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Psychedelics for Alzheimer's Disease Palliative Care

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Introduction

Alzheimer's disease (AD) affects an estimated 6.2 million Americans aged 65 and over -- a number anticipated to double by 2050.[1] There is no cure for AD and the clinical promise of the current therapeutic pipeline, at present heavily focused on anti-amyloid and -tau antibody treatments, remains unclear. Absent a cure or effective disease modifying therapies, palliative approaches are essential and mainstay treatments for providing maximum quality of life benefits to patient and caregiver. Palliative care represents an integral approach to medical practice aiming to alleviate disease-related symptoms and distress for improved quality of life. Often initially misconstrued by patient-caregiver dyads as cessation of treatment, palliative care generally gains broad support once its patient-aligned purpose is better understood.[2] Psychedelic-based treatments have appreciated a resurgence of interest in the past decade, with a growing number of high-quality clinical trials marking their collective promise as a paradigm-shifting intervention in psychiatric and palliative care medicine. Of the multiple palliative care domains defined by the National Coalition for Hospice and Palliative Care[3], potential psychedelic-based treatments for patients with AD and their caregivers fall largely under *Psychological and Psychiatric, Social,* and *Spiritual* aspects of care. Herein, we review and discuss potential synergies between psychedelic research and these specific palliative care domains in AD, with specific focus on indolamines (e.g., psilocybin and ayahuasca) and semi-synthetic ergolines (e.g., Lysergic acid diethylamide (LSD)).

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Psychological and Psychiatric Care

Psychiatric care for neurobehavioral symptoms of AD

Neurobehavioral symptoms such as apathy, depression, anxiety, agitation, and cognitive-perceptual disturbance (e.g., delusions, hallucinations) are highly comorbid along the continuum of AD severity, including the prodromal period.[4] For example, depression and anxiety affect an estimated 40% to 80% of patients, respectively.[5,6] Behavioral symptoms in AD can also exacerbate cognitive deficits, presenting as decline in executive functioning[7], creativity[8], and openness to experiences.[9] These neurobehavioral symptoms confer significant distress and burden on patient-caregiver dyads as well, with caregivers' perceived level of burden and overall quality of life being correlated with symptom severity in patients.[10] Moreover, familial caregivers are rarely adequately trained to manage and cope with chronic agitation and psychosis.[11] Thus, effectively managing neurobehavioral symptoms is a central part of comprehensive AD treatment.

Neurobehavioral symptom management in AD is tailored to the patient and their circumstances and does not solely involve psychotropic medications. Rather, a rounded approach involving treatment of medical conditions and pain, settling into or adjustment of living environment, and treatment of pre-existing psychiatric conditions is prioritized. While there are currently no FDA approved medications for AD neurobehavioral symptoms, geriatric-appropriate doses of common psychotropic medications are routinely prescribed. Drug classes include SSRIs, atypical antidepressants (e.g., trazodone and mirtazapine), non-benzodiazepine anxiolytics for neurovegetative symptoms and anxiety, and mood stabilizers or atypical antipsychotics for aggressive behaviors. The benefits of such treatments can be clinically meaningful to both patients and caregivers[12]; however, side effects should not be overlooked, such as sedation, increase risk of falls, and a small but significant increase in risk of strokes and mortality with antipsychotics (leading to clear American Psychiatric Association guidelines[13] and an FDA black box warning).

Psychedelic effects on neurobehavioral symptoms

Many of the recent studies described below were conducted using collectively termed *psychedelic-assisted psychotherapy* (PAP), which emphasizes the drug as a tool to enhance the psychotherapy experience. Some of the earliest and most robust mood-enhancing outcomes have come from psilocybin clinical trials. An early open-label trial of psilocybin-assisted therapy (two doses one week apart) significantly reduced depression scores in a study of treatment-resistant depression (N=22), with sustained effects for six months.[14] Two more recent studies found similarly encouraging outcomes. In a study of intensive psilocybin PAP for major depressive disorder (MDD), which enrolled subjects up to age 75, Davis et al. (2021) observed impressive treatment response and remission for at least one month.[15] Carhart-Harris et al. (2021) also found that several outcomes generally favored psilocybin over the SSRI escitalopram in a 6-week trial of 59 adults (up to 80 years old) that used the same therapy setup in both groups, though these differences were not statistically significant.[16] The nuances of these studies are worth further exploration, particularly regarding methods of placebo or comparative drug control and specific PAP protocols.

Several small trials with ayahuasca have shown positive effects of this often-homebrewed N, N-dimethyltryptamine/Monoamine oxidase inhibitors (DMT/MAOI) combination treatment for depression and anxiety. Two related open-label trials of single dose ayahuasca on six subjects in an inpatient psychiatric unit and seventeen non-hospitalized subjects with active MDD saw significant reductions in depression within one day and lasting through the twenty-one day observation period.[17,18] Most recently, a randomized controlled trial of ayahuasca for treatment resistant depression found a significant difference in response to treatment compared to the placebo group.[19]

Our understanding of the neural mechanisms of psychedelics and their relationship to neurobehavioral treatment effects remains limited. The indoleamine and ergoline classes of psychedelics confer potent receptor-specific effects in the brain. While the mechanisms of action of these drugs are unique from traditional psychotropics used in current AD neurobehavioral therapies, there are also important overlapping properties which may provide face validity for their consideration as alternative or supplemental treatments (see Box 1). While a thorough review of the neurobiology of psychedelics is outside the scope of this review, major themes include changes in early sensory gating and processing; decreased activation of subcortical brain regions strongly linked to fear processing, such as the amygdala[20]; induction of plasticity, or the measurable restructuring of neuronal communication networks (e.g., through synaptogenesis) that underlie learning and memory[21,22]; and complex changes in the awake, resting state activity in the brain (i.e., the default mode network[23]).

Psychedelics for palliation of AD-related neurobehavioral symptoms

One might argue that the promising mood enhancing effects of psychedelics and PAP, as briefly reviewed above, provides no stronger a case for application of these novel compounds to AD than towards any affective disorder. In recognition of this fair critique, it is also important to acknowledge the subtle ageism impacting geriatric mental healthcare; that is, the systemic undertreatment of psychiatric symptoms in older adults. This is true of both community- and institutionally dwelling individuals.[24] One might therefore flip the question to ‘why not prioritize this population’ given the high prevalence and individual and societal costs of AD-related neuropsychiatric comorbidities.

Still, palliative care of AD-related neurobehavioral symptoms should extend beyond treatment of mood/neurovegetative symptoms. Regarding other neurobehavioral symptoms of AD, there is little recent literature supporting the use of psychedelics for treatment of psychosis. This may be in part due to their pro-hallucinatory effects, giving rise to their classic label as psychotomimetics. Studies from the 1950s explored the use of LSD in psychotic depression and schizophrenia, with some reports of null effect, and others of improved insight and ‘ventilation of emotion’.[25] An important element of coping with delusional or psychotic symptoms is degree of insight into the nature of one’s thought disorder. Insight scales have been included in several clinical studies investigating the effects of psychedelics on various psychiatric disorders, from depression to addiction.[26,27] Whether the type of insight gained using psychedelic treatment, often described as ‘emotional breakthroughs’ or ‘peak experiences’, is at all related to the clinical insight of patients

suffering from primary psychotic disorders[28] is unclear. However, should psychedelic treatments provide an access point for reality testing in delusional or disordered thinking in AD, this may be an avenue to explore for the palliative care of these challenging neurobehavioral features.

Safety of psychedelics in individuals with AD

Starting any new pharmacological intervention in a medically complex and / or frail individual confers several additional challenges, the solutions for which include the well-known mantra 'start low, and go slow,' as well as thorough safety studies in an appropriately age-matched and comorbid population. In general, the indolamine and ergoline classes of psychedelics have a relatively mild physiological safety profile.[29] Older adults may experience poorer tolerance of the sympathetic changes induced by many psychedelics (e.g. short-term tachycardia, hypertension, and hyperthermia). For this reason, use of psychedelics in patients with chronic cardio- and neurovascular diseases may be contraindicated. The risk of falls and fractures, already inherent in this population, could also increase with psychedelic treatment given hyperreflexia, weakness, and possible disorientation. Slower drug metabolism in older individuals may extend the drugs' half-lives, though it is worth noting that there have been no documented human deaths from LSD overdose, and even in extreme overdoses, patients survived without residual consequences.[30] For comparison of safety risk, it is important to point out that electroconvulsive therapy remains the gold standard treatment for severe depression in the elderly[31], despite many similar risks (e.g., sympathetic activation and concerns with use in vascular disease). Safety will continue to be a priority as psychedelic-based treatments are considered for new patient populations, and less restrictive inclusion criteria may benefit the field. It is encouraging that two recent trials of psilocybin[15,16] enrolled patients up to 75 and 80 years old, respectively.

From a mental health risk perspective, the safe and therapeutic setting of drug administration advanced by recent clinical trials promises improved psychiatric well-being as compared to the uncontrolled environment of recreational drug use.[32] A recent meta-analysis of twenty-four clinical trials of classic psychedelics found no long term negative psychological effects.[33] To the AD patient population, psychological risks of psychedelic use are poorly understood. One might imagine, for instance, given the non-linear trajectory of neurobehavioral and cognitive symptoms in AD, that psychedelic-induced changes in primary sensory processing and association could lead to unpredictable episodes of confusion, disorientation, fear, or aggression, which in turn may not be amenable to therapeutic rationalization depending on disease severity. Another important consideration is the feasibility or value of PAP in this diverse population, wherein depending on degree of cognitive impairment, the patient may or may not be able to fully integrate preparatory or integrative therapy into the psychedelic experience. This may argue for tailored PAP modalities along the continuum of AD staging, such as modifications to PAP that allow for caregiver integration into the process. Should patients be unable to benefit from the preparatory, supportive, and integrative elements, it is possible that the psychological risks of the psychedelic treatment would be different than in a cognitively intact person. Clarification on PAP-based approaches, and thoughtful psychological safety and well-being assessments

will be essential in availing this patient population to the potential benefits of psychedelic-based treatments for neurobehavioral symptoms of AD.

Social Care

Social aspects of care in AD

Cognitive and neurobehavioral symptoms of AD can hinder patients' ability to communicate and interact socially[34], leading to disengagement and isolation. Conversely, decreased social engagement can also increase the risk for developing AD, as individuals with few or no social ties have increased risk of cognitive decline even after adjusting for baseline cognitive status and sociodemographics.[35] Changes in environment, from the common geriatric challenge of diminished social network, to loss of partner, physical relocation, or perhaps disease-specific changes such as institutionalization, all contribute to isolation and loneliness. Caregivers are no more immune to social isolation than patients, particularly if they become more tethered to the ongoing needs of the beneficiary.

Structuring and maintaining social networks emphasizes the development of interpersonal relationships between the patient-caregiver dyad, family, communities, and between the dyad and their medical care team.[36] Many strategies have been employed for strengthening social aspects of care. These include physical, art, and music therapy[37], as well as intentional interpersonal communications through one-on-one, group, or family-based practices (e.g., reminiscence-based therapy[38]). As with all palliative treatments, strategies should be tailored to the individual. For instance, art therapy can provide a new avenue not only for self-expression but also for communication between patients and peers, caregivers, and family that may circumvent communication deficits inherent with debilitating cognitive function.[39] For individuals at later stages of the disease, more passive forms of social interaction-based therapy, such as collective listening to music, serve not only to reduce neurobehavioral symptoms such as anxiety and depression[40,41], but provide a purposeful passive social opportunity.

Psychedelics and social care

Psychedelics and PAP are imbued with potent social connectivity-related properties. Watts et al. reported on patients' perceptions of themselves and their relationship to others before and after psilocybin-based PAP[42]. Prior to treatment, subjects described significant intrapersonal disconnection, using phrases such as feeling 'trapped in their minds,' and living in a 'mental prison,' which in turn contributed to profound social detachment, as subjects also reported feeling isolated, having little in common with peers, and sometimes feeling unable to leave their bed. After treatment, however, many responders described a sudden and dramatic reconnection to oneself, with greater openness to new values and perspectives, interest in new activities, and increased desire for connection to others. Several self-report studies of the long-term effects of psychedelics and social interaction have also noted positive effects on social behavior up to and beyond one year after initial drug treatment (see [43] for perspective).

Some of the same means for nurturing intra- and interpersonal connectedness in AD have been studied for use alongside of psychedelics. The use of psychedelics recreationally, spiritually, and therapeutically has long been closely linked with the creative arts, including music and visual art, wherein the subjective experience is often dramatically affected and creativity enhanced.[44] Music accompaniment has been written into many clinical psychedelic protocols.[45] Under acute psychedelic influence, sensory processing in the brain is enhanced, whereas sensory association and integrative processing of sensory input is diminished, perhaps allowing for reinterpretation of experience.[43]

PAP is an intimate social instrument that provides a safe and therapeutic interaction in the modified setting of psychedelic drug experience. One of the oft-cited goals of PAP is increased connectedness with one's inner sense of self, which nurtures self-compassion and offers an internal locus of healing. PAP involves extensive interpersonal exchange as well, with each step in PAP, from preparation to medication and integration[46], emphasizing a close interpersonal connection between therapist(s) and patient. Preparation, for instance, involves the therapist building a connection with the patient by understanding their life history and intentions for PAP, and integration involves interpretation of the psychedelic experience by patient and therapist, with the intention of enacting long-term change.[47] Thus, connectedness to oneself and to the therapist through the multistep process of PAP offers a direct form of social connectedness.

Psychedelics and social care for AD

The bearing of psychedelics on social care in AD blend the vast unmet social needs of this population with the promise of psychedelics for prompting robust changes in desire for connectedness, empathy, creativity, and self-identity. As one example, psychedelic use in the setting of music can lead the individual to connect the song to their own memories.[48] Should similar effects be observed in individuals with AD, in whom autobiographical memory declines along with self-identity, the increased capacity to experience autobiographical scenes while listening to music may offer a novel means of access and reconnection to one's social identity.[49]

There are also opportunities to overlay the psychedelic / PAP experience with the existing web of social connectedness programs for AD, though practically speaking this would require significant further development and resources, particularly dependent on the prescribing mechanism. Beyond state and federal restrictions currently in place for most psychedelic compounds, FDA approval is unlikely to mean take-home drugs from the pharmacy, but rather pharmaceutical companies seeking approval for a protocol of drug-assisted therapy – for instance, this may take place on the heels of the successful Phase 3 clinical trial of MDMA for treatment of post-traumatic stress disorder.[50,51] While such factors apply to the broader scope of purposing psychedelic treatments for AD and other indications, it may have particular significance in the context of social connectedness goals: PAP protocols may require modification to specifically target aspects of social connectedness, such as inclusion of others outside of the patient-therapist(s) model, like caregivers and family, other patients (should group-based treatment be deemed feasible), or with particular focus, such as the creative arts versus introspective or unstructured therapy.

In prioritizing the needs of patients with AD, the caregiver is commonly overlooked. Caregivers' sense of isolation and loneliness, paired with chronic stress and, for many, grieving, does not meet the diagnostic criteria for a psychiatric disorder *per se*, unless such elements are not managed or alleviated, leading to possible manifestation of a depressive or anxiety disorder. One regulatory hurdle is the challenge of prescribing a tightly controlled substance to individuals without diagnostic indication; social isolation and loneliness are not found in the current psychiatric Diagnostic and Statistics Manual (DSM-5). Notwithstanding this and other regulatory challenges, one can envision many meaningful opportunities to employ psychedelics to foster greater patient / caretaker self-identity, spurring creativity, fostering empathy, and enhancing the desire for and quality of interpersonal connectedness.

Spiritual, Religious, and Existential Aspects of Care

Spiritual care and well-being in AD

The degenerative nature of AD can leave affected individuals with a profound sense of existential angst due to the looming and inevitable degradation of cognition and functional independence. These existential concerns can have a devastating effect on emotional and psychological well-being, especially in earlier disease stages when a patient's insight is less likely to be compromised. Therefore, an important facet of AD palliative care across the disease severity spectrum should be aimed at ameliorating the overwhelming and disorienting impact of receiving an Alzheimer's diagnosis. In this vein, spiritual or religious coping may be an effective approach for older adults suffering from progressive or terminal conditions, including dementia.[52] This is relevant in a palliative context, as spiritual coping could help reframe the meaning of such a diagnosis by, for example, shifting one's perspective toward acceptance and reflection, and away from perceived loss of control.[53] There is limited empirical data on the use of spiritual care in a palliative context for dementia, and most research examining spirituality as a coping resource for AD is derived from personal anecdotes from patients.[52] However, there is a small body of research suggesting spiritual coping may improve quality of life in patients with AD by facilitating meaning-making and sense of personhood.[54] Effective coping through spirituality may also have indirect palliative benefits through associated stress reduction and improved cognitive function.[53] Thus, utilizing spiritual care to improve the quality of life in this population could be highly effective for those who consider spirituality an important part of their value and belief system.

Psychedelics and spiritual care

Psychedelics have often been considered alongside constructs of spirituality due to their historical uses in indigenous spiritual and religious ritual.[55] However, there is also growing contemporary interest in exploring this intersection given that psychedelic experiences are often described as profoundly moving, transcendent, and transformative. While such experiences vary depending on the specific compound, situational context, and characteristics of the individual[56,57], they are often associated with an increased sense of well-being[58]. This highlights the potential value of enhancing spiritual care with psychedelics across a range of clinical contexts – an approach sometimes called "psychedelic chaplaincy" when spiritual care providers (e.g., priest, rabbi, minister, etc.)

give support or counsel to people preparing for, undergoing, or integrating psychedelic experiences. Moreover, the positive psychotherapeutic outcomes observed across a broad range of PAP studies to date have commonly involved a spiritual dimension. For example, a recent case series examining the use of psilocybin to treat alcohol dependence found that participants reported profound spiritual experiences following treatment, including communion with "a deceased loved one, with a holy figure, and with the Divine".[59] In addition, a clinical trial on smoking cessation found that psilocybin-facilitated treatment was associated with increased rates of abstinence, and that 86% of participants rated their psilocybin sessions as being "among the five most spiritually significant experiences" of their lives.[60] In another study of undergraduate students, greater lifetime psychedelic usage was associated with higher levels of spirituality, which in turn predicted better emotional regulation and decreased symptoms of depression, anxiety, and disordered eating.[61]

Psychedelics and spiritual care for AD

The examples outlined above illustrate the promising role for psychedelics in the spiritual care of individuals with AD, particularly those struggling with behavioral and psychological symptoms. While very little is known about how psychedelics might augment or enhance spiritual care aimed specifically at alleviating existential distress in AD, there is a related literature focused on other terminally ill medical populations (e.g., cancer). This research has shown that the spiritual or transcendental effects exerted by psychedelics are often correlated with positive therapeutic outcomes related to existential distress, such as coping with overwhelming changes, death anxiety, and lack of meaning.[62] These psychedelic effects hold significant promise in a palliative context given the emphasis on existential and spiritual themes.[62] Whether this extends to patients with AD, however, will largely hinge on their level of insight, as the presence of anosognosia – a neurologically mediated impairment in disease self-awareness, and a relatively common feature of AD – would be a clear obstacle in therapeutic efforts aimed at fostering acceptance and reframing the personal and spiritual meaning of an AD diagnosis. That said, other established forms of dementia therapy could be augmented toward similar ends. For example, reminiscence therapy (RT), sometimes referred to as life review therapy, involves discussion and reflection around past activities, events, and life experiences, often with the aid of sensory prompts such as photographs or music recordings from a person's past.[63] A variation of RT known as spiritual reminiscence therapy (SRT) has been developed as an approach to enhancing meaning in life for those with dementia. Some promising recent findings demonstrated that hope, life satisfaction, and spiritual well-being could be significantly improved with a 6-week course of SRT in those with mild *or* moderate dementia.[64] Given the immersive sensory and spiritual/mystical experiences associated with psychedelics, exploring their potential to enhance the therapeutic effects of SRT is an intriguing clinical and research question, especially considering the parallel emphasis on sensory and spiritual elements in SRT.

Conclusions

As clinical trials of psychedelic-based treatments and PAP expand to new indications over the next several years, their potential value to AD palliative care deserves consideration.

Patients suffering from AD can, like other older adults without dementia, suffer from many of the same psychological disorders as younger individuals, though the neurovegetative symptoms may present differently and tend to be overlooked. Some neurobehavioral manifestations of AD (e.g., mood-related symptoms) could clearly benefit from psychedelic-based treatment, whereas others (e.g., psychotic symptoms and agitation) need further study. The risks of psychedelic use in AD include those generalizable to older adults, as well as the potential depreciation of PAP with worsening cognitive decline and anosognosia in later disease stages. Social connectedness contributes greatly to quality of life, and psychedelic compounds enhance not only self-identity, but empathy, relatedness to others, creativity, and sense of purpose, all of which may benefit patient and caregiver alike. Finally, though AD is not considered an acutely life-threatening illness, the disease course is nevertheless progressive and terminal, thus warranting consideration of the application of psychedelics to AD palliative care, particularly early in disease course, as these compounds have been successful in reducing anxiety, supporting reminiscence, and reducing existential distress in other related populations. Given the recent resurgence in interest in psychedelics for psychiatric disorders and palliative care, we are confident that the continued growth of rigorously designed clinical trials will overcome some of the complex regulatory and practical challenges associated with these promising compounds.

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Box 1:

The neurochemistry of AD neurobehavioral treatments compared to psychedelics

Traditional psychotropics

The monoamine 5-HT, or serotonin, acts on receptors in the brain's limbic system to regulate a wide-range of neurobehavioral functions, from mood and aggression to circadian rhythmicity and appetitive behaviors. Psychotropic compounds, such as selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, and monoamine oxidase inhibitors, increase synaptic 5-HT levels by blocking reuptake of serotonin into the presynaptic cell. Clinical improvement of mood disorders by SSRIs takes weeks to months of continuous administration to be appreciated, thought to be related to chronically elevated synaptic 5-HT levels leading to decreased post-synaptic serotonin receptors, increases in other neurotransmitters such as norepinephrine, and increased second-messenger activity (e.g. cAMP) and target gene expression (e.g. brain derived neurotrophic factor – BDNF).[65]

A recent meta-analysis found efficacy of SSRIs in improving a range of neurobehavioral symptoms of dementia (for instance, as seen by improved scores on the multi-domain neuropsychiatric inventory), as well as agitation, depression, and perceived care burden[12], noting greater beneficial effects in patients with AD than non-AD dementia. Other serotonin-receptor modulating compounds commonly prescribed for neurobehavioral symptom management in AD include trazodone (5HT2A and 5HT2B receptor antagonist, partial agonist of 5HT1A, along with non-5HT receptor targets), which may improve agitation symptoms[12], buspirone (5HT1A agonist), and mirtazapine (5HT2A and 5HT2C antagonist with non-5HT receptor targets). Commonly prescribed antipsychotics used for neurobehavioral symptoms of AD include quetiapine (5HT1A partial agonist and 5HT2A, -2B, and -2C antagonist among other 5HT and non-5HT receptor targets) and olanzapine (5HT2A inverse agonist among other 5HT and non-5HT receptor targets).

Neurochemical properties of the indolamine and ergoline classes of psychedelics

Indoleamine and ergoline psychedelics have an aromatic indole core akin to serotonin, and function as partial agonists to multiple serotonin 5HT receptors. They have particularly high affinity for the 5HT2A receptor, understood as the dominant drug-receptor combination responsible for a multitude of psychedelic-based behavioral and psychological changes in humans[66–68], with lower affinities for other 5HT receptors dependent on the specific compound. Use of the 5HT-2A receptor antagonist ketanserin blocks and reverses all subjective drug effects.[66] Aside from serotonergic activity of these drugs, LSD also targets D1 and D2 dopamine receptors and adrenergic receptors[69], and some of the mood states of euphoria and depersonalization seen with these drug classes may be due to direct or indirect striatal dopamine release.[70]

The serotonergic commonalities between SSRI and non-SSRI psychotropics and the indolamine and ergoline psychedelics is cursory and limited by receptor targeting and

likely neuroanatomical specificity. Nonetheless, SSRIs and these psychedelics bear common neurobehaviorally-supportive downstream pathways. The psychedelic 5HT2A agonism, like continuous use of SSRIs, leads to increased BDNF levels via some of the same transcriptional activation pathways. Psychedelics also increase BDNF levels in the prefrontal cortex. Via interaction with the TrkB receptor, this growth factor can induce changes in neuritogenesis and spinogenesis[71], accounting for BDNF's effects on neuroplasticity – i.e., the adaptive changes of neurons thought to underlie many of the beneficial neuropsychiatric effects of SSRIs.[72]

Synopsis

Psychedelic compounds (psilocybin, LSD, ayahuasca) paired with psychotherapy offer great potential for addressing multiple aspects of unmet palliative care needs for aging patients with Alzheimer's disease and their caregivers. In this review, we integrate recent findings from psychedelic and psychedelic-assisted therapy clinical research with key domains of Alzheimer's disease palliative care, from neurobehavioral symptom management to social and spiritual aspects of care in patients and their caregivers. In doing so, we provide a framework for approaching use of these exciting compounds in the Alzheimer's disease population, while recognizing some of the practical challenges faced.

Key Points

- Psychedelics and psychedelic-assisted psychotherapy have seen remarkable successes across multiple domains relevant to palliative care.
- Alzheimer's disease presents a major challenge and opportunity for incorporating the unmet palliative care needs of patients and their caregivers.
- Developing clinical trials of psychedelics and psychedelic-assisted therapies for palliative care treatment of Alzheimer's disease could foster meaningful benefits for this vulnerable population.