

[87] Andritzky W. Sociopsychotherapeutic functions of ayahuasca healing in Amazonia. J Psychoactive Drugs. 1989;21(1):77–89. doi: 10.1080/02791072.1989.10472145

[88] Scott MJ, Cohen AB. Surviving and thriving: fundamental social motives provide purpose in life. Pers Soc Psychol Bull. 2020;46(6):944–960. doi: 10.1177/0146167219883604

[89] Boyle PA, Buchman AS, Barnes LL, et al. Effect of a purpose in life on risk of incident Alzheimer disease and mild cognitive impairment in community-dwelling

older persons. Arch Gen Psychiatry. 2010;67(3):304–310. doi: 10.1001/archgenpsychiatry.2009.208

[90] Boyle PA, Wang T, Yu L, et al. Purpose in life may delay adverse health outcomes in old age. Am J Geriatr Psychiatry. 2022;30(2):174–181. doi: 10.1016/j.jagp.2021.05.007

[91] Griffiths R, Johnson MW, Richards WA, et al. Psilocybin-occasioned mystical-type experience in combination with meditation and other spiritual practices produces enduring positive changes in psychological functioning and in trait measures of prosocial attitudes and behaviors. J Psychopharmacol. 2018;32(1):49–69. doi: 10.1177/0269881117731279

[92] Griffiths R, Richards W, Johnson M, et al. Mystical-type experiences occasioned by psilocybin mediate the attribution of personal meaning and spiritual significance 14 months later. J Psychopharmacol. 2008;22(6):621–632. doi: 10.1177/0269881108094300

[93] Griffiths R, Richards WA, McCann U, et al. Psilocybin can occasion mystical-type experiences having substantial and sustained personal meaning and spiritual significance. Psychopharmacology (Berl). 2006;187(3):268–283. doi: 10.1007/s00213-006-0457-5

[94] Johnson MW, Hendricks PS, Barrett FS, et al. Classic psychedelics: an integrative review of epidemiology, therapeutics, mystical experience, and brain network function. Pharmacol Ther. 2019;197:83–102. doi: 10.1016/j.pharmthera.2018.11.010

[95] MacLean KA, Johnson MW, Griffiths RR. Mystical experiences occasioned by the hallucinogen psilocybin lead to increases in the personality domain of openness. J Psychopharmacol. 2011;25(11):1453–1461. doi: 10.1177/0269881111420188

[96] Nicholas CR, Henriquez KM, Gassman MC, et al. High dose psilocybin is associated with positive subjective effects in healthy volunteers. J Psychopharmacol. 2018;32(7):770–778. doi: 10.1177/0269881118780713

[97] Schmid Y, Liechti ME. Long-lasting subjective effects of LSD in normal subjects. Psychopharmacology (Berl). 2018;235(2):535–545. doi: 10.1007/s00213-017-4733-3

[98] Thomson S, Thomacos N. Utilizing psychedelics to enhance well-being: a systematic review. J Psychoactive Drugs. 2025:1–17. doi: 10.1080/02791072.2025.2484380

[99] Seligman MEP. Flourish: A Visionary NewUnderstanding of Happiness and Well-Being., New YorkFree Press; 2011. 978-1-4391-9075-3.

[100] Carvalho LC, Encantado J, Kettner H, et al. A scoping review of research in naturalistic studies with psychedelics. J Psychoactive Drugs. 2025:1–14. doi: 10.1080/02791072.2025.2520221