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PSYCHEDELIC TREATMENT FOR NEURODEGENERATIVE DISORDERS: A REVIEW OF THE RESEARCH

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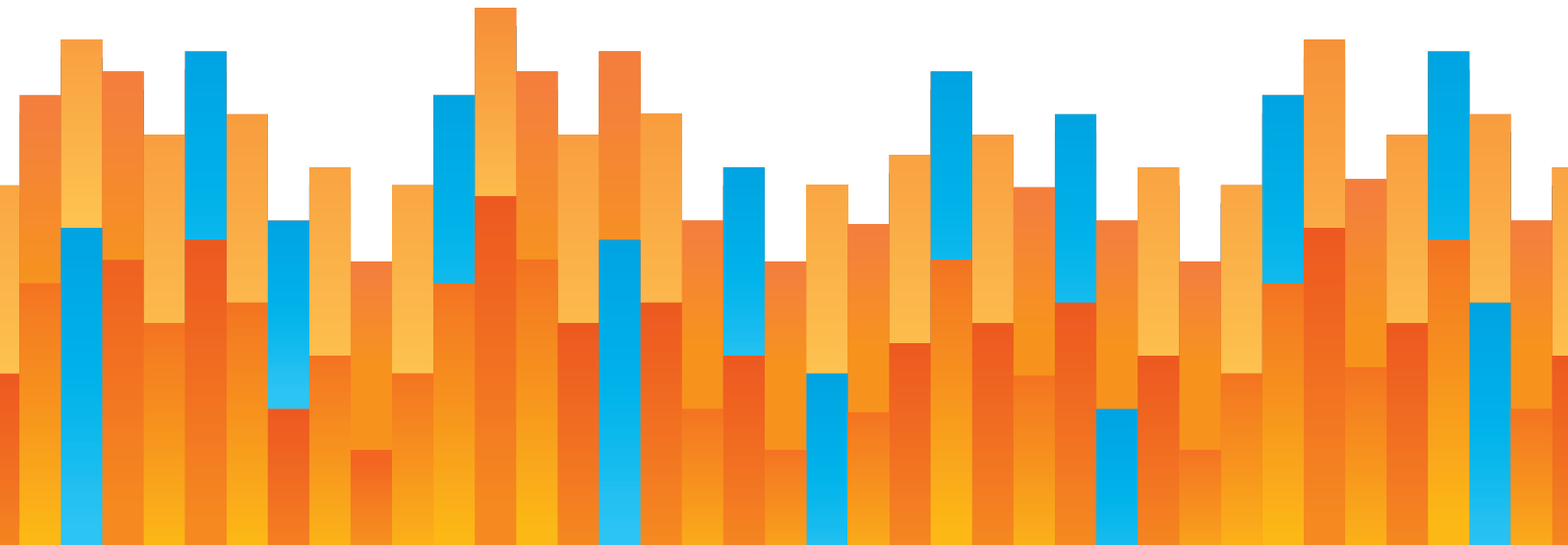

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EXECUTIVE SUMMARY

Neurodegenerative disorders, such as Alzheimer's disease (AD) and Parkinson's disease (PD), affect millions of people, and no current treatments can effectively stop or reverse disease progression. As these diseases worsen over time and become increasingly more prevalent, they place a growing financial burden on patients, families, and healthcare systems. Current treatments are falling short, and millions of people continue to suffer, underscoring a need for innovative treatments.

> *Recent research suggests that psychedelics, such as psilocybin and LSD, show strong potential as effective treatments for neurodegenerative disorders.*

Recent research suggests that psychedelics, such as psilocybin and LSD, show strong potential as effective treatments for neurodegenerative disorders. Unlike traditional medications that mainly manage symptoms, psychedelics may offer a pathway to disease modification through mechanisms like enhanced neuroplasticity (the brain's ability to adapt and reorganize itself), reduction of neuroinflammation, and promotion of cellular regeneration. These effects could be crucial in counteracting underlying disease causes, such as neuron loss and cognitive decline.

Psychedelics have also shown strong potential in treating depression and anxiety, both in terminal illness and potentially in neurodegenerative disorders. Given that neuropsychiatric symptoms are prevalent in AD and worsen the disease's course, these findings are significant. Although the preliminary results are promising, the small sample sizes, short duration, and the use of healthy or non-AD populations limit the generalizability of these findings to AD. Larger, long-term trials specifically involving AD patients are needed to establish safety, efficacy, and optimal dosing strategies.

Regulated psychedelic-assisted therapy (PAT) centers represent a pivotal opportunity in the development of psychedelic treatments. These centers create a controlled and structured environment for administering psychedelic therapies under clinical supervision. PAT centers allow for both therapeutic practices and rigorous data collection to occur, ensuring that the treatment protocols are consistently monitored and evaluated.

Data gathered from these centers can provide early evidence of the safety and efficacy of psychedelic substances in a therapeutic setting, crucial for addressing regulatory and medical concerns. Insights gained from this early-stage data can accelerate the integration of psychedelics into standard treatment regimens, laying the groundwork for larger and more extensive clinical trials.

The U.S. Food and Drug Administration (FDA) has previously recognized the potential of psychedelics, granting "breakthrough therapy" designations to treatments incorporating substances like psilocybin, MDMA, and LSD for treating various mental health conditions.

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offer significant improvements over existing treatments and could similarly be sought for psychedelic treatments aimed at neurodegenerative diseases.

Implementation of regulated PAT centers could generate early data that may help certain psychedelics achieve breakthrough therapy designation for neurodegenerative disorders. Breakthrough designation will help bridge the gap between early-stage research and large-scale clinical adoption, accelerating the availability of these treatments for patients in need.

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PART 1

INTRODUCTION

Neurodegenerative disorders are a group of debilitating medical conditions that progressively damage the brain and nervous system, impairing essential functions like mobility, coordination, strength, sensation, and cognition.[1] Diseases like Alzheimer's (AD) and Parkinson's (PD) are among the most common of these disorders. Alzheimer's is primarily characterized by progressive cognitive decline, beginning with memory loss and advancing to severe impairments in language, motor skills, and daily functioning.[2] Parkinson's, meanwhile, predominantly affects movement and coordination.[3] These conditions, which are most common in older adults, worsen over time and currently affect around 8 million Americans, with that number expected to double by 2050.[4] Currently, there are no treatments capable of stopping or reversing these diseases, leaving millions of patients and families with limited and often inadequate treatment options.

1 Sarah Davis, Abagail B. Cirincione, Ana Catya Jimenez-Torres, and Jun Zhu, "The Impact of Neurotransmitters on the Neurobiology of Neurodegenerative Diseases," *International Journal of Molecular Sciences*, 30 Aug. 2023, ncbi.nlm.nih.gov/pmc/articles/PMC10607327/.

2 Anil Kumar, Jaskirat Sidhu, Forshing Lui, and Jack Tsao, "Alzheimer Disease," StatPearls [Internet], StatPearls Publishing, 12 Feb. 2024, ncbi.nlm.nih.gov/books/NBK499922/.

3 "Parkinson's Disease," American Association of Neurological Surgeons, 30 April 2024, aans.org/patients/conditions-treatments/parkinsons-disease/ (30 Sept. 2024).

4 "Disease Connections: Alzheimer's and Parkinson's," American Brain Foundation, 6 Feb. 2024, americanbrainfoundation.org/disease-connections-alzheimers-and-parkinsons/ (30 June 2024).

However, recent research suggests that psychedelics, particularly psilocybin and LSD, may offer therapeutic potential in treating neurodegenerative diseases. Once known mainly for their mind-altering effects, psychedelics are now being studied for their ability to facilitate neuroregeneration and enhance brain function. Researchers have found that psychedelics enhance neuroplasticity (the brain's ability to adapt and reorganize itself), reduce inflammation, and promote cellular regeneration–mechanisms that are directly relevant in the treatment of diseases like Alzheimer's and Parkinson's.[5] Classic psychedelics refer to the most well-studied and culturally significant psychedelics, including mescaline, 5-MeO-DMT, lysergic acid diethylamide (LSD), psilocybin, and dimethyltryptamine (DMT).[6]

Researchers have found that psychedelics enhance neuroplasticity (the brain's ability to adapt and reorganize itself), reduce inflammation, and promote cellular regeneration–mechanisms that are directly relevant in the treatment of diseases like Alzheimer's and Parkinson's.

The U.S. Food and Drug Administration (FDA) has acknowledged the potential of psychedelics since 2017, granting breakthrough therapy designations for treatments incorporating MDMA to fight post-traumatic stress disorder (PTSD), psilocybin to address treatment-resistant depression (2018) and major depressive disorder (2019), and most recently LSD to address generalized anxiety disorder (2024). This designation is reserved for treatments that show substantial improvement over available therapies for serious or life-threatening conditions based on preliminary clinical evidence.

5 Michael Winkelman et al., "The Potential of Psychedelics for the Treatment of Alzheimer's Disease and Related Dementias," *European Neuropsychopharmacology,* Vol. 76 (2023), sciencedirect.com/science/article/pii/S0924977X23001347 (10 July 2024).

6 Andreas Halman, Geraldine Kong, and Daniel Perkins, "Psychedelic Therapy: Current Trends and Future Directions," *Journal of Psychopharmacology*, Vol. 38 (2023), journals.sagepub.com/doi/10.1177/02698811231211219 (17 April 2024).

> *Research indicates that classic psychedelics are non-addictive and carry a low risk of abuse.*

In contrast to many traditional pharmaceuticals, psychedelics have demonstrated a favorable safety profile in controlled clinical settings. Research indicates that classic psychedelics are non-addictive and carry a low risk of abuse.[7] These substances pose no risk of physical dependence and minimal risk for psychological dependence, especially in therapeutic contexts. Furthermore, psychedelics have low toxicity, with adverse effects being rare and typically related to the psychological and environmental conditions in which psychedelics are administered rather than the substances themselves. This combination of therapeutic potential, low toxicity, and minimal abuse risk positions psychedelics as promising candidates for further exploration in the treatment of neurodegenerative disorders.

[7] James Elsey, "Psychedelic drug use in healthy individuals: A review of benefits, costs, and implications for drug policy," Drug Science, Policy and Law, Vol. 3 (2017), journals.sagepub.com/doi/full/10.1177/2050324517723232 (30 March 2024).

PART 2

U.S. BURDEN OF NEURODEGENERATIVE DISORDERS

With nearly 8 million Americans currently suffering from AD and PD, and these numbers expected to double by 2050, the economic and social impacts of neurodegenerative disorders are immense.[8] These disorders place a significant financial burden on healthcare systems while profoundly diminishing the quality of life for both patients and their families. The lack of effective treatments aggravates these burdens by failing to halt disease progression or alleviate the long-term costs associated with care.

Between 2016 and 2017, neurodegenerative diseases impacted an estimated 4.7 to 6 million people in the U.S. These conditions accounted for 272,644 deaths and a loss of 3,011,484 disability-adjusted life years (DALYs)—a measure of the years of healthy life lost to illness, disability, or early death—in 2016.[9]

8 "Disease Connections: Alzheimer's and Parkinson's," American Brain Foundation, 6 Feb 2024, americanbrainfoundation.org/disease-connections-alzheimers-and-parkinsons/ (30 June 2024).

9 "The U.S. Burden of Neurodegenerative Disease," Partnership to Fight Chronic Disease, fightchronicdisease.org. fightchronicdisease.org/resources/us-burden-neurodegenerative-disease (16 April 2024).

In 2014, 1.6% of the U.S. population, approximately 5 million individuals aged 65 and older, were living with Alzheimer's disease and Related Dementias (ADRD). By 2060, cases are projected to double to 3.3%, affecting 13.9 million adults.[10] Alzheimer's alone accounts for 60-80% of all diagnosed dementia cases.[11]

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The management of neurodegenerative diseases is among the most expensive healthcare challenges due to their chronic, progressive nature. The annual cost ADRD, Parkinson's, and other related neurodegenerative diseases reached approximately $655 billion in 2020 USD, according to estimates from Emory University professors. This encompasses both direct medical and non-medical expenses, as well as indirect costs like lost productivity and unpaid caregiving hours.[12] Of this $655 billion burden, about $607 billion can be attributed to ADRD costs.[13] Meanwhile, Parkinson's accounts for nearly $55 billion of annual costs.[14]

10 Kevin Matthews et al., "Racial and Ethnic Estimates of Alzheimer's Disease and Related Dementias in the United States (2015–2060) in Adults Aged ≥65 Years," *Alzheimer's and Dementia*, Vol. 15 (2019), ncbi.nlm.nih.gov/pmc/articles/PMC6333531/ (30 Sept. 2024).

11 "What Is Dementia?" Alzheimer's Association, alz.org/alzheimers-dementia/what-is-dementia (24 Aug. 2024).

12 Kenneth Thorpe, Allan Levey, and Jacob Thomas, "The Neurodegenerative Disease Burden on the U.S.," Partnership to Fight Chronic Disease, May 2021, www.fightchronicdisease.org/sites/default/files/May%202021%20Neurodegenerative%20Disease%20Burden%20on%20US%20-%20FINAL%20.pdf (30 Aug. 2024).

13 "2021 Alzheimer's disease facts and figures," *Alzheimer's & Dementia*, Vol. 16 (2021), pubmed.ncbi.nlm.nih.gov/33756057/ (12 May 2024).

14 Wenya Yang et al., "Current and projected future economic burden of Parkinson's disease in the U.S.," *npj Parkinson's Disease,* Vol. 6 (2020), https://doi.org/10.1038/s41531-020-0117-1 (12 May 2024).

FIGURE 1: TOTAL ECONOMIC BURDEN OF ALZHEIMER'S DISEASE AND RELATED DEMENTIAS (ADRD) IN THE U.S. IN 2021 (ADJUSTED TO 2020 U.S. DOLLARS, IN BILLIONS)

Medicaid	$58 billion
Medicare	$179 billion
Out-of-pocket spending	$75 billion
Other payment sources (private insurance, health maintenance organizations, other managed care organizations, and uncompensated care)	$38 billion
Informal (unpaid) caregiving	$257 billion
Total economic burden of ADRD	**$607 billion**

Source(s): Kenneth Thorpe, Allan Levey, and Jacob Thomas, "The Neurodegenerative Disease Burden on the U.S.," www.fightchronicdisease.org/sites/default/files/May%202021%20Neurodegenerative%20Disease%20Burden%20on%20US%20-%20FINAL%20.pdf & "2021 Alzheimer's disease facts and figures," *Alzheimer's & Dementia*, Vol. 16 (2021), pubmed.ncbi.nlm.nih.gov/33756057/.

FIGURE 2: TOTAL ECONOMIC BURDEN OF PARKINSON'S DISEASE IN THE U.S. IN 2017 (ADJUSTED TO 2020 USD, IN BILLIONS)

Direct medical	$26.8 billion
Non-medical costs (home renovations, motor vehicle modifications, expenditures for daily non-medical care, and other expenses)	$7.9 billion
Absenteeism (disease-related number of days missed from work)	$5.4 billion
Disability income	$5.1 billion
Presenteeism (disease-related unproductive work days while working)	$3.1 billion
Reduced employment	$2.9 billion
Premature death	$2.6 billion
Social productivity loss in volunteer work	$1 billion
Total economic burden of PD (direct medical costs + indirect and non-medical costs)	$54.8 billion

Source: Wenya Yang et al., "Current and projected future economic burden of Parkinson's disease in the U.S.," *npj Parkinson's Disease*, Vol. 6 (2020), https://doi.org/10.1038/s41531-020-0117-1.

In 2021, the annual cost of ADRD in the U.S. was $352 billion, including medical and long-term care, with $75 billion stemming from out-of-pocket expenses.[15] The lifetime cost of care for an individual with dementia was estimated at $320,000, compared to just $140,000 for those without dementia.[16] From the age of 65 until their death, individuals with dementia incur about $46,000 more in medical and long-term care costs than other aging individuals, and 98% of these costs are related to nursing home care.[17] For Medicare beneficiaries with dementia, five-year incremental costs were around $17,000 higher per patient than those without dementia, with out-of-pocket medical spending consuming 32% of total household wealth in the five years before death, compared to 11% for those without dementia.[18,19]

While Parkinson's disease (PD) is less common than Alzheimer's, it also presents a significant burden. In 2016-2017, between 0.7 and 1.04 million adults in the U.S. were living with PD,[20, 21] causing an estimated 26,000 deaths and nearly 356,000 DALYs lost—a 22.4% increase in death and 15% increase in lost DALYs since 1990.[22]

15 Kenneth Thorpe, Allan Levey, and Jacob Thomas, "The Neurodegenerative Disease Burden on the U.S.," Partnership to Fight Chronic Disease, May 2021, www.fightchronicdisease.org/sites/default/files/May%202021%20Neurodegenerative%20Disease%20Burden%20on%20US%20-%20FINAL%20.pdf (30 Aug. 2024).

16 Eric Jutkowitz, "The Impact of Dementia on Health Care Utilization and Costs," *Journal of the American Geriatrics Society*, Vol. 65 (2017), ncbi.nlm.nih.gov/pmc/articles/PMC5657516/ (10 May 2024).

17 Péter Hudomiet, "The Prevalence of Dementia in the United States: The Aging, Demographics, and Memory Study," *The Journal of the Economics of Ageing,* Vol. 14 (2019), ncbi.nlm.nih.gov/pmc/articles/PMC6874215/ (7 June 2024).

18 Lindsay White et al., "Medicare Expenditures Attributable to Dementia," *Health Services Research*, Vol. 54 (2019), doi:10.1111/1475-6773.13134, ncbi.nlm.nih.gov/pmc/articles/PMC6606539/.

19 Amy Kelley et al., "The Burden of Health Care Costs for Patients With Dementia in the Last 5 Years of Life," *Annals of Internal Medicine*, Vol. 163 (2015), doi:10.7326/M15-0381,ncbi.nlm.nih.gov/pmc/articles/PMC4809412/ (5 May 2024).

20 Earl Dorsey et al., "Global, Regional, and National Burden of Parkinson's Disease, 1990–2016: A Systematic Analysis for the Global Burden of Disease Study," *The Lancet Neurology*, Vol. 17 (2018), thelancet.com/journals/laneur/article/PIIS1474-4422(18)30295-3/ (12 April 2024).

21 Zhou Yang and Allan Levey, "Gender Differences: A Lifetime Analysis of the Economic Burden of Alzheimer's Disease," *Women's Health Issues,* Vol. 25 (2015), pubmed.ncbi.nlm.nih.gov/26363924/.

22 Earl Dorsey et al., "Global, Regional, and National Burden of Parkinson's Disease, 1990–2016: A Systematic Analysis for the Global Burden of Disease Study," *The Lancet Neurology*, Vol. 17 (2018), thelancet.com/journals/laneur/article/PIIS1474-4422(18)30295-3/ (12 April 2024).

Researchers from the Lewin Group and Michael J. Fox Foundation estimated the economic burden of PD at $55 billion in 2017 (in 2020 U.S. dollars), with $27 billion attributed to direct medical expenses and $28 billion to indirect costs. Indirect costs include $15 billion in lost future earnings and caregiver burdens, $7.9 billion in non-medical costs, and $5.1 billion in disability income received by individuals with Parkinson's. Of the $27.9 billion in indirect and non-medical costs, $21 billion were direct costs to individuals with Parkinson's, and the remaining $6.9 billion were due to productivity losses from informal caregiving. By 2037, direct and indirect costs are projected to rise to $83.4 billion in 2037, with the major cost drivers including direct medical costs, productivity loss, disability income, long-term care costs, and caregiver productivity loss.[23]

For Medicare beneficiaries with PD, annual direct medical costs averaged $24,000 to $26,000 per person from 2013-2015, with costs increasing as the disease progresses.[24, 25] Inpatient hospital services, institutional care, outpatient visits, and prescription medication are the major cost drivers. Direct medical costs for PD patients have been shown to rise by an average of 16.7% annually following diagnosis, while average annual indirect costs per person are $26,935, primarily driven by productivity loss and non-medical care.[26, 27]

> *The financial burden associated with neurodegenerative disorders go beyond medical expenses. Costs related to home modifications, transportation, and specialized equipment are common, while long-term care, particularly in nursing homes, often represents the largest financial strain.*

[23] Wenya Yang et al., "Current and projected future economic burden of Parkinson's disease in the U.S.," *npj Parkinson's Disease,* Vol. 6 (2020), https://doi.org/10.1038/s41531-020-0117-1 (12 May 2024).

[24] Nabila Dahodwala et al., "Projected Growth of Parkinson Disease in the United States and the Rest of the World," *Movement Disorders*, Vol. 36 (2021), pubmed.ncbi.nlm.nih.gov/33031604/.

[25] Sneha Mantri, "The Importance of Diversity in Parkinson's Disease Research," *npj Parkinson's Disease*, Vol. 5 (2019), nature.com/articles/s41531-019-0074-8 (30 April 2024).

[26] Scott Johnson et al., "Overview of Parkinson's Disease: Pathology, Symptoms, and Management," *Pharmacoeconomics,* Vol. 31 (2013), pubmed.ncbi.nlm.nih.gov/23907717/.

[27] Zhou Yang and Allan Levey, "Gender Differences: A Lifetime Analysis of the Economic Burden of Alzheimer's Disease," *Women's Health Issues,* Vol. 25 (2015), pubmed.ncbi.nlm.nih.gov/26363924/.

The financial burden associated with neurodegenerative disorders go beyond medical expenses. Costs related to home modifications, transportation, and specialized equipment are common, while long-term care, particularly in nursing homes, often represents the largest financial strain. Moreover, as the demand for such care continues to rise, the financial sustainability of these arrangements becomes increasingly questionable.

The burden of neurodegenerative diseases extends beyond financial costs, posing significant social and emotional challenges, particularly for caregivers. According to 2023 estimates, around 11 million Americans were providing unpaid care for individuals with Alzheimer's or other dementias, contributing over 18 billion hours of care annually—valued at $347 billion.[28] The cumulative impact of these burdens reflects the immense reliance on family members and gaps in formal caregiving services for patients with neurodegenerative disorders.

Caregiving for individuals with AD or PD is often a full-time responsibility that imposes substantial physical, emotional, and financial strain on caregivers that can last for many years. Caregivers often reduce their work hours or leave their jobs entirely, with lost income and benefits exacerbating financial strain.[29] The cumulative impact of these costs can be devastating, forcing families to make difficult choices about care and quality of life.

Neurodegenerative disorders also carry broader societal implications. As their prevalence increases, the strain on public health systems and social services will intensify, potentially diverting funds from other essential services. The demand for specialized care facilities and trained healthcare workers is also rising, imposing additional pressure on an already strained healthcare infrastructure. By 2050, it is estimated that Medicare spending on people with Alzheimer's disease alone will total a projected $453 billion. This will account for nearly one in every three dollars of Medicare spending.[30]

The social isolation and stigma associated with neurodegenerative disorders can lead to a decline in the quality of life for both patients and caregivers. Many individuals with

28 "2024 Alzheimer's Disease Facts and Figures," *Alzheimer's & Dementia*, Vol. 20 (2024), ncbi.nlm.nih.gov/pmc/articles/PMC11095490/ (5 June 2024).

29 Sally Duplantier, "Barriers and Facilitators of Health and Well-Being in Informal Caregivers of Dementia Patients: A Qualitative Study," *International Journal of Environmental Research and Public Health,* Vol. 20 (2023), ncbi.nlm.nih.gov/pmc/articles/PMC10001898/ (5 April 2024).

30 "Costs of Alzheimer's to Medicare and Medicaid," Alzheimer's Association, Alzheimer's Impact Movement, 2024, portal.alzimpact.org/media/serve/id/62509c7a54845.

dementia face challenges in maintaining social connections and participating in community activities, which can exacerbate feelings of loneliness and depression.[31] The ripple effects of these challenges extend beyond immediate families, affecting communities and society at large as the resources needed to support patients grow increasingly scarce.

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The failure of current treatments to alter the course of neurodegenerative diseases compounds these issues. As patients' conditions deteriorate, the need for more intensive and costly care increases, perpetuating a cycle of escalating costs and declining quality of life. This underscores the urgent need for more effective treatments that slow disease progression, reduce long-term care needs, and ease the burdens on families, caregivers, and communities.

Psychedelic therapies, with their potential to address multiple aspects of neurodegeneration, offer a novel approach that could reduce the long-term costs of care while improving the quality of life for patients and caregivers alike. By potentially slowing disease progression and minimizing the need for intensive care, these therapies may provide significant cost savings for healthcare systems and alleviate some of the financial and emotional burdens on families and caregivers. As such, the exploration and integration of these novel treatments into standard care practices warrants serious consideration.

[31] Helen Macpherson, "The Impact of Loneliness and Social Isolation on Cognitive Aging: A Narrative Review," *Journal of Alzheimer's Disease Reports*, Vol. 7 (2023), ncbi.nlm.nih.gov/pmc/articles/PMC10357115/ (15 April 2024).

PART 3

CURRENT TREATMENTS FOR NEURODEGENERATIVE DISORDERS

Current treatments of neurodegenerative disorders primarily aim to alleviate symptoms and improve patients' quality of life. Despite the availability of various medications, the therapeutic landscape remains limited, offering only modest benefits and often accompanied by significant side effects. Crucially, none of these treatments modify the progression of these diseases.[32]

Commonly prescribed drugs include apomorphine, levodopa, baclofen, donepezil, and entacapone. Apomorphine is used in PD to manage motor symptoms, while donepezil is prescribed for AD to enhance cognitive function. Baclofen is often commonly administered to alleviate muscle spasticity in conditions like multiple sclerosis, and entacapone is used alongside other drugs to enhance Parkinson's treatment by inhibiting the breakdown of dopamine.[33]

[32] Richard Lamptey, "A Review of the Common Neurodegenerative Disorders: Current Therapeutic Approaches and the Potential Role of Nanotherapeutics," *International Journal of Molecular Sciences*, Vol. 23 (2022), ncbi.nlm.nih.gov/pmc/articles/PMC8837071/.

[33] Ibid.

While these medications may offer some degree of symptomatic relief, they do not alter disease progression.[34] Their benefits are also often short-lived and diminish as the disease progresses, leaving patients and caregivers with fewer options as the disease advances.

The inadequacies of these medications stem from their failure to address the underlying neurodegenerative processes that drive the progression of these diseases, such as the loss of neurons, synaptic dysfunction, and neuroinflammation.[35] As a result, patients experience unabated functional decline and reduced quality of life.

“The inadequacies of these medications stem from their failure to address the underlying neurodegenerative processes that drive the progression of these diseases, such as the loss of neurons, synaptic dysfunction, and neuroinflammation. As a result, patients experience unabated functional decline and reduced quality of life.”

The use of these medications is also frequently accompanied by a range of side effects, which can be both physically and psychologically burdensome. Donepezil, for example, is associated with gastrointestinal disturbances, insomnia, and bradycardia (slow heart rate), which is particularly concerning for elderly Alzheimer’s patients with existing cardiac risks.[36]

As a key feature of Parkinson’s disease is the degeneration of dopamine-producing brain cells, PD treatment strategies primarily focus on dopaminergic therapies to manage motor symptoms, the cornerstone being levodopa. Levodopa helps replenish the brain’s dopamine levels and is often combined with carbidopa to prevent levodopa from breaking down

[34] Ibrahim Mortada, “Immunotherapies for Neurodegenerative Diseases,” *Frontiers in Neurology*, Vol. 12 (2021), frontiersin.org/journals/neurology/articles/10.3389/fneur.2021.654739/ (15 June 2024).

[35] Michael Winkelman et al., “The Potential of Psychedelics for the Treatment of Alzheimer's Disease and Related Dementias,” *European Neuropsychopharmacology,* Vol. 76 (2023), sciencedirect.com/science/article/pii/S0924977X23001347 (10 July 2024).

[36] Anil Kumar, Jaskirat Sidhu, Forshing Lui, and Jack Tsao, “Alzheimer Disease,” StatPearls [Internet], StatPearls Publishing, 12 Feb. 2024, ncbi.nlm.nih.gov/books/NBK499922/.

before it reaches the brain. While levodopa can significantly improve motor function, its long-term use is associated with motor complications, including dyskinesias (involuntary movements) and motor fluctuations, in which the drug's effectiveness becomes inconsistent and leads to periods of reduced mobility.[37] Entacapone, although beneficial for prolonging levodopa's effects in Parkinson's patients, can cause diarrhea, liver damage, and dyskinesias, adding to the complexity of managing PD.[38]

Apomorphine, while helpful in relieving the motor symptoms of PD, can cause nausea, dizziness, and involuntary movements, which may be as debilitating as the symptoms of Parkinson's disease itself.[39] Baclofen, while effective in reducing muscle spasticity, can lead to sedation, confusion, and muscle weakness, further compromising patient mobility and quality of life.[40]

Non-motor symptoms of Parkinson's, such as depression, cognitive impairment, and autonomic dysfunction, are significant contributors to the burden of PD but are often inadequately addressed by current treatments.[41] For instance, the use of antidepressants is complicated by interactions with PD medications that may worsen motor symptoms.[42] Additionally, cognitive enhancers used to improve memory, alertness, and concentration in PD patients provide only limited benefit and come with the same side effects experienced by Alzheimer's patients using such treatment.[43]

The burden of medication side effects is especially extreme for elderly patients, particularly those with multiple diseases or conditions. Polypharmacy—the concurrent use of multiple medications to treat one or multiple conditions—further complicates treatment, increasing

37 Peter LeWitt, "Levodopa for the Treatment of Parkinson's Disease," *The New England Journal of Medicine*, Vol. 359 (2008), www.nejm.org/doi/10.1056/NEJMct0800326.

38 Kristin Holm and Caroline Spencer, "Entacapone: A Review of Its Use in Parkinson's Disease," *Drugs*, Vol. 58 (1999), pubmed.ncbi.nlm.nih.gov/10439935/.

39 "Apomorphine (Subcutaneous Route) Side Effects," Mayo Clinic, mayoclinic.org/drugs-supplements/apomorphine-subcutaneous-route/side-effects/drg-20068366 (15 July 2024).

40 "Side Effects of Baclofen," National Health Service, nhs.uk/medicines/baclofen/side-effects-of-baclofen (18 July 2024).

41 Amy Amara, "Effects of Exercise on Non-Motor Symptoms of Parkinson's Disease," *Clinical Therapeutics,* Vol. 40 (2018), ncbi.nlm.nih.gov/pmc/articles/PMC5875718/ (20 June 2024).

42 Ramón Cacabelos, "Parkinson's Disease: From Pathogenesis to Pharmacogenomics," *International Journal of Molecular Sciences,* Vol. 18 (2017), ncbi.nlm.nih.gov/pmc/articles/PMC5372567/ (12 July 2024).

43 Gabbie Portlock et al., "Therapeutic Dilemmas: Cognitive Enhancers and Risk of Falling in Older Adults—A Clinical Review," *European Geriatric Medicine,* Vol. 14 (2023), ncbi.nlm.nih.gov/pmc/articles/PMC10447592/ (22 June 2024).

the risk of drug interactions, adverse reactions, and poor adherence to treatment regimens.[44]

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The challenge in treating neurodegenerative disorders, therefore, lies in both the limited efficacy of these drugs and the difficulty of balancing side effects while maintaining symptom control. Novel therapeutic approaches are needed that target the root causes of neurodegenerative diseases while minimizing adverse effects. Whereas traditional medications focus on a single pathway, psychedelics may target a broader range of processes, with early research suggesting they promote neuroplasticity, reduce neuroinflammation, and increase brain function, potentially offering a more effective and tolerable treatment strategy for patients with neurodegenerative disease.

[44] Ramón Cacabelos, "Parkinson's Disease: From Pathogenesis to Pharmacogenomics," *International Journal of Molecular Sciences,* Vol. 18 (2017), ncbi.nlm.nih.gov/pmc/articles/PMC5372567/ (12 July 2024).

PART 4

A BRIEF HISTORY OF PSYCHEDELICS

Psychedelics have a long history, with naturally occurring substances, such as psilocybin-containing mushrooms, mescaline-containing cacti (like peyote and San Pedro), and the N,N-dimethyltryptamine-containing ayahuasca brew, being used for millennia by various indigenous societies. These substances have been central to healing practices, spiritual ceremonies, and other ritualistic purposes for over 5,000 years.[45]

The modern era of psychedelic research began in 1897, when German pharmacologist Arthur Heffter isolated mescaline as the psychoactive alkaloid in peyote, marking the first scientific identification of a naturally occurring psychedelic compound.[46] However, widespread interest in psychedelics is often attributed to the accidental discovery of the psychotropic effects of LSD (lysergic acid diethylamide) by Swiss chemist Albert Hofmann in 1943. Hofmann's discovery was followed by his successful isolation of psilocybin, the psychoactive compound in "magic mushrooms," in 1958.[47] These breakthroughs set the stage for the scientific exploration of psychedelics and their potential therapeutic uses.

45 Javier Artal, "Hallucinogenic Drugs in Pre-Columbian Mesoamerican Cultures," *Journal of Psychoactive Drugs*, Vol. 43 (2011), pubmed.ncbi.nlm.nih.gov/21893367/ (3 April 2024).

46 James Rucker et al., "Psychiatry & the Psychedelic Drugs: Past, Present & Future," *Neuropharmacology*, Vol. 142 (2018), sciencedirect.com/science/article/pii/S002839081730638X (28 July 2024).

47 Albert Hofmann, *LSD: My Problem Child*, 2013 ed., Oxford University Press, 2013.

Psychedelic-assisted therapy (PAT) began to gain popularity in the early 1950s with LSD, followed by psilocybin later that decade. This period saw a surge in clinical experimentation across North America and Europe, with hundreds of clinical studies involving thousands of patients. These early studies focused on the potential of psychedelics to treat conditions such as depression, anxiety, and alcoholism.[48] However, as the use of LSD and psilocybin extended beyond clinical settings and became associated with the counterculture movement of the 1960s, public and government backlash grew.[49]

Psychedelic-assisted therapy (PAT) began to gain popularity in the early 1950s with LSD, followed by psilocybin later that decade. This period saw a surge in clinical experimentation across North America and Europe, with hundreds of clinical studies involving thousands of patients.

Partly in response to growing concerns about the widespread and uncontrolled use of psychedelics, the U.S. Congress passed the Controlled Substances Act in 1970. This law classified all psychedelics, including LSD and psilocybin, as Schedule I drugs, a category that denotes substances with a high potential for abuse and no accepted medical use.[50] This classification effectively halted all clinical research on psychedelics for the next two decades.

Despite these legal barriers, the belief in the therapeutic potential of psychedelics persisted. Scientists, practitioners, and advocates continued to explore these substances, slowly rekindling interest in psychedelic research. Today, this renewed interest has led to the current wave of studies investigating the therapeutic applications of psychedelics, which are increasingly recognized for their potential to treat various medical conditions.

48 Sean Belouin and Jack Henningfield, "Psychedelics: Where We Are Now, Why We Got Here, What We Must Do," *Neuropharmacology*, Vol. 142 (2018), doi:10.1016/j.neuropharm.2018.02.018.

49 James Rucker et al., "Psychiatry & the Psychedelic Drugs: Past, Present & Future," *Neuropharmacology*, Vol. 142 (2018), sciencedirect.com/science/article/pii/S002839081730638X (28 July 2024).

50 Belouin and Henningfield, "Psychedelics: Where We Are Now, Why We Got Here, What We Must Do."

4.1

PSYCHEDELIC TREATMENT FOR MENTAL HEALTH CONDITIONS

Psychedelics have demonstrated therapeutic value across a range of neuropsychiatric conditions (neurology-related mental health disorders), often producing lasting benefits after just a single administration. As a result, some treatments incorporating psychedelics, including psilocybin, LSD, and MDMA, have been recognized by the FDA as "breakthrough therapies" for use in treating specific mental health disorders.

Historically, the healing properties of psychedelics have been predominantly associated with their capacity to address emotional and psychological trauma, with the assumption that mental healing could subsequently lead to physical well-being. This notion aligns with broader theories in psychology and medicine that emphasize the interconnectedness of mental and physical health, such as psychoneuroimmunology (PNI), which explores how psychological resilience can contribute to physical resilience.[51] However, it's possible that both mental and physical healing are grounded in the same biological processes: cellular regeneration and repair in response to stress, inflammation, and trauma.

> *Current research suggests classic psychedelics can promote the growth of cortical neurons (nerve cells in the brain's outer layer), activate mechanisms that enhance neuronal survival, and modulate the immune system.*

Current research suggests classic psychedelics can promote the growth of cortical neurons (nerve cells in the brain's outer layer), activate mechanisms that enhance neuronal survival, and modulate the immune system. These effects position psychedelics as promising candidates for treating neuropsychiatric disorders characterized by cortical atrophy,

[51] Estherina Trachtenberg, "The Beneficial Effects of Social Support and Prosocial Behavior on Immunity and Health: A Psychoneuroimmunology Perspective," *Brain, Behavior, and Immunity - Health*, Vol. 37 (2024), doi:10.1016/j.bbih.2024.100758.

conditions that involve the loss and dysfunction of brain cells, such as depression, anxiety, post-traumatic stress disorder (PTSD), and substance use disorder (SUD). Clinical trials have reported significant improvements with psychedelic-assisted therapies, supporting their efficacy in treating these disorders.

The effects of psychedelics on the brain observed in the treatment of neuropsychiatric disorders may also explain their broader therapeutic benefits for other cognitive conditions, particularly neurodegenerative diseases such as AD and PD. Because cortical atrophy underlies many of the mood, memory, and cognitive symptoms seen in neurodegenerative diseases, psychedelics may offer a novel approach to their treatment. For example, many of the memory, thinking, and mood problems in Alzheimer's disease are linked to issues with certain brain receptors called 5-HT2A receptors.[52] Psychedelics can activate these receptors, which suggests they may have potential as a treatment for such conditions.

[52] Gongliang Zhang and Robert Stackman Jr., "The Role of Serotonin 5-HT2A Receptors in Memory and Cognition," *Frontiers in Pharmacology*, Vol. 6 (2015), doi:10.3389/fphar.2015.00225.

PART 5

MECHANISMS OF ACTION IN NEURODEGENERATIVE DISORDERS

Neurodegenerative disorders are characterized by significant neuron loss and weakened connections between nerve cells. In Alzheimer's, brain regions shrink and connections between brain cells weaken, leading to memory loss, confusion, and behavioral changes. Alzheimer's also causes an overactive immune response in the brain, causing inflammation that further damages brain cells.

Psychedelics, particularly psilocybin and LSD, show promise in promoting neuroplasticity—the ability for the brain to adapt or change over time by creating new neurons and building new networks. In neurodegenerative diseases like Alzheimer's, synaptic density and dendritic spines are reduced, impairing neuronal communication and contributing to cognitive decline.[53] Psychedelics may reverse these deficits by enhancing neuroplasticity, compensating for neural damage, and potentially slowing or reversing cognitive decline by fostering new neural connections.

[53] Matt Puderbaugh and Prabhu Emmady, "Neuroplasticity," StatPearls [Internet], StatPearls Publishing, updated 1 May 2023, ncbi.nlm.nih.gov/books/NBK557811/ (10 June 2024).

The therapeutic effects of psychedelics are often tied to the mystical, intense, and deeply meaningful experiences that occur during treatment. These powerful experiences correlate with long-term improvements in brain connectivity and cognitive resilience. As a result, enhanced neuroplasticity may preserve cognitive function—particularly in the early stages of AD where the goal is to slow cognitive decline—by maintaining the brain's adaptability.

Classic psychedelics act primarily by activating 5-HT2A serotonin receptors, which are abundant in the brain regions most affected by neurodegeneration, such as the prefrontal cortex and hippocampus. This activation increases brain-derived neurotrophic factor (BDNF) and other growth factors that support synaptic growth and neurogenesis.[54] BDNF plays a critical role in synaptic plasticity, learning, and memory. By upregulating BDNF, psychedelics may strengthen existing synaptic connections and promote formation of new ones, counteracting the synaptic loss that characterizes neurodegenerative diseases, potentially reversing the structural brain changes associated with AD and improving cognitive function.

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One of the earliest signs of Alzheimer's disease is disruption of the default mode network (DMN)—a network of brain regions that become active when we are not focused on the outside world and is involved in daydreaming, recalling memories, and introspection. In healthy individuals, the DMN is highly active during rest and mind-wandering but less active during tasks that require external focus. In AD patients, however, the DMN remains unusually active even when they are engaged in tasks, leading to issues with memory, attention, and overall cognitive function. Clinical trials have shown that psilocybin can

[54] Blerida Banushi and Vince Polito, "A Comprehensive Review of the Current Status of the Cellular Neurobiology of Psychedelics," *Biology (Basel)*, Vol. 12 (2023), doi:10.3390/biology12111380.

decouple DMN connectivity, allowing for a profound reorganization of thought patterns and brain activity.[55] For patients with AD, where DMN hyperactivity contributes to the persistence of negative self-referential thoughts and cognitive rigidity, psilocybin's ability to modulate and reset DMN connectivity may be particularly useful.

Neuroinflammation also plays a key role in the progression of neurodegenerative diseases. In AD, chronic inflammation exacerbates neuronal damage and accelerates cognitive decline. Psychedelics like psilocybin have demonstrated potent anti-inflammatory effects that along with the promotion of a more neuroprotective environment, may slow the progression of neurodegeneration and preserve cognitive function for a longer period.

5.1 A CLOSER LOOK AT ALZHEIMER'S DISEASE

Alzheimer's disease (AD) is fundamentally a brain disease, where the neurons (nerve cells) progressively degenerate and eventually die as a result. This degeneration is closely linked to two hallmark features observed in the brains of AD patients: amyloid-β (Aβ) plaques and neurofibrillary tangles. Aβ plaques are clumps of proteins that accumulate between neurons, disrupting communication between them. Neurofibrillary tangles, on the other hand, are twisted fibers of another protein, tau, that form inside neurons and impair their function.[56]

The buildup of these abnormal proteins leads to widespread neuronal damage and death, resulting in the loss of synapses (connections between neurons) and significant brain atrophy (shrinkage). This is why people with AD experience a gradual decline in memory, reasoning, language, and other cognitive abilities.[57]

AD does not develop overnight; it has a long "silent" phase that can start up to 20 years before symptoms become noticeable. During this time, amyloid plaques begin to

[55] Lukasz Smigielski, "Psilocybin-Assisted Mindfulness Training Modulates Self-Consciousness and Brain Default Mode Network Connectivity with Lasting Effects," *NeuroImage*, Vol. 196 (2019), doi:10.1016/j.neuroimage.2019.04.009.

[56] Michael Winkelman et al., "The Potential of Psychedelics for the Treatment of Alzheimer's Disease and Related Dementias," *European Neuropsychopharmacology,* Vol. 76 (2023), sciencedirect.com/science/article/pii/S0924977X23001347 (10 July 2024).

[57] Lily Aleksandrova and Anthony Phillips, "Neuroplasticity as a Convergent Mechanism of Ketamine and Classical Psychedelics," *Trends in Pharmacological Sciences*, Vol. 42 (2021), pubmed.ncbi.nlm.nih.gov/34565579/ (3 Aug. 2024).

accumulate in the brain, leading to subtle changes in brain function that are not yet severe enough to cause symptoms. This stage is known as the prodromal phase.[58]

Over time, the accumulation of amyloid plaques triggers the formation of tau tangles, leading to further neuronal damage and the onset of symptoms. This cascade of events primarily affects areas of the brain involved in memory, such as the hippocampus, before spreading to other regions responsible for different cognitive functions. The damage becomes more extensive as the disease progresses, leading to the full-blown symptoms of AD.

...studies in mice have shown that psychedelics can enhance cognitive function associated with AD by reducing neuroinflammation, suggesting that decreasing inflammation in humans could mitigate AD pathology and symptoms.

Neuroinflammation is a core mechanism in the pathogenesis of AD and related dementias, with dysregulated inflammatory glial functions exacerbating disease progression. Psychedelics, particularly those acting on the 5-HT2A and Sig-1R receptors, have demonstrated potent anti-inflammatory effects in preclinical studies.[59, 60] For example, studies in mice have shown that psychedelics can enhance cognitive function associated with AD by reducing neuroinflammation, suggesting that decreasing inflammation in humans could mitigate AD pathology and symptoms.[61] This effect is thought to result from the activation of 5-HT2A receptors, which modulate immunomodulatory and anti-

58 Juliet A. Moncaster, "Alzheimer's Disease Amyloid-β Pathology in the Lens of the Eye," *Experimental Eye Research*, Vol. 221 (2022) sciencedirect.com/science/article/pii/S0014483522000550 (26 July 2024).

59 Thomas Flanagan et al., "Structure–Activity Relationship Analysis of Psychedelics in a Rat Model of Asthma Reveals the Anti-Inflammatory Pharmacophore," *ACS Pharmacology & Translational Science*, Vol. 4 (2021), pubs.acs.org/doi/10.1021/acsptsci.0c00063.

60 Attila Szabo, "Psychedelics and Immunomodulation: Novel Approaches and Therapeutic Opportunities," *Frontiers in Immunology*, Vol. 6 (2015), www.frontiersin.org/journals/immunology/articles/10.3389/fimmu.2015.00358/.

61 Hannah Saeger and David Olson, "Psychedelic-inspired Approaches for Treating Neurodegenerative Disorders," *Journal of Neurochemistry*, Vol. 162 (2022), onlinelibrary.wiley.com/doi/10.1111/jnc.15544.

inflammatory responses, promoting cortical neuron growth and countering age-induced chronic inflammation.[62]

In AD, the brain's immune cells, called microglia, become overactive, causing chronic inflammation and further damage to neurons. Psychedelics have been shown to calm this overactivity by reducing the production of inflammatory molecules like IL-6 and TNF-alpha. This may create a healthier immune environment in the brain and prevent inflammation-driven neuronal death. Hence, enhancing microglial function with psychedelics could help reduce neuronal damage and remove dead brain cells, potentially alleviating AD symptoms.[63, 64]

62 Lily Aleksandrova and Anthony Phillips, "Neuroplasticity as a Convergent Mechanism of Ketamine and Classical Psychedelics," *Trends in Pharmacological Sciences*, Vol. 42 (2021), pubmed.ncbi.nlm.nih.gov/34565579/ (3 Aug 2024).

63 Thomas Flanagan et al., "Structure–Activity Relationship Analysis of Psychedelics in a Rat Model of Asthma Reveals the Anti-Inflammatory Pharmacophore," *ACS Pharmacology & Translational Science*, Vol. 4 (2021), pubs.acs.org/doi/10.1021/acsptsci.0c00063.

64 Hannah Saeger and David Olson, "Psychedelic-inspired Approaches for Treating Neurodegenerative Disorders," *Journal of Neurochemistry*, Vol. 162 (2022), onlinelibrary.wiley.com/doi/10.1111/jnc.15544.

PART 6

MECHANISMS OF ACTION IN PSYCHEDELICS

Psychedelics primarily act on serotonin receptors in the brain, particularly the serotonin 2A receptor (5-HT2AR), which plays a crucial role in mood regulation, cognition, and neuroplasticity (the brain's ability to adapt and reorganize itself). Psychedelics, such as psilocybin and LSD, act as agonists of the 5HT2A receptor (5HT2A-R). This receptor is found in high concentrations in brain regions susceptible to AD, such as the prefrontal cortex and hippocampus.[65] Recent studies have shown that psychedelics may offer several therapeutic benefits relevant to neurodegenerative disorders, including promoting neuroplasticity, reducing neuroinflammation, and improving mental health outcomes.

Psychedelics offering these benefits may be considered "psychoplastogens," a term coined by Kacper Lukasiewicz et al. (2021) to describe psychedelics that possess broad therapeutic effectiveness through catalyzing increased brain neuroplasticity and reforming neuronal networks.[66] This property of psychedelics holds particular promise for treating neurodegenerative disorders such as Alzheimer's disease, where slowing down or even

[65] Simon Vann Jones and Allison O'Kelly, "Psychedelics as a Treatment for Alzheimer's Disease Dementia," *Frontiers in Synaptic Neuroscience*, Vol. 12 (2020), www.frontiersin.org/journals/synaptic-neuroscience/articles/10.3389/fnsyn.2020.00034/.

[66] Kacper Lukasiewicz et al., "Serotonergic Psychedelics in Neural Plasticity," *Frontiers in Molecular Neuroscience*, Vol. 14 (2021), frontiersin.org/journals/molecular-neuroscience/articles/10.3389/fnmol.2021.748359/ (16 July 2024).

reversing brain atrophy and enhancing cognitive function could provide a novel approach to pharmacotherapy for conditions that currently lack effective treatment options.

The term "plastogens" refers to the ability of these compounds to induce structural and functional plasticity in the brain, making them ideal candidates for addressing the complex pathophysiology of neurodegenerative diseases. Psychedelics, such as psilocybin and LSD, have shown to promote structural and functional neuroplasticity in preclinical studies. One study found that a single dose of psilocybin led to a significant increase in dendritic spine density (small structures on neurons that help brain cells communicate) in mice. These changes persisted for at least one month after administration, indicating potential long-term benefits that may eventually prove crucial for maintaining cognitive function in human AD patients.[67] These findings align with the idea that psychedelics stimulate neuroprotective pathways, thereby increasing neurogenesis and cognitive flexibility, leading to long-lasting neural changes.[68, 69]

> *Psychedelics produce rapid and robust plastogenic effects on various cognitive processes, including learning and memory.*

Psychedelics produce rapid and robust plastogenic effects on various cognitive processes, including learning and memory.[70, 71] These effects are accompanied by significant therapeutic outcomes, which include the modulation of structural and functional

67 Ling-Xiao Shao et al., "Psilocybin Induces Rapid and Persistent Growth of Dendritic Spines in Frontal Cortex In Vivo," *Neuron*, Vol. 109 (2021), pubmed.ncbi.nlm.nih.gov/34228959/ (6 April 2024).

68 Danilo De Gregorio et al., "Lysergic Acid Diethylamide (LSD) Promotes Social Behavior Through mTORC1 in the Excitatory Neurotransmission," *Proceedings of the National Academy of Sciences*, Vol. 118 (2021), pnas.org/doi/full/10.1073/pnas.2020705118 (1 Aug. 2024).

69 Maxemiliano Vargas et al., "Psychedelics and Other Psychoplastogens for Treating Mental Illness," *Frontiers in Psychiatry*, Vol. 12 (2021), frontiersin.org/journals/psychiatry/articles/10.3389/fpsyt.2021.727117/ (1 Aug. 2024).

70 Albert Garcia-Romeu et al., "Psychedelics as Novel Therapeutics in Alzheimer's Disease: Rationale and Potential Mechanisms," *Current Topics in Behavioral Neurosciences*, Vol. 56 (2022), pubmed.ncbi.nlm.nih.gov/34734390/ (8 April 2024).

71 Hannah Saeger and David Olson, "Psychedelic-inspired Approaches for Treating Neurodegenerative Disorders," *Journal of Neurochemistry*, Vol. 162 (2022), onlinelibrary.wiley.com/doi/10.1111/jnc.15544.

neuroplasticity, modification of synaptic plasticity, induction of anti-inflammatory effects, and the rewiring of faulty neurocircuitry.[72, 73] Such properties make psychedelics particularly well-suited for treating both the neurological and psychological symptoms associated with cortical or subcortical atrophy seen in neurodegenerative conditions.

The mechanisms by which psychedelics exert their effects involve the activation of serotonin receptor target genes, which in turn induce and regulate synaptic, structural, and functional changes in prefrontal cortex pyramidal neurons.[74] This leads to the upregulation of neurotrophic factors that promote neuronal survival and enhance glutamate-driven neuroplasticity in these neurons. The result is improved regional synaptic homeostasis, counteracting the synaptic deficits and neuronal atrophy that are hallmark features of neurodegenerative diseases.

Some studies have illustrated that psychedelics, as serotonergic 5-HT2A agonists, promote both structural and functional plasticity of synapses, thereby enhancing brain functional connectivity.[75, 76] These compounds induce neuroplasticity through post-acute changes in signaling pathways and exhibit anti-inflammatory effects, making them relevant for AD treatment as neuroplasticity-enhancing agents capable of addressing the diverse mechanisms underlying neurodegeneration.[77, 78]

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72 Lily Aleksandrova and Anthony Phillips, "Neuroplasticity as a Convergent Mechanism of Ketamine and Classical Psychedelics," *Trends in Pharmacological Sciences*, Vol. 42 (2021), pubmed.ncbi.nlm.nih.gov/34565579/ (3 Aug. 2024).

73 Michael Bogenschutz et al., "Psilocybin-Assisted Treatment for Alcohol Dependence: A Proof-of-Concept Study," *Journal of Psychopharmacology*, Vol. 29 (2015), pubmed.ncbi.nlm.nih.gov/25586396/ (27 June 2024).

74 Lily Aleksandrova and Anthony Phillips, "Neuroplasticity as a Convergent Mechanism of Ketamine and Classical Psychedelics," *Trends in Pharmacological Sciences*, Vol. 42 (2021), pubmed.ncbi.nlm.nih.gov/34565579/ (3 Aug 2024).

75 Antonio Inserra et al., "Psychedelics in Psychiatry: Neuroplastic, Immunomodulatory, and Neurotransmitter Mechanisms," *Proceedings of the National Academy of Sciences*, Vol. 73 (2021), pnas.org/doi/full/10.1073/pnas.2020705118 (2 Aug. 2024).

76 Calvin Ly et al., "Psychedelics Promote Structural and Functional Neural Plasticity," *Cell Reports*, Vol. 23 (2018), pmc.ncbi.nlm.nih.gov/articles/PMC6082376/ (13 Aug. 2024).

77 Albert Garcia-Romeu et al., "Psychedelics as Novel Therapeutics in Alzheimer's Disease: Rationale and Potential Mechanisms," *Current Topics in Behavioral Neurosciences*, Vol. 56 (2022), pubmed.ncbi.nlm.nih.gov/34734390/ (8 April 2024).

78 Cato de Vos et al., "Psychedelics and Neuroplasticity: A Systematic Review Unraveling the Biological Underpinnings of Psychedelics," *Frontiers in Psychology*, Vol. 12 (2021), www.frontiersin.org/journals/psychiatry/articles/10.3389/fpsyt.2021.724606/ (2 Aug. 2024).

Acute psychedelic effects, characterized by profound perceptual, cognitive, and emotional changes, are believed to be mediated by short-term action potential transfers through synaptic 5-HT2A receptors or fast-acting mechanisms that induce long-lasting structural modifications.[79] However, it is the long-term neuroplastic changes, likely related to intracellular metabotropic serotonin receptors, that hold the most promise for reversing neurocognitive deficits associated with dementias.[80] Through the fine-tuning of neuroplasticity, psychedelics may offer a means of mitigating or even reversing the cognitive decline that characterizes these debilitating disorders.

Through the fine-tuning of neuroplasticity, psychedelics may offer a means of mitigating or even reversing the cognitive decline that characterizes these debilitating disorders.

6.1 CLINICAL RESEARCH

Support for the potential of psychedelics in treating neurodegenerative disorders comes from a growing body of animal models, preclinical studies, neuroimaging research, and clinical trials.

Studies of the effects of psychedelics on animals provide insight into how psychedelics might treat neurodegenerative conditions. For example, a study using a mouse model of Alzheimer's disease found that frequent low doses of LSD improved the mice's performance in memory and learning tasks, suggesting that LSD may offer protective benefits against cognitive decline in AD by enhancing neuroplasticity and cognitive flexibility. Hence, psychedelics like LSD may be useful in treating early-stage AD, with the primary aim of slowing cognitive deterioration.

79 Lily Aleksandrova and Anthony Phillips, "Neuroplasticity as a Convergent Mechanism of Ketamine and Classical Psychedelics," *Trends in Pharmacological Sciences*, Vol. 42 (2021), pubmed.ncbi.nlm.nih.gov/34565579/ (3 Aug. 2024).

80 Joël Bockaert et al., "Neuronal 5-HT Metabotropic Receptors: Fine-Tuning of Their Structure, Signaling, and Roles in Synaptic Modulation," *Cell and Tissue Research*, Vol. 326 (2006), doi.org/10.1007/s00441-006-0286-1.

Research in animals has also shown that psilocybin might improve the health of brain connections, which are often damaged early in Alzheimer's disease. A study on pigs found that just one dose of psilocybin increased levels of a protein called SV2A in the hippocampus and prefrontal cortex—two important areas for memory and thinking. SV2A is a marker of healthy brain connections, so its increase suggests that psilocybin might help strengthen these connections, which could slow down the early stages of cognitive decline in AD.

Research in animals has also shown that psilocybin might improve the health of brain connections, which are often damaged early in Alzheimer's disease. A study on pigs found that just one dose of psilocybin increased levels of a protein called SV2A in the hippocampus and prefrontal cortex—two important areas for memory and thinking.

In rodent models, psychedelics such as psilocybin and LSD have induced both structural and functional neuroplasticity, evidenced by increased dendritic spine density and enhanced synaptic connections in the prefrontal cortex. These findings suggest a potential mechanism by which psychedelics could slow or reverse cognitive decline in AD when synaptic loss is a major contributor to its progression.[81]

One study, a phase 1 double-blind, placebo-controlled, randomized trial, evaluated the safety and tolerability of repeated low-dose oral LSD (5 µg, 10 µg, and 20 µg) in 48 healthy older adults (aged 55-75). Participants received their assigned dose every fourth day over 21 days, with six total dosing sessions.

The findings showed that LSD was well-tolerated across all dosage groups, with mild adverse events like headaches, similar in frequency of adverse events to the placebo group.

[81] Calvin Ly et al., "Psychedelics Promote Structural and Functional Neural Plasticity," *Cell Reports*, Vol. 23 (2018), pmc.ncbi.nlm.nih.gov/articles/PMC6082376/ (13 Aug. 2024).

Importantly, cognitive function, balance, and proprioception were unaffected, suggesting that low doses do not impair daily activities. Pharmacokinetically, LSD was detectable in plasma at 10 µg and 20 µg doses, peaking 30 minutes after administration, with no accumulation over time.[82]

These results support the safety and tolerability of repeated low-dose LSD in older adults and suggest potential for further development as a therapeutic option for Alzheimer's disease. LSD's ability to reduce inflammation, particularly through 5-HT2A receptor signaling, makes it a promising candidate for addressing the neuroinflammatory aspects of Alzheimer's and related conditions.

LSD's ability to reduce inflammation, particularly through 5-HT2A receptor signaling, makes it a promising candidate for addressing the neuroinflammatory aspects of Alzheimer's and related conditions.

Another study examined how psilocybin, combined with mindfulness meditation, can produce long-lasting positive changes in brain function and self-consciousness. Specifically, it focused on how psilocybin affects the brain's Default Mode Network (DMN), which plays a crucial role in self-referential thinking, identity, and mental health. Disruptions in DMN activity are linked to conditions like depression, anxiety, and neurodegenerative diseases such as Alzheimer's disease.[83]

The study involved 38 experienced meditators participating in a five-day silent mindfulness retreat. They were randomly assigned psilocybin or a placebo in a double-blind design, with brain scans taken before and after the retreat to track changes. Results showed that psilocybin significantly altered DMN connectivity, particularly between the medial prefrontal cortex (mPFC) and posterior cingulate cortex (PCC). This decoupling is associated

[82] Neiloufar Family et al., "Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Low Dose Lysergic Acid Diethylamide (LSD) in Healthy Older Volunteers," *Psychopharmacology*, Vol. 237 (2020), ncbi.nlm.nih.gov/pmc/articles/PMC7036065/ (1 Aug. 2024).

[83] Lukasz Smigielski, "Psilocybin-Assisted Mindfulness Training Modulates Self-Consciousness and Brain Default Mode Network Connectivity with Lasting Effects," *NeuroImage*, Vol. 196 (2019), doi:10.1016/j.neuroimage.2019.04.009.

with ego dissolution, a therapeutic effect where the boundaries of self-awareness dissolve, allowing for profound shifts in perception and consciousness.

Participants who experienced ego dissolution reported lasting improvements in their mental health and psychosocial functioning, even four months after the retreat. This suggests that psilocybin, in combination with mindfulness meditation, can promote long-term brain reorganization, leading to better mental well-being.

The study's findings are relevant for treating neurodegenerative diseases like AD, where the DMN is one of the first brain networks to show dysfunction, contributing to memory loss, confusion, and altered self-awareness. Psilocybin's ability to enhance neuroplasticity and rewire brain networks could help counteract cognitive decline in AD. Additionally, psilocybin's potential to reduce rigid patterns of self-referential thinking might alleviate neuropsychiatric symptoms common in AD, such as anxiety and depression.

"…psilocybin's potential to reduce rigid patterns of self-referential thinking might alleviate neuropsychiatric symptoms common in AD, such as anxiety and depression."

There may also be an importance of context, or "set and setting," in psychedelic therapy. The structured, supportive environment of the mindfulness retreat likely enhanced the positive effects observed, highlighting a potential need for carefully designed therapeutic protocols that combine psychedelics with mindfulness-based practices for maximum benefit.

Another study investigated effects of a low dose of LSD on cognitive functions 24 hours after administration, aiming to determine whether LSD could lead to both positive and negative changes in thinking and memory.[84] Findings showed that LSD improved episodic memory, as participants performed better on tasks that required them to recall and

[84] Isabel Wießner et al., "LSD, Afterglow and Hangover: Increased Episodic Memory and Verbal Fluency, Decreased Cognitive Flexibility," *European Neuropsychopharmacology*, Vol. 60 (2022), sciencedirect.com/science/article/abs/pii/S0924977X22001249 (1 Aug. 2024).

organize visual information, suggesting that the drug may enhance how memories are formed and retained. This improvement is believed to be related to LSD's action on specific receptors in the brain, especially in areas like the hippocampus that are involved in memory.

Additionally, the study found that LSD improved phonological verbal fluency, which involves retrieving words based on their sounds. This suggests that LSD may enhance certain brain functions related to word recall and strategic thinking.

However, there were also some observed negative effects. LSD impaired cognitive flexibility, which refers to the ability to switch between tasks or adapt to new information. Participants struggled with tasks that measured this ability, making more errors and showing difficulty in adapting their thinking. This might be due to how LSD affects brain receptors related to executive control. Despite these effects, LSD did not significantly impact other cognitive areas, such as attention, self-control, or visual problem-solving.

Additionally, recent clinical research highlights the potential of psychedelics for their anti-inflammatory effects, primarily through 5-HT2A receptor signaling. Some psychedelics may offer therapeutic benefits for neurodegenerative diseases like Alzheimer's, where neuroinflammation plays a key role.

> *"By reducing neuroinflammation, psychedelics may help to create a less neurotoxic environment, potentially slowing the progression of AD pathology."*

Preclinical studies have demonstrated that psychedelics can exert potent anti-inflammatory effects by activating the 5HT2A receptor. Inflammation is a key driver of AD pathology, and reducing neuroinflammation could help slow disease progression. For instance, in rodent models of AD, activation of 5HT2A receptors has shown neuroprotective effects by reducing inflammatory markers and promoting mitochondrial health, both of which are crucial for neuronal survival. Given that neuroinflammation significantly contributes to the progression of AD, the ability of psychedelics to modulate these inflammatory responses represents a promising therapeutic pathway. By reducing neuroinflammation, psychedelics

may help to create a less neurotoxic environment, potentially slowing the progression of AD pathology.

Recent research has explored how psychedelics can influence epigenetic factors, with promising results. One study examined the effects of LSD on cognitive function in animal models of Alzheimer's disease (AD).[85] Findings showed that LSD caused significant changes in DNA methylation patterns in the prefrontal cortex, a brain area critical for decision-making and memory. These changes were linked to enhanced neuroplasticity, leading to improved cognitive performance. Results further suggest that psychedelics could help modify the brain's epigenetic landscape in ways that increase cognitive resilience and potentially delay the onset of cognitive decline in AD.

> *Recent neuroimaging and neurophysiological studies have provided insights into the effects of psilocybin on brain function, with promising implications for both psychiatric and neurodegenerative disorders.*

Research on other psychedelics, like DMT (dimethyltryptamine), supports similar findings. DMT and related compounds are believed to work through epigenetic changes that protect neurons, as seen in both human stem cell studies and animal models of stroke. For example, one study demonstrated that psychedelics such as DMT could promote neurogenesis—the process by which new neurons are formed in the brain. Neurogenesis is particularly relevant for AD treatment as the disease is characterized by significant neuronal loss. The study found that DMT stimulates the proliferation and differentiation of neural progenitor cells in the hippocampus, a region critical for memory and learning.[86]

85 Antonio Inserra et al., "Modulation of DNA Methylation and Protein Expression in the Prefrontal Cortex by Repeated Administration of D-Lysergic Acid Diethylamide (LSD): Impact on Neurotropic, Neurotrophic, and Neuroplasticity Signaling," *Progress in Neuro-Psychopharmacology & Biological Psychiatry,* Vol. 119 (2022), www.sciencedirect.com/science/article/abs/pii/S0278584622000860.

86 Jose Morales-Garcia et al., "N,N-Dimethyltryptamine Compound Found in the Hallucinogenic Tea Ayahuasca Regulates Adult Neurogenesis In Vitro and In Vivo," *Translational Psychiatry*, Vol. 10 (2020), www.nature.com/articles/s41398-020-01011-0 (4 Aug. 2024).

These effects suggest that psychedelics may help to counteract the neuronal loss and cognitive decline associated with AD by promoting the generation of new neurons.

Recent neuroimaging and neurophysiological studies have provided insights into the effects of psilocybin on brain function, with promising implications for both psychiatric and neurodegenerative disorders. A 2019 fMRI study demonstrated that a single high dose of psilocybin led to long-term neuroplastic changes, with benefits observed up to four months later in a group of meditators.[87]

Other studies have found that psilocybin increases global brain glucose metabolism, particularly in areas such as the frontal and medial temporal cortex, which are typically affected in AD. Functional MRI (fMRI) scans also showed enhanced connectivity in brain regions responsible for emotion regulation and cognitive processing, indicating that psilocybin may help reorganize dysfunctional neural circuits that contribute to cognitive decline in AD.[88]

> *In addition to these findings, a study on psilocybin's impact on synaptic connectivity found that psilocybin significantly increased functional connectivity in brain networks associated with memory, self-awareness, and cognition.*

[87] Lukasz Smigielski, "Psilocybin-Assisted Mindfulness Training Modulates Self-Consciousness and Brain Default Mode Network Connectivity with Lasting Effects," *NeuroImage*, Vol. 196 (2019), doi:10.1016/j.neuroimage.2019.04.009.

[88] Robin Carhart-Harris and David Nutt, "Serotonin and Brain Function: A Tale of Two Receptors," *Journal of Psychopharmacology*, Vol. 31 (2017), pubmed.ncbi.nlm.nih.gov/28858536/ (14 May 2024).

In addition to these findings, a study on psilocybin's impact on synaptic connectivity found that psilocybin significantly increased functional connectivity in brain networks associated with memory, self-awareness, and cognition.[89] This enhancement of synaptic connectivity could counteract the disconnection and synaptic loss observed in AD, potentially preserving cognitive function and slowing the progression of the disease.

[89] Robin Carhart-Harris et al., "Psilocybin with Psychological Support for Treatment-Resistant Depression: An Open-Label Feasibility Study," *The Lancet Psychiatry*, Vol. 3 (2016), www.thelancet.com/journals/lanpsy/article/PIIS2215-0366(16)30065-7/ (21 June 2024).

PART 7

PSYCHEDELIC TREATMENT TO ENHANCE QUALITY OF LIFE

Depression and anxiety are prevalent among AD patients and can exacerbate their cognitive decline. Clinical trials have shown that psychedelics can alleviate anxiety and depression, offering promising implications for neurodegenerative disease patients suffering from these debilitating symptoms.

Approximately 40% of AD patients experience significant anxiety, yet conventional treatments, including selective serotonin reuptake inhibitors (SSRIs) and talk therapy, often show limited efficacy in this population.[90] Moreover, as neurodegenerative diseases progress, the effectiveness of standard treatments diminishes, leaving patients and caregivers with fewer options for managing psychiatric symptoms.

Given the limitations of standard therapies, researchers like those at Johns Hopkins University, have explored psychedelics for neuropsychiatric conditions. Johns Hopkins researchers have studied the psychological effects of psilocybin for over two decades for patients with conditions such as cancer, major depression, and anorexia. That research has

[90] Mario Mendez, "The Relationship Between Anxiety and Alzheimer's Disease," *Journal of Alzheimer's Disease Reports*, Vol. 5 (2021), pubmed.ncbi.nlm.nih.gov/33981954/ (26 June 2024).

demonstrated compelling results, for instance finding that psilocybin reduced depression and anxiety in cancer patients, with over 80% reporting improved life satisfaction.[91]

Drs. Albert Garcia-Romeu and Nathan Rosenberg from the Center for Psychedelic & Consciousness Research at Johns Hopkins University are currently investigating the effects of psilocybin on neuropsychiatric patients, such as those with mild cognitive impairment (MCI) and early-stage Alzheimer's disease. Dr. Garcia-Romeu observed that, "In some patient populations, psilocybin is very helpful in reducing depression, reducing anxiety, and improving quality of life. Those types of benefits could be really useful in a population with Alzheimer's."[92]

Dr. Garcia-Romeu observed that, "In some patient populations, psilocybin is very helpful in reducing depression, reducing anxiety, and improving quality of life. Those types of benefits could be really useful in a population with Alzheimer's.

The two largest randomized double-blind Phase 2 trials on psilocybin for anxiety and depression in cancer patients were conducted at Johns Hopkins University and New York University. The Johns Hopkins team released its study results, involving 51 adult patients, concurrently with researchers from New York University Langone Medical Center, who conducted a similarly designed study on 29 participants.

The John Hopkins study reported that about 80% of participants experienced clinically significant and lasting reductions in anxiety and depression six months after a single

91 Meghan McCarthy, "Can Psychedelics Help Patients with Dementia?" Penn Memory Center, posted 19 April 2023, www.pennmemorycenter.org/psychedelics-dementia/ (26 March 2024).

92 Ibid.

psilocybin session, with about 60% showing symptom remission into the normal range, in combination with pre- and post-session psychotherapy.[93, 94]

At the six-month follow-up, participants completed a questionnaire that measured self-reported positive and negative changes in attitudes, mood, behavior, and spirituality. The questionnaire included three final questions: How meaningful was the experience? (rated from 1 for everyday experiences to 8 for the single most meaningful experience of one's life); How spiritually significant was the experience? (rated from 1 for no significance to 6 for the single most spiritually significant experience); Has the experience impacted your personal well-being or life satisfaction? (rated from +3 for greatly increased to -3 for greatly decreased).

Sixty-seven percent of participants rated their psilocybin experience as one of the "top five most meaningful experiences of their lives, including single most." About 70% described it as one of their "top five most spiritually significant experiences, including single most." Additionally, 83% of patients reported increases in well-being or life satisfaction. Given the high prevalence of anxiety and depression among individuals with neurodegenerative conditions such as Alzheimer's disease and Parkinson's disease, these results are highly relevant.

Such profound experiences can have significant and long-lasting benefits, including improved self-understanding, greater empowerment, and more active participation in treatment. This may help patients confront and process difficult emotions, reduce suffering, and increase their adaptability and resilience. As such, these findings suggest that psychedelics may alleviate neuropsychiatric symptoms and significantly improve quality of life for AD patients and their caregivers.

As research advances, the application of psilocybin-assisted therapy in neurodegenerative disease could represent a critical step in tackling the complex and intertwined challenges of anxiety, depression, and cognitive decline. By offering symptom relief as well as

[93] Roland Griffiths et al., "Psilocybin Produces Substantial and Sustained Decreases in Depression and Anxiety in Patients with Life-Threatening Cancer: A Randomized Double-Blind Trial," *Journal of Psychopharmacology*, Vol. 30 (2016), www.pubmed.ncbi.nlm.nih.gov/27909165/ (15 April 2024).

[94] Vanessa McMains, "Hallucinogenic Drug Found in 'Magic Mushrooms' Eases Depression, Anxiety in People with Life-Threatening Cancer," Johns Hopkins University, 1 Dec 2016, hub.jhu.edu/2016/12/01/hallucinogen-treats-cancer-depression-anxiety/ (2 July 2024).

profound personal insights, this approach has the potential to significantly improve patient quality of life and reduce burdens on caregivers.

> *By offering symptom relief as well as profound personal insights, this approach has the potential to significantly improve patient quality of life and reduce burdens on caregivers.*

Preliminary clinical findings also support the potential role of psilocybin and LSD in treating chronic pain, a symptom experienced by more than 80% of people with Parkinson's disease.[95, 96] Research dating back to the 1960s has shown that LSD is effective for patients with severe cancer-related pain.[97] Additionally, decades of research supports the use of LSD and psilocybin for chronic headache disorders, showing lasting therapeutic benefits after limited dosing.[98, 99] Researchers theorize that this analgesic effect may be related to psychedelics' influence on 5-HT2A receptors, which are involved in the transmission and processing of pain signals.[100] Disruption of 5-HT2A receptors, whether due to diseases, such as AD and PD, or injury, can alter pain processing, leading to heightened pain and feedback loops. By binding to these receptors, psychedelics like LSD may change the perception of

95 Christopher L. Robinson et al., "Scoping Review: The Role of Psychedelics in the Management of Chronic Pain," *Journal of Pain Research*, Vol. 17 (2024), pmc.ncbi.nlm.nih.gov/articles/PMC10941794/ (22 March 2024).

96 "Pain in Parkinson's Disease," Parkinson's Foundation, www.parkinson.org/library/fact-sheets/pain (24 March 2024).

97 Daniel Kelly et al., "Psychedelic-Assisted Therapy and Psychedelic Science: A Review and Perspective on Opportunities in Neurosurgery and Neuro-Oncology," *Neurosurgery*, Vol. 92 (2023), journals.lww.com/neurosurgery/fulltext/2023/04000/psychedelic_assisted_therapy_and_psychedelic.5.aspx (6 June 2024).

98 Farah Zia et al., "Are Psychedelic Medicines the Reset for Chronic Pain? Preliminary Findings and Research Needs," *Neuropharmacology*, Vol. 234 (2023), sciencedirect.com/science/article/pii/S0028390823001181 (1 Aug. 2024).

99 Kai Kupferschmidt, "LSD Alleviates 'Suicide Headaches': Patients Taking Analog of Psychedelic Drug Report Fewer and Less Intense Cluster Headaches," Science.org, 27 June 2011, www.science.org/content/article/lsd-alleviates-suicide-headaches (12 July 2024).

100 Christopher L. Robinson et al., "Scoping Review: The Role of Psychedelics in the Management of Chronic Pain," *Journal of Pain Research*, Vol. 17 (2024), pmc.ncbi.nlm.nih.gov/articles/PMC10941794/ (22 March 2024).

pain and support the functioning of 5-HT2A receptors, potentially reducing the risk and symptoms of chronic pain.

7.1 CLINICAL PROCEDURES AND SAFETY

The "set and setting" psychedelic-assisted therapy (PAT) model, established in the 1960s, is currently part of all clinical trial models and is designed to achieve a safe patient experience.[101] PAT can be likened to a complex surgical procedure where the success and safety of the treatment depend on several crucial factors: the expertise of facilitators, thorough patient screening and preparation, careful attention to "set and setting," which emphasizes careful preparation and a controlled environment, adherence to safety protocols, and post-session psychological counseling, also known as integration. In PAT approaches, the therapeutic journey is meticulously structured, beginning with a detailed patient screening process to assess suitability and identify any factors warranting exclusion.

> *Preparation involves several psychological counseling sessions that take place in the days or weeks leading up to the psychedelic session. These psychological sessions help the patient mentally and emotionally prepare for the experience, fostering a mindset that supports a positive and transformative outcome.*

Preparation involves several psychological counseling sessions that take place in the days or weeks leading up to the psychedelic session. These psychological sessions help the patient mentally and emotionally prepare for the experience, fostering a mindset that supports a positive and transformative outcome. The psychedelic session, in which psychedelics are administered under carefully controlled conditions, is followed by the first integration session the following day, during the "afterglow" period when patients are more

[101] Daniel Kelly et al., "Psychedelic-Assisted Therapy and Psychedelic Science: A Review and Perspective on Opportunities in Neurosurgery and Neuro-Oncology," *Neurosurgery*, Vol. 92 (2023), journals.lww.com/neurosurgery/fulltext/2023/04000/psychedelic_assisted_therapy_and_psychedelic.5.aspx (6 June 2024).

receptive to processing insights gained. Additional integration sessions occur over several weeks, allowing patients to incorporate the experience into their daily lives, fostering lasting positive changes in behavior and outlook.[102]

For example, a patient facing terminal illness might experience profound meaning and resolution during a psychedelic experience, leading to a reduction in feelings of demoralization, hopelessness, and anxiety about death. This outcome can significantly improve the quality of life and acceptance of the dying process. The transformative effects seen in PAT are thought to be driven by the neuroplastogenic properties of psychedelics, which may facilitate structural and functional changes in the brain, contributing to these profound psychological and behavioral shifts.

This structured approach to PAT ensures that patients are supported throughout the entire process—from preparation to integration—maximizing the therapeutic benefits of the psychedelic experience and minimizing risks.

...trials must adhere to rigorous protocols to ensure participant safety and research integrity, given the legal and ethical complexities surrounding these substances.

Conducting clinical trials with non-FDA–approved investigational Schedule I psychedelics, such as psilocybin, LSD, and MDMA, involves navigating stringent regulatory and safety requirements. Additionally, trials must adhere to rigorous protocols to ensure participant safety and research integrity, given the legal and ethical complexities surrounding these substances. One of the key requirements is the presence of a medical doctor on-site, alongside a clinical psychologist trained in psychedelic-assisted therapy (PAT), to manage any medical or psychological issues that may arise during the study.

Other guides, including registered nurses, physician assistants, nurse practitioners, and marriage or family therapists, may also support patients during the psychedelic experience, provided they have undergone specialized PAT training. Training programs from

[102] Ibid.

institutions like the California Institute of Integral Studies and the Multidisciplinary Association for Psychedelic Studies equip healthcare providers with the knowledge and skills necessary to safely guide patients through psychedelic-induced experiences.

With experienced guides and thorough patient preparation, PAT is typically a deeply meaningful and transformative process, though it can sometimes be challenging. The risk of adverse experiences, such as a "bad trip," is low, and serious long-term effects, like hallucinogen-persisting perceptual disorder, are rare.[103] Additionally, serotonin toxicity has not been reported in clinical trials, though most studies exclude participants on medications that affect serotonin levels, such as antidepressants, to mitigate any potential risk.[104]

Practitioners must adhere to ethical standards, prioritizing patient safety and well-being. This includes maintaining a system of peer review and supervision to ensure PAT practices continue to evolve grounded in ethical practice and scientific rigor.

> *Physiologically, classic psychedelics like psilocybin, LSD, and MDMA, are notable for their high safety profiles and low potential for addiction.*

[103] Matthew Johnson, William Richards, and Roland Griffiths, "Human Hallucinogen Research: Guidelines for Safety," *Journal of Psychopharmacology*, Vol. 22 (2008), pmc.ncbi.nlm.nih.gov/articles/PMC3056407/ (27 July 2024).

[104] Benjamin Malcolm and Kelan Thomas, "Serotonin Toxicity of Serotonergic Psychedelics," *Psychopharmacology (Berlin)*, Vol. 239 (2022), link.springer.com/article/10.1007/s00213-021-05876-x (27 June 2024).

Physiologically, classic psychedelics like psilocybin, LSD, and MDMA, are notable for their high safety profiles and low potential for addiction. Although these substances can cause mild-to-moderate increases in blood pressure, pulse, and respiration, these effects are generally well-tolerated.[105]

Recent data from clinical trials further supports the safety of these substances. In trials using the "set and setting" paradigm, serious adverse events have been rare.[106] This success is largely attributed to strict adherence to safety protocols and thorough patient screening to exclude individuals with a personal or family history of psychotic disorders, such as schizophrenia and bipolar disorder. None of the seven most recent randomized, placebo-controlled trials involving high-dose psilocybin, LSD, or MDMA (totaling 249 patients), reported any serious medical or psychiatric adverse events among participants.[107,108,109,110,111,112,113] These findings highlight the potential for psychedelics to be safely integrated into therapeutic settings with proper protocols.

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105 Daniel Kelly et al., "Psychedelic-Assisted Therapy and Psychedelic Science: A Review and Perspective on Opportunities in Neurosurgery and Neuro-Oncology," *Neurosurgery*, Vol. 92 (2023), journals.lww.com/neurosurgery/fulltext/2023/04000/psychedelic_assisted_therapy_and_psychedelic.5.aspx (6 June 2024).

106 Ibid.

107 Robin Carhart-Harris et al., "Trial of Psilocybin Versus Escitalopram for Depression," *The New England Journal of Medicine*, Vol. 384 (2021), www.nejm.org/doi/full/10.1056/NEJMoa2032994 (13 Aug. 2024).

108 Alan Davis et al., "Effects of Psilocybin-Assisted Therapy on Major Depressive Disorder: A Randomized Clinical Trial," *JAMA Psychiatry*, Vol. 78 (2021), jamanetwork.com/journals/jamapsychiatry/fullarticle/2772630 (12 June 2024).

109 Roland Griffiths et al., "Psilocybin Produces Substantial and Sustained Decreases in Depression and Anxiety in Patients with Life-Threatening Cancer: A Randomized Double-Blind Trial," *Journal of Psychopharmacology*, Vol. 30 (2016), www.pubmed.ncbi.nlm.nih.gov/27909165/ (15 April 2024).

110 Jennifer Mitchell et al., "MDMA-Assisted Therapy for Severe PTSD: A Randomized, Double-Blind, Placebo-Controlled Phase 3 Study," *Nature Medicine*, Vol. 27 (2021), www.nature.com/articles/s41591-021-01336-3 (19 July 2024).

111 Stephen Ross et al., "Rapid and Sustained Symptom Reduction Following Psilocybin Treatment for Anxiety and Depression in Patients with Life-Threatening Cancer: A Randomized Controlled Trial," *Journal of Psychopharmacology*, Vol. 30 (2016), pubmed.ncbi.nlm.nih.gov/27909164/ (9 June 2024).

112 Michael Bogenschutz et al., "Percentage of Heavy Drinking Days Following Psilocybin-Assisted Psychotherapy vs Placebo in the Treatment of Adult Patients With Alcohol Use Disorder: A Randomized Clinical Trial," *JAMA Psychiatry*, Vol. 79 (2022), jamanetwork.com/journals/jamapsychiatry/fullarticle/2795625 (3 June 2024).

113 Franz Holze et al., "Direct Comparison of the Acute Effects of Lysergic Acid Diethylamide and Psilocybin in a Double-Blind Placebo-Controlled Study in Healthy Subjects," *Neuropsychopharmacology*, Vol. 47 (2022), www.nature.com/articles/s41386-022-01297-2 (2 June 2024).

7.2 RESEARCH LIMITATIONS

The legal status of psychedelics poses one of the primary challenges of psychedelic research. Currently classified as Schedule I drugs under the Controlled Substances Act, psychedelics are subject to stringent regulations that make clinical trials both costly and limited in scope. These legal barriers slow the progress of research into the efficacy and safety of PAT, restrict access to these treatments outside clinical settings, and limit the ability to conduct large-scale trials that could provide more robust evidence.

Although there is growing evidence of psychedelics' effects on neuroplasticity, inflammation, and mood regulation, direct studies on their use in neurodegenerative disorders, particularly Alzheimer's, remain sparse. Larger and more diverse long-term human studies are needed to explore whether the initial benefits observed with psychedelics are sustainable and can alter the course of neurodegenerative disorders.

Larger and more diverse long-term human studies are needed to explore whether the initial benefits observed with psychedelics are sustainable and can alter the course of neurodegenerative disorders.

Another limitation in existing research is the variability in dosing protocols. Some studies focus on microdosing—low, sub-perceptual doses of psychedelics—while others use a single high dose, making it difficult to determine the most effective and safe dosing regimen. Standardized protocols are essential to ensure consistency and comparability across studies to identify optimal dosing strategies for various patient populations. Given the cognitive impairments and neuropsychiatric symptoms often present in neurodegenerative patients, there is concern that high-dose psychedelic therapy could exacerbate these issues. Ethical considerations, particularly around obtaining informed consent from patients with cognitive impairment, adds another layer of complexity to this research.

While psychedelics are generally considered safe in controlled settings, acute adverse effects—such as anxiety, paranoia, and confusion—can occur, especially at higher doses. These effects may be more problematic in AD patients due to their heightened vulnerability

from cognitive decline. Further research is needed to understand these concerns regarding high-dose treatment for AD.

Finally, neurodegenerative disorders like AD are highly heterogeneous, with varying symptoms, progression rates, and underlying biological mechanisms across patients. This variability complicates the generalizability of findings from one study or subgroup of patients to other subgroups or the broader population. Therefore, while psychedelics show promise in treating a range of diseases and conditions, more large-scale, long-term human studies are crucial to fully evaluate their potential as a treatment for neurodegenerative disorders.

> *While psychedelics are generally considered safe in controlled settings, acute adverse effects—such as anxiety, paranoia, and confusion—can occur, especially at higher doses. These effects may be more problematic in AD patients due to their heightened vulnerability from cognitive decline.*

In summary, despite the encouraging preclinical data, there are significant limitations in the current research. Many studies have small sample sizes, short follow-up periods, and lack placebo controls, making it difficult to draw definitive conclusions. Moreover, the optimal dosing regimen and frequency for achieving therapeutic benefits in AD remain unknown. Ethical and safety concerns, particularly regarding the use of high-dose psychedelics in vulnerable populations like those with AD, must be considered. Legal barriers, such as the Schedule I status of psychedelic substances, only further complicate researcher's ability to conduct proper clinical trials.

PART 8

FUTURE RESEARCH

Given the promising preclinical and clinical data, there is a strong rationale for exploring the use of psychedelics as a treatment for neurodegenerative disorders, especially AD. Several mechanisms—neuroplasticity, reduced neuroinflammation, and improved serotonergic function—suggest that psychedelics could offer both symptomatic relief and potentially disease-modifying effects.

> *... there is a need for more longitudinal studies to assess the long-term effects of psychedelics on neurodegeneration and cognitive function.*

To build on these findings, ongoing and future clinical trials are essential. Future research should focus on several aspects. First, there is a need for more longitudinal studies to assess the long-term effects of psychedelics on neurodegeneration and cognitive function. Additionally, researchers should continue to explore optimal dosing in order to maximize neuroprotective effects while minimizing cognitive impairments. Researchers should further investigate whether psychedelics could be combined with other neuroprotective agents or therapies to enhance treatment efficacy. Most importantly, while initial results are encouraging, more rigorous, large-scale trials are needed to confirm these findings and

establish safety and efficacy in patients with neurodegenerative disorders. Such trials should focus specifically on psychedelic treatment for neurodegenerative disorders.

For example, one ongoing trial is currently investigating the safety and efficacy of psilocybin by testing moderate to high doses of psilocybin (15 mg/70 kg and 25 mg/70 kg) in patients with early-stage AD or mild cognitive impairment (MCI) who also suffer from depressive symptoms.[114] Initial findings, although not yet fully published, suggest that psilocybin could significantly reduce depressive symptoms, which are common in AD and are known to worsen cognitive decline. This study is among the first to directly target neuropsychiatric symptoms in AD with psychedelics, aiming to explore both mood improvements and potential cognitive benefits. It's likely the results of this study and other similar studies will help determine whether psychedelics can slow or even reverse the progression of AD, as well as improve the quality of life in AD patients.

Expanding the legalization or decriminalization of psychedelics in some states would allow for additional research to be conducted beyond the strictures of the Drug Enforcement Administration's (DEA) regulations.

Expanding the legalization or decriminalization of psychedelics in some states would allow for additional research to be conducted beyond the strictures of the Drug Enforcement Administration's (DEA) regulations. Additional research, even on a small-scale, is beneficial for examining the safety and efficacy of psychedelic treatments for neurodegenerative disorders. Although the FDA does not accept these state-level studies as sufficient evidence to support a New Drug Application (NDA), additional research could generate the kind of preliminary data and clinical insights that influence the FDA to grant a "breakthrough therapy" designation, accelerating the development and approval process for psychedelic treatments. In this way, state-led reforms could catalyze a broader shift in the regulatory landscape, ultimately facilitating the integration of innovative psychedelic therapies into mainstream medical practice.

[114] "Psilocybin for Depression in People with Mild Cognitive Impairment or Early Alzheimer's Disease," ClinicalTrials.gov. clinicaltrials.gov/study/NCT04123314 (1 Aug. 2024).

PART 9

CONCLUSION

While current pharmacological treatments for neurodegenerative disorders provide some symptomatic relief, they fall short of addressing the causal mechanisms of these diseases. The search for more effective, disease-modifying therapies remains a critical priority, and innovative approaches such as psychedelic-assisted treatments may offer a new and promising avenue for improving patient outcomes.

One particular concern is Alzheimer's Disease, as it presents a formidable challenge, both for individuals and society. As the population ages, the prevalence of AD will only increase, highlighting the urgent need for new and effective treatments. Psychedelics, particularly psilocybin and LSD, show promise as potential therapies for neurodegenerative disorders given their unique ability to promote neuroplasticity, reduce inflammation, and improve neuropsychiatric symptoms.

> *"As clinical research continues to explore these possibilities, the role of psychedelics in medicine may expand, offering new hope for treatments that integrate mental and physical health in a way that has long been overlooked."*

Psychedelics may also offer an innovative therapeutic approach that addresses the full spectrum of human health, from emotional and psychological well-being to physical resilience. As clinical research continues to explore these possibilities, the role of psychedelics in medicine may expand, offering new hope for treatments that integrate mental and physical health in a way that has long been overlooked.

However, current research is still in its early stages, and more rigorous, large-scale trials are necessary to fully understand their potential in treating AD and other neurodegenerative diseases. Ongoing research into the mechanisms of psychedelics and their potential applications in neurodegenerative diseases could pave the way for new treatments—ones that target the underlying causes of the disease, rather than just alleviating its symptoms.

Legislators should prioritize supporting innovative research and establishing policy frameworks that promote the responsible exploration of psychedelic therapies. Decriminalization or legalization of psychedelics in some states would allow for regulated psychedelic-assisted therapy (PAT) centers to exist in those states. These centers may generate early data that could significantly advance research. If state-level research supports psychedelics as safe and effective treatment options, psychedelics may gain breakthrough designations for certain neurodegenerative diseases. In short, expanding access to this research could lead to significant breakthroughs in the treatment of neurodegenerative diseases, ultimately improving the lives of millions of people.

ABOUT THE AUTHOR

Madison Carlino is a policy analyst at Reason Foundation, where she focuses on drug policy issues in the United States, including emerging areas like psychedelic medicine and marijuana legislation. Her work explores the evolving role of drug policy in shaping public health and individual freedoms. Carlino has written several policy briefs at Reason, including one on ibogaine treatment for opioid use disorder and another exploring psilocybin as a potential treatment for mental health conditions.

Before joining Reason, Carlino worked at the James Madison Institute (JMI) in Tallahassee, Florida, as a research intern and grant writer. At JMI, she focused on education policies that gave Florida parents more options in tailoring their children's education. Her research also examined how constitutional rights support democracy and freedom. While at JMI, she wrote grant proposals to secure funding for initiatives promoting educational choice, constitutional rights, such as free speech on college campuses, and public policy research.

During her time at Florida State University, Carlino worked as a policy analyst at the DeVoe L. Moore Center. She led research on topics like how Cuban enclaves influence wages in Miami and developed a business plan aimed at improving high school graduation rates through alternative education methods.

Carlino graduated summa cum laude from Florida State University with a degree in economics, double majoring in economics and media/communication studies, and minoring in business. She plans to continue her work in policy and research, with future goals of earning a Ph.D. in economics and public policy.