ARTICLE IN PRESS

International Psychogeriatrics xxx (xxxx) xxx

Contents lists available at ScienceDirect

International Psychogeriatrics

journal homepage: www.sciencedirect.com/journal/inpsyc

Review article

# From depression symptom management to dementia prevention: Considering next decade research, treatment, and advocacy priorities to reduce the impact of depression in neurocognitive disorders

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A B S T R A C T

Depression and mood dysregulation are among the most prevalent and clinically consequential neuropsychiatric symptoms (NCD-NPS) across the spectrum of neurocognitive disorders (NCD). These symptoms impair quality of life, increase carer burden, and are associated with accelerated functional and cognitive decline. At the same time, major depressive disorder across the lifespan represents a potentially modifiable risk factor for later-life dementia, while late-onset depressive symptoms may signal prodromal neurodegeneration. This dual role positions depression at a critical intersection between symptom management and dementia prevention. This International Psychogeriatric Association (IPA) white paper was developed through expert consensus meetings held in Buenos Aires (2024) and Kanazawa (2025) to identify key knowledge gaps and define global priorities in nomenclature, biomarkers, treatment, and prevention. Current diagnostic frameworks inadequately capture dementia-specific depressive phenotypes and the marked heterogeneity of depression in NCD, including variation by disease stage, dementia subtype, symptom profile, apathy overlap, sleep and circadian disruption, exposomic risk, caregiver context, and treatment response. Although advances in neuroimaging, inflammatory markers, molecular biomarkers, digital phenotyping, and life-course risk assessment offer promise, none are yet validated for routine diagnostic stratification or treatment selection. Pharmacologic therapies demonstrate modest and inconsistent efficacy, and no agent is specifically approved for depression comorbid with dementia. Psychosocial, behavioral, caregiver-inclusive, sleep-focused, and multimodal interventions remain essential but require greater scalability and integration into care systems. The IPA Depression Workgroup proposes a next-decade roadmap emphasizing NCD-specific diagnostic criteria, biomarker-informed and exposome-aware subtyping, development of targeted and scalable interventions, routine attention to sleep health and caregiver context, and integration of depression prevention into brain health and NCD care frameworks to advance precision psychiatry and dementia risk reduction.

## 1. Introduction

Depression and mood dysregulation are among the most common and distressing neuropsychiatric symptoms (NPS) across the spectrum of neurocognitive disorders (NCD). These symptoms substantially impair quality of life, increase caregiver burden, and are associated with accelerated disease progression. Despite their high prevalence and clinical relevance, advances in both clinical care and translational research remain limited by several persistent knowledge gaps. These include: [1] the lack of a shared and precise diagnostic nomenclature; [2] the absence of validated biomarkers to support accurate diagnosis, prognostic stratification, and personalized treatment planning; and [3]

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https://doi.org/10.1016/j.inpsyc.2026.100226
Received 27 February 2026; Received in revised form 27 May 2026; Accepted 29 May 2026



Please cite this article as: J. Karp, M. Butters, L. Crivelli et al., From depression symptom management to dementia prevention: Considering next decade research, treatment, and advocacy priorities to reduce the impact of depression in neurocognitive disorders, International Psychogeriatrics, https://doi.org/10.1016/j.inpsyc.2026.100226

limited availability and access to safe and effective interventions, spanning pharmacological, psychosocial, and neuromodulation approaches. Importantly, a fourth and critical knowledge gap relates to the role of depression across the lifespan in dementia risk and prevention—particularly when occurring in midlife—as a modifiable risk factor for later-life dementia [1]. In parallel, depressive symptoms may also represent an early clinical manifestation of neurodegenerative disease, emerging during preclinical stages, subjective cognitive decline (SCD), or mild cognitive impairment (MCI). Improved recognition of depression as both a risk factor and a potential prodromal symptom of dementia may therefore enhance early detection strategies and inform preventive interventions. Advancing the science at this intersection holds promise for delaying dementia onset, reducing population-level prevalence, and promoting brain health across the lifespan.

## 2. Methods

A meeting of key opinion leaders in science and clinical practice was held in association with the International Psychogeriatric Association (IPA) Congress in Buenos Aires, Argentina, on September 28th and 29th, 2024, and then again in Kanazawa, Japan, on September 28 and 29, 2025, to address these knowledge gaps in the field of Depression in NCD. This initiative was led by Dr. Mary Sano, Dr. Jeff Cummings, and Dr. Jacobo Mintzer, with Dr. Jordan F. Karp and Dr. Maria Lapid selected to co-lead the Depression Workgroup. The Depression Workgroup included experts in neurobiology, biomarkers, psychosocial and pharmacological interventions, clinical characterization, and prevention, as well as early career investigators. An initial virtual meeting was held prior to the in-person event to gather input from group members and external collaborators. On the first day of the 2024 in-person meeting, recent advances in the understanding and treatment of depression in the context of NPS were reviewed. The second day focused on developing key recommendations for future research and policies. Over the next year, this white paper was drafted and finalized at the 2025 meeting.

This white paper summarizes the main scientific and clinical insights agreed upon by the contributing experts, with the goals of: (a) providing a concise overview of the current state of depression and mood dysregulation in NCD in four major domains—nomenclature, biomarkers, treatments, and prevention; and (b) identifying a set of global priorities to guide research, clinical care, and policy over the next decade.

## 3. Results

### 3.1. Incidence, prevalence, and clinical course

#### 3.1.1. Rates

Depression is a common yet often underrecognized comorbidity in NCDs, including mild cognitive impairment (MCI) and Alzheimer's Disease and Related Dementias (ADRD). Across studies, the prevalence of depression in MCI ranges from ~24–75%, while in ADRD, it ranges from ~4–39%, depending on the diagnostic criteria, population, and assessment tools [2,3]. Facility-based studies, in particular, indicate high rates of subthreshold depressive symptoms in NCDs where individuals may not describe low mood or sadness but more often anxiety or irritability complicating both recognition and treatment [4].

#### 3.1.2. Depression as a unique and potentially preventable risk factor for dementia

Depression stands apart from other NPS [2,3,5–7] because major depressive disorder is a clearly defined, highly prevalent, clinical diagnosis that occurs across the lifespan. MDD represents a risk factor for development of ADRD even when occurring in midlife and can precede cognitive decline by years. Late-onset depression symptoms may also represent a prodrome for NCDs. Therefore, depression/depressive symptoms may be a modifiable risk factor, a co-occurring disorder, a prodrome, and/or in some cases a direct consequence of ADRD. Late-life depression is associated with increased risk of ADRD [8], likely through shared pathophysiologic mechanisms including neuroinflammation, hypothalamic-pituitary-adrenal (HPA) axis dysregulation, cerebrovascular changes, and early Alzheimer's pathology. Other neuropsychiatric conditions such as bipolar disorder, psychotic spectrum illnesses such as schizophrenia, and anxiety also increase the risk of dementia. Thus, prioritizing successful treatment of neuropsychiatric illness (and addiction) across the lifespan may promote brain health and reduce incidence or delay onset of ADRD.

This dual role demands a two-pronged approach:

(1) treatment strategies that bring depression to full remission to maximize quality of life and function and possibly reduce or delay incidence of NCDs.
(2) preventive strategies targeting populations enriched for incident or recurrent depression to delay or prevent incident ADRD.

Across both approaches, early detection of depression, integration of mental health care into primary and geriatric care, and targeted interventions for subsyndromal or prodromal depressive states represent critical leverage points to reduce the long-term burden of dementia. Addressing these challenges requires advances across several interrelated domains, including clearer diagnostic nomenclature, identification of reliable biomarkers, development and optimization of treatment strategies, and implementation of effective prevention approaches. The following sections review current evidence and key knowledge gaps across these four domains.

### 3.2. Nomenclature, diagnostic assessment, and differential diagnosis

#### 3.2.1. Nomenclature: defining depression in dementia – a critical unmet need

Current diagnostic frameworks, such as the DSM−5 [9] and ICD−11 [10], inadequately address depression within NCDs, thereby perpetuating inconsistencies in both research and clinical practice. These frameworks, originally designed for MDD in cognitively intact populations, fail to account for dementia-specific manifestations. These include symptoms such as emotional lability or irritability, as well as neurovegetative changes and anhedonia, which often manifest even in the absence of a pervasive depressive mood —a clinical presentation frequently described as "depression without sadness" —symptoms observed in 40% of Alzheimer's patients [11]. A particularly challenging source of diagnostic ambiguity is the substantial phenomenologic overlap between depression and apathy in dementia, where shared features such as diminished motivation, reduced initiative, and social withdrawal may obscure affective symptoms. The DSM−5's category of "depression due to another medical condition" lacks criteria specific to dementia, resulting in the underdiagnosis of subsyndromal cases [12] and the misclassification of overlapping symptoms, such as apathy and anxiety [13]. The overlap between depression and apathy, and its implications, are discussed in greater detail in the companion IPA Apathy in NCD consensus paper.

Innovative approaches have sought to bridge these gaps. For instance, the NIMH-dAD criteria [14] refine traditional frameworks by expanding core symptoms to include social withdrawal and adjusting the threshold for anhedonia to better suit the dementia context. Furthermore, conceptual models like the "Affective Dysregulation in NCDs" model [15], emphasize a lifespan perspective on neuropsychiatric symptoms, a shift that informed the development of the Mild Behavioral Impairment Checklist (MBI-C). However, these newer operationalizations require rigorous validation against neurobiological markers—such as amygdala atrophy or serotonin receptor dysfunction— across various dementia subtypes, such as frontotemporal dementia (FTD) and Lewy body dementia (LBD). This underscores a

critical priority for the coming decade: the harmonization of diagnostic criteria with biomarker research to facilitate the identification of biologically grounded subtypes.

Inconsistent diagnostic definitions result in prevalence estimates ranging from 10% to 50%, depending on the criteria used, which hinders biomarker discovery and complicates intervention trials. Misclassification leads to both over- and under-treatment; for instance, apathy misdiagnosed as depression may result in ineffective SSRI prescriptions, while subsyndromal cases remain untreated despite potential benefits from targeted non-pharmacological interventions [16].

Next-Decade Imperatives:

1. Adopt NCD-specific diagnostic criteria, such as NIMH-dAD, in both research and clinical trials.
2. Integrate multimodal biomarkers, such as emerging plasma-based markers of neural health and imaging, to define biologically informed subtypes.
3. Develop validated dementia staging models to align interventions with affective symptom progression within the broader context of NCD stages.
4. Systematically include caregiver-reported symptoms, integrated with patient observation, as utilized in tools like the Cornell Scale for Depression in Dementia (CSDD), or through emerging scales that reflect newer diagnostic criteria.

Until revised frameworks are fully validated, clinicians may consider employing a combination of DSM−5-TR criteria, dimensional tools like the CSDD (which incorporates both patient and caregiver input), and caregiver reports to assess severity across affective, behavioral, and cognitive domains. Increasingly accurate nomenclature will facilitate more accurate epidemiologic estimates, targeted interventions, and translational research, which are essential components of the IPA's 10-year roadmap.

### *3.3. Etiology and contributing risk and protective factors: from biological to social determinants*

The etiology of depression in NCDs is multifactorial, arising from a complex interplay between neurodegenerative processes, systemic biological changes, and psychosocial determinants. Understanding these underlying mechanisms is crucial for moving beyond descriptive clinical observations toward a mechanistic framework of NCD-NPS. The following section explores emerging biomarkers as windows into these pathophysiological pathways, highlighting how structural, functional, and molecular alterations—ranging from proteinopathies to neuroinflammation—drive the onset and progression of affective symptoms in the aging brain.

Research into biomarkers for depression within NCDs possesses significant potential to enhance diagnostic precision, prognostic accuracy, and the development of personalized treatment strategies. In addition to informing pathophysiological mechanisms, emerging biomarkers may also help identify individuals at highest risk for progression within the NCD continuum, including those presenting with depressive symptoms, thereby supporting risk stratification and targeted prevention strategies (e.g., plasma p-tau217). Despite this potential, no biomarkers currently available can reliably differentiate depression in NCD from primary depressive disorders or other NCD-NPS, nor can they consistently inform therapeutic decisions or predict treatment responses. This gap underscores both the complexity of mood dysregulation in neurodegenerative diseases and the limitations inherent in existing diagnostic paradigms. A recent study showed that plasma proteins associated with inflammation and amyloid-β metabolism are causally linked to a higher ADRD risk in individuals with MDD [17]. While this observation is about risk for NCD and not depression diagnostic precision, it is an example of emerging science that will guide more precise management of NCD.

Neuroimaging studies have identified convergent structural and functional abnormalities in late-life depression (LLD) and NCDs, underscoring shared neural substrates. Structural MRI findings, such as hippocampal atrophy, white matter hyperintensities, and disruptions in frontal-subcortical circuits, are well-documented in older adults with depression [18–21]. Functional imaging also highlights disruptions in networks that regulate mood, especially concerning the connection between the anterior cingulate cortex (ACC) and the amygdala. While alterations in the connection between the anterior cingulate cortex (ACC) and the amygdala are seen across the lifespan in MDD, in LLD these disruptions often occur alongside a distinct pattern of significant changes in the functional coupling between the subgenual ACC and the amygdala resembling the early neurodegenerative alterations seen in AD [22–24]. This overlap complicates clinical differentiation, as similar imaging phenotypes may reflect either a primary mood disorder or prodromal neurodegeneration. Furthermore, molecular imaging has revealed that approximately half of patients clinically diagnosed with LLD exhibit significant tau pathology, suggesting that what appears to be a primary affective disorder may often represent an early manifestation of an underlying proteinopathy [25].

Parallel advances in fluid biomarker research highlight intersecting pathophysiological pathways. Pro-inflammatory cytokines, including IL−6 and TNF-α, are elevated in both depression and NCDs, suggesting a common or overlapping inflammatory mechanism [26,27].

Notably, emerging evidence implicates cellular senescence and the senescence-associated secretory phenotype (SASP) in this process, linking systemic aging to neuroinflammation and depressive symptoms in NCD [28]. Monoaminergic dysfunction, evidenced by reduced CSF levels of the serotonin metabolite 5-HIAA and diminished serotonin transporter binding on PET imaging, further differentiates depression in NCDs from other neuropsychiatric symptoms [29–31]. Alzheimer's-associated biomarkers—such as low CSF β-amyloid and elevated tau—are more prevalent in depressed older adults who later develop dementia, reinforcing depression's role as a prodromal state [32,33].

Despite promising advances, clinical translation faces significant hurdles. Current studies often suffer from small sample sizes, reliance on single biomarker measurements, and inconsistent diagnostic criteria for depression in NCDs. These limitations obscure clear biomarker-symptom relationships. Future research must adopt multimodal strategies—combining neuroimaging, fluid biomarkers (e.g., SASP profiles), relevant genotyping, and digital phenotyping tools such as wearables for continuous physiological monitoring or Ecological Momentary Assessment (EMA) to capture real-time behavioral and affective fluctuations. These tools are particularly valuable for identifying disruptions in behavioral patterns, such as sleep-wake cycles and circadian rhythms, which are closely linked to both depression and dementia progression [34]. This integrated approach aims to define biologically distinct subtypes (e.g., "inflammatory-depression" or "neurodegenerative-depression"). Large-scale longitudinal studies with harmonized protocols, such as those led by Alzheimer's Association International Society to Advance Alzheimer's Research and Treatment (ISTAART), are essential to validate these approaches. This will enable earlier detection of high-risk patients and personalized treatments, aligning with IPA's precision psychiatry roadmap.

### *3.4. Exposomic determinants of depression and dementia risk*

Exposomics refers to the totality of non-genetic environmental exposures—biological, psychological, social, and behavioral—across the life course that influence health trajectories and interact with genetic vulnerability [35]. A growing literature indicates that exposomic influences are central to the lifelong interplay of sleep, mood, and cognition, with cumulative effects that become particularly consequential in late life. Adverse childhood experiences (ACEs), chronic stress, social isolation, sleep disruption, cardiometabolic burden, and substance exposures shape stress responsivity, circadian regulation, and cognitive

aging, increasing vulnerability to late-life depression and dementia [1, 36, 37].

Exposomic effects intersect closely with genetic and epigenetic mechanisms that together form the risk architecture linking depression and dementia. Polygenic risk for depression and Alzheimer's disease modifies sensitivity to environmental stressors, while epigenetic processes—such as DNA methylation and chromatin remodeling—provide a biological interface through which exposures such as early adversity, sleep loss, inflammation, and substance use exert long-lasting effects on brain structure and function [38, 39]. These gene–environment interactions help explain the marked heterogeneity of late-life depression and dementia in clinical presentation, symptom burden, and treatment response.

Substance exposures are an increasingly salient component of the late-life exposome. Alcohol use—even at moderate levels—has been associated with sleep fragmentation, depressive symptoms, hippocampal atrophy, and accelerated cognitive decline, challenging prior assumptions about safety thresholds in older adults [40]. Emerging evidence also links cannabis exposure, particularly chronic or late-onset use, to impairments in mood regulation, executive functioning, and sleep architecture, raising concerns about downstream effects on cognitive aging [41, 42]. These exposures may amplify vulnerability in individuals with depression or prodromal cognitive impairment.

From a clinical and public-health perspective, attending to the exposome reframes late-life depression and dementia care toward prevention, resilience, and brain health promotion. As emphasized by Jeste and colleagues, successful aging requires integrating social, behavioral, and environmental determinants alongside disease-based models [43]. Incorporating exposomic assessment—encompassing sleep health, life stress, substance use, and social context—offers a scalable strategy to prevent depression, support cognition, and potentially delay neurodegenerative processes in later life.

### 3.5. Approaches to symptom reduction and management

#### 3.5.1. Prevention

Preventing the onset of depression across the lifespan and adequately treating depressive episodes when they occur has tremendous potential to delay the onset and reduce the incidence of ADRD. Indeed, current interventions for depression exert multilevel effects on brain networks and biological pathways implicated in neurodegeneration and dementia risk. At the network level, antidepressant treatment, psychotherapy, and neuromodulation modulate fronto-limbic, default mode, and cognitive control networks whose dysfunction characterizes late-life depression and predicts cognitive decline [44, 45]. Neuroimaging studies demonstrate treatment-related normalization of emotion regulation and reward circuitry, with implications for resilience against neurodegenerative trajectories [46, 47]. At cellular and molecular levels, effective depression treatment reduces inflammatory burden, reverses stress-related hippocampal toxicity, and enhances neurotrophic signaling, particularly BDNF, supporting synaptic integrity and plasticity [48]. Converging evidence suggests that treating depression may modify dementia risk by targeting shared network, inflammatory, and neuroplastic mechanisms rather than providing purely symptomatic relief [47, 48].

Depression prevention within dementia care remains an underexplored yet promising avenue for improving long-term outcomes, reflecting the broader complexity of depression in old age and in the context of neurodegenerative disease. Late-life and dementia-related depression represent an immersion in heterogeneity across multiple levels, including pathogenesis (e.g. neurodegeneration, vascular and inflammatory burden, sleep disturbance), clinical presentation (e.g. dysphoria, apathy, executive dysfunction), and response to treatment [39, 44, 49]. These features underscore the need for a prevention framework that integrates traditional public-health concepts of primary, secondary, and tertiary prevention with the Institute of Medicine/National Academy of Medicine (IOM/NAM) taxonomy of universal, selective, and indicated prevention [50, 51].

Primary prevention, which overlaps with universal prevention, emphasizes promoting healthy aging behaviors across the population, including regular physical activity, balanced nutrition, cognitive stimulation, sound sleep, and sustained social engagement. Public-health initiatives that reduce social isolation, address caregiver burden, and combat ageism may indirectly lower depression risk while supporting brain health and dementia prevention [1, 52]. Selective prevention targets individuals at elevated risk—such as those with a prior history of depression, sleep disorders, medical or neurologic comorbidity, or emerging cognitive impairment—offering opportunities for timely intervention that may delay both depressive episodes and cognitive decline.

Secondary prevention, corresponding closely to indicated prevention, involves systematic identification and treatment of subthreshold or prodromal depressive symptoms, particularly in primary care and geriatric specialty settings. Tools such as the Geriatric Depression Scale and the Cornell Scale for Depression in Dementia support early detection, though their interpretation must be adapted across levels of cognitive impairment [39]. Tertiary prevention focuses on reducing relapse, disability, neuropsychiatric complications, and caregiver distress once depression and dementia are established, through maintenance pharmacotherapy and/or psychotherapy, community supports, and caregiver education [53].

Importantly, prevention is bidirectional: effective treatment and prevention of depression itself may support cognitive resilience and delay dementia onset. Meta-analytic and longitudinal evidence demonstrates that late-life depression increases dementia risk, reinforcing the importance of timely, sustained intervention [48]. Embedding depression prevention into dementia care therefore requires interdisciplinary collaboration, attention to heterogeneity, and research strategies capable of addressing complexity across the lifespan.

#### 3.5.2. Sleep and brain health

Sleep health is now recognized as foundational to brain health across the lifespan and central to the prevention and treatment of both depression and neurodegeneration. Disturbances in sleep architecture, particularly reductions in slow-wave sleep, are robustly associated with incident depression, recurrence of mood disorders, impaired emotional regulation, and executive dysfunction, with especially strong effects in later life [39, 54]. Longitudinal studies demonstrate that short or fragmented sleep predicts both first-onset and recurrent depression, while interventions that optimize sleep reduce depressive symptoms and relapse risk, including among older adults [37, 55]. Importantly, the relevance of sleep extends well beyond mood: poor sleep is independently associated with accelerated cognitive aging, amyloid and tau accumulation, and increased dementia risk even in individuals without depression [56–58].

Mechanistically, convergent animal and human evidence shows that slow-wave sleep promotes glymphatic clearance of β-amyloid and tau and supports synaptic homeostasis, neuronal resilience, and memory consolidation, providing a biological link between sleep disruption and neurodegeneration [59, 60]. These findings support sleep as an active neuroprotective process rather than a passive biomarker. Reflecting this evidence, sleep has been formally incorporated into the American Heart Association's "Life's Essential 8" framework for cardiovascular health [52]. Sleep health should also be considered an important cross-cutting target within dementia prevention frameworks. While the 2024 Lancet Commission [1] does not include sleep as one of its 14 formally modelled modifiable dementia risk factors, sleep disturbance interacts with several Commission-identified risks—including depression, obesity, diabetes, hypertension, physical inactivity, excessive alcohol use, and social isolation—and therefore warrants clinical assessment and research attention in prevention-oriented models of brain health.

Taken together, routine assessment and targeted treatment of sleep disturbances should be considered essential components of clinical care for depression at all ages, particularly in late life. Moreover, prioritizing sleep health in individuals without depression represents a promising, scalable strategy to preserve brain health and potentially prevent or delay neurodegenerative disease, underscoring sleep as a critical clinical and research priority going forward.

#### 3.5.3. Treatment overview

Patient characteristics strongly influence treatment response when depression occurs in the context of dementia. Greater baseline depression severity, preserved insight, lower dementia severity, and fewer vascular and neuropsychiatric comorbidities are associated with better treatment response, whereas prominent apathy, executive dysfunction, and cerebrovascular burden predict poorer outcomes [44, 61]. Evidence for pharmacologic efficacy is mixed. Early randomized trials demonstrated modest antidepressant benefits in Alzheimer's disease, but subsequent studies and reviews have shown limited superiority over placebo and increased adverse events (62; 63). Overall, antidepressants may improve affective symptoms without reliably preventing relapse or altering dementia trajectory [48]. When cognitive benefits are observed, they are typically confined to attention and executive functioning, likely reflecting indirect effects of mood improvement rather than disease modification [44].

Non-pharmacologic and caregiver-inclusive interventions show more consistent benefits across clinical domains. Problem-solving therapy, behavioral activation, and environmental adaptations tailored for cognitive impairment significantly reduce depressive symptoms, functional disability, and caregiver burden, with favorable safety and durability [53, 62, 63]. Affective symptoms such as dysphoria, anxiety, apathy, and social withdrawal improve more reliably than global cognition, although gains in functional executive abilities are sometimes observed [63]. Importantly, these interventions reduce caregiver distress and enhance quality of life by addressing behavioral triggers and care demands [53, 64]. Combined pharmacologic and behavioral approaches appear particularly promising for patients with moderate dementia and high psychosocial stress, suggesting additive or synergistic effects on mood and daily functioning [65].

More recent evidence further supports integrated and non-pharmacologic strategies. A large randomized clinical trial demonstrated that cognitive remediation combined with non-invasive brain stimulation significantly slowed cognitive decline in older adults with major depression and mild cognitive impairment, highlighting the potential for interventions to modify both affective and cognitive trajectories relevant to dementia risk [58]. In parallel, updated reviews emphasize that while antidepressants offer limited benefit in dementia-related depression, structured psychosocial and caregiver-inclusive interventions consistently improve depressive symptoms, functional outcomes, and caregiver well-being with superior tolerability [66].

#### 3.5.4. Behavioral and psychosocial treatment

Nonpharmacologic interventions are essential in managing depression in dementia, especially since pharmacotherapy is often ineffective, poorly tolerated, and carries significant risks. These approaches can be tailored to the individual's stage of cognitive decline, functional abilities and preferences, and are most effective when integrated into interdisciplinary care models [67,68]. Importantly, effective non-pharmacologic strategies also exist for older adults in more advanced stages of dementia, focusing on sensory engagement, comfort-based activities, and relational approaches that preserve emotional connection and quality of life [69,70].

Among these interventions, psychosocial therapies play a central role in addressing the emotional, social, and existential dimensions of depression in dementia. They aim to preserve autonomy, enhance dignity, and improve quality of life through meaningful engagement and social connectedness. Key modalities are summarized in Table 1. For these interventions to be effective along the spectrum of disease severity and to also engage and support caregivers, a dyadic approach that includes caregivers as partners in the treatment may be needed. An example is Problem Adaptation Therapy (PATH) for Older Adults with major depression and cognitive impairment [81].

#### 3.5.5. Pharmacologic and neuromodulation treatment

Medication treatment of depression in dementia presents challenges due to limited efficacy and the associated risk of adverse effects. Although antidepressants are commonly used in this population, evidence from randomized controlled trials (RCTs) and meta-analyses show a lack of efficacy in improving depressive symptoms or cognition [16,82–84]. However, a 2024 meta-analysis of SSRIs showed significant reductions in depressive symptoms in patients with AD [85].

First-line treatments typically include selective serotonin reuptake inhibitors (SSRIs) such as sertraline and escitalopram, which are preferred for their relatively favorable safety profile compared to tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs), which are generally avoided due to anticholinergic and cardiovascular risks [16,86,87]. Nevertheless, SSRIs pose risks for older adults, including falls, bleeding, and hyponatremia; (es)citalopram requires caution due to QTc prolongation [88–91]. Alternative agents, such as mirtazapine for coexisting insomnia or appetite loss, bupropion for reduced energy, and serotonin–norepinephrine reuptake inhibitors (SNRIs) like duloxetine, are used in practice, but evidence in dementia-specific populations remains limited. Mirtazapine was shown to have benefits in a subgroup of depressed dementia patients experiencing primarily psychological symptoms (e.g., anxiety, sadness, low self-esteem) but no other subtypes [92]. Emerging treatments, including NMDA receptor antagonists (ketamine, esketamine) and multimodal serotonergic agents, are under early investigation for late-life depression, though data in dementia populations are sparse [93–95]. To date, no antidepressant has received regulatory approval specifically for major depressive disorder comorbid with dementia [93,96]. Given the modest benefits and potential harms, intervention decisions should be based on a shared decision- a critical approach in both LLD and younger MDD populations- that consider disease stage, frailty, comorbidities, polypharmacy, and patient–carer preferences. Pharmacotherapy is best implemented alongside psychosocial and behavioral interventions, rather than as a stand-alone strategy. Clinical attention should also address symptoms that transcend the depression, agitation, and psychosis domains of NCD-NPS. These include anxiety and irritability (which often overlap with both depression and agitation), as well as circadian rhythm dysregulation, which may drive or exacerbate various sleep disruptions (e.g., insomnia). An imperative for the next decade is to develop and test pharmacologic treatments specifically designed for depression and associated symptoms in neurodegenerative diseases, informed by biomarker-defined subtypes and tailored to the unique neurobiology of NCDs.

In addition to pharmacological approaches, a range of neuromodulation techniques are being explored for their potential to improve mood and cognition in NCDs. These interventions vary in their level of invasiveness and evidence, but collectively they offer additional options when traditional therapies are insufficient. A summary of these modalities is presented in Table 2.

The future of depression management in dementia likely resides in multimodal interventions. Depression treatment should be patient-centered, integrating behavioral, sensory, psychosocial, and biologic elements to enhance neuroplasticity and restore, or at least stabilize, both affective and cognitive functions. Treatment imperatives for the next decade include expanding the evidence base for effective, scalable, culturally-adaptable interventions. It is essential to integrate these strategies into multimodal treatment plans that are guided by biomarker and symptom profiles. Priority should be given to interventions that offer dual cognitive and mood benefits, such as combined physical and cognitive training programs. Additionally, embedding caregiver training and support into standard dementia care pathways is crucial to sustain long-term benefits.

**Table 1**
Behavioral and Psychosocial Interventions for Depression in NCD.

| Intervention | Description & Current Evidence | References |
|---|---|---|
| Problem-Solving Therapy (PST) | Structured, goal-oriented approach that helps individuals cope with everyday stressors. Demonstrated benefit in mild to moderate cognitive impairment. | [71,72] |
| Interpersonal Therapy (IPT) | Addresses grief, role transitions, and social withdrawal—common in older adults with dementia. | [73,74] |
| Behavioral Activation (BA) | Promotes re-engagement in pleasurable and purposeful activities; effective in institutional settings. | [75,76] |
| Group-Based Interventions (e.g., support groups, life review, reminiscence) | Reduce loneliness, enhance emotional expression, and promote peer support. | [77,78] |
| Reminiscence Therapy | Recall of positive past experiences, memories and life events through photographs, music or familiar objects | [79,80] |

*3.5.6. Considering suicide in dementia*

Depression is a robust risk factor for suicidal ideation and behavior in later life, but the relationship is modified by the presence and stage of dementia. Evidence suggests that suicide risk is highest in individuals with depression and early or evolving dementia, when insight, autonomy, and decisional capacity are relatively preserved [107,108]. As dementia progresses, overt suicidal behavior generally declines, though distress-driven passive death wishes may persist [109]. Neurocognitive models emphasize impaired cognitive control, hopelessness, and altered reward processing as key mechanisms linking depression, cognitive decline, and suicidality [39, 110]. Depression also shapes preferences regarding goals of care, often increasing desire for comfort-focused approaches and reducing perceived benefits of life-prolonging interventions [49,111]. Early identification and treatment of depression may therefore reduce suicide risk and support values-concordant care planning.

## 4. Recommendations

### *4.1. IPA global priorities and call to action*

Drawing from the IPA Congresses in Buenos Aires and Kanazawa and the evidence synthesized in this white paper, the IPA Depression Workgroup identifies the following global priorities to guide research, clinical practice, training, advocacy, and policy over the next decade. These priorities are intended to accelerate progress toward precision psychiatry for depression in neurocognitive disorders (NCDs), while also advancing prevention-oriented, person-centered, and globally scalable models of care.

1. **Develop targeted treatments for depression in neurodegenerative diseases**. Current pharmacologic options are largely adapted from general adult and geriatric psychiatry and do not adequately address the unique neurobiology, cognitive context, frailty, multimorbidity, and care needs of persons with dementia-related depression. Regulatory agencies, funders, and investigators should prioritize therapies specifically designed and tested for depression in NCD populations, including pharmacologic, neuromodulatory, psychosocial, behavioral, sleep-focused, and multimodal interventions.
2. **Establish an updated, accurate definition of depression in NCDs**. A revised nomenclature is urgently needed to reflect the heterogeneous symptomatology, course, and functional consequences of depression in dementia. Such a framework should account for dementia stage and subtype, age of depression onset, overlap with apathy and anxiety, caregiver-observed symptoms, and longitudinal trajectories. Emerging concepts such as “Affective Dysregulation Associated with NCD” deserve systematic evaluation and validation.
3. **Advance biomarker research for diagnosis, subtyping, prognosis, and treatment monitoring**. Validated biomarkers are needed to differentiate depression from overlapping syndromes such as apathy, frailty, sleep disruption, delirium, and cognitive decline; identify biologically meaningful subtypes; guide personalized intervention; and track treatment response over time. Priority domains include structural and functional neuroimaging, inflammatory and neurodegenerative markers, serotonergic signaling, genomic and epigenomic predictors, plasma-based Alzheimer’s disease biomarkers, and digital phenotyping.
4. **Develop interventions that address cognitive symptoms of depression**. Depression in NCD is frequently accompanied by deficits in executive function, attention, processing speed, memory, motivation, and functional problem-solving. Future interventions should move beyond mood-focused outcomes alone and incorporate cognitive and functional targets into pharmacologic, neuromodulatory, psychosocial, behavioral, and rehabilitation-based strategies.
5. **Account for heterogeneity in depression across the NCD continuum**. Depression in dementia is not a unitary syndrome. It varies by pathogenesis, clinical presentation, dementia subtype, illness stage, age of onset, vascular and inflammatory burden, sleep and circadian disruption, exposomic risk, caregiver context, and

**Table 2**
Neuromodulatory Techniques for Depression in NCD.

| Intervention | Description & Current Evidence | References |
|---|---|---|
| Electroconvulsive Therapy (ECT) | Most established and effective for severe or treatment-resistant depression in dementia; requires close cognitive monitoring. | [97] |
| Repetitive Transcranial Magnetic Stimulation (rTMS) and Intermittent Theta Burst Stimulation (iTBS) | Shows promise in improving mood and cognition in both MCI and dementia. | [98,99] |
| Transcranial Direct Current Stimulation (tDCS) | Non-invasive, portable; growing evidence of dual efficacy for mood and cognition, especially in MCI. | [100–103] |
| Ketamine | Evidence for use in depression associated with dementia is limited to theoretical mechanistic rationale and a small number of case reports suggesting rapid antidepressant effects with generally tolerable short-term safety, but remains insufficient to support routine clinical use without controlled, dementia-specific trials. | [104–106] |

treatment responsiveness. Future clinical trials and observational studies should be designed to identify clinically and biologically meaningful subtypes and to match interventions to patient characteristics, disease stage, and care goals.

6. **Integrate exposomics and life-course risk assessment into prevention and care**. Depression and dementia risk are shaped by cumulative non-genetic exposures across the life course, including adverse childhood experiences, chronic stress, social isolation, sleep disturbance, cardiometabolic disease, alcohol and other substance exposures, environmental adversity, and caregiving context. These exposures interact with genetic and epigenetic vulnerability and may help explain heterogeneity in late-life depression, dementia risk, and treatment response. Exposomic assessment should be incorporated into research protocols and, where feasible, into clinical care to identify modifiable prevention targets.
7. **Prioritize sleep and circadian health as modifiable targets for depression and dementia prevention**. Sleep health is central to mood regulation, cognitive resilience, and brain health across the lifespan. Sleep disturbance should be routinely assessed and treated in persons at risk for, or living with, depression and NCD. Future research should test whether interventions targeting insomnia, sleep-disordered breathing, circadian disruption, and slow-wave sleep can improve mood, preserve cognition, reduce caregiver burden, and modify neurodegenerative trajectories.
8. **Improve understanding of sex and gender differences in depression in dementia**. Sex- and gender-related factors, including hormonal, genetic, vascular, psychosocial, caregiving, and sociocultural influences, affect depression risk, symptom presentation, treatment response, and caregiver dynamics. Research should systematically examine these differences to inform tailored prevention and intervention strategies.
9. **Embed caregiver-inclusive and dyadic models into standard care pathways**. Because depression in NCD affects both patients and carers, interventions should routinely include caregiver education, support, and skills training. Dyadic and family-centered models may improve detection, enhance adherence, reduce caregiver distress, and sustain treatment benefits over time.
10. **Develop globally scalable and culturally adaptable implementation strategies**. The global burden of NCD requires interventions that can be adapted across health systems, cultures, resource settings, and levels of specialist availability. Priorities include task-sharing models, integration into primary care and dementia care pathways, digital and remote-delivered interventions, community-based prevention programs, and training resources for clinicians, trainees, caregivers, and lay health workers.

### *4.2. Strategic messaging for stakeholders*

Achieving these calls to action will require more than scientific consensus; it will require clear, audience-specific communication that translates the IPA roadmap into priorities that are understandable, actionable, and compelling for different stakeholder groups. Clinicians, patients, caregivers, trainees, researchers, funders, regulators, and policy makers each engage with depression in NCD from different vantage points and with different responsibilities, constraints, and informational needs. Effective messaging should therefore avoid a one-size-fits-all approach and instead emphasize the specific relevance of depression in NCD to each group: diagnostic accuracy and treatment planning for clinicians; hope, validation, and practical support for patients and caregivers; education and workforce development for trainees; methodological rigor and innovation for researchers; and scalable, equitable implementation for health systems and policy makers. Aligning language with stakeholder priorities can reduce stigma, promote earlier detection and treatment, support caregiver engagement, accelerate research investment, and improve uptake of prevention-oriented and precision-care models. In this way, strategic messaging becomes an essential implementation tool for transforming the IPA Depression Workgroup's recommendations into measurable improvements in care, research, and global brain health.

| Stakeholder Group | Key Messages | Intended Actions |
|---|---|---|
| Primary Care Providers & Psychiatrists | We need a more accurate and inclusive diagnostic framework for depression in NCDs. Familiarize clinicians with emerging terminology and assessment tools, including 'affective dysregulation.' | Integrate updated definitions into practice; adopt screening tools suited for NCDs. |
| Patients & Caregivers | "Depression is toxic to the brain." Evidence shows that treating depression may reduce dementia risk. Early engagement and lifestyle-based prevention matter. | Promote early help-seeking, reduction of stigma, adherence to treatment, and engagement in prevention programs. |
| Medical Trainees & Early-Career Clinicians | Dementia affects more than memory and cognition. Behavioral and psychological symptoms (BPSD) and mild behavioral impairment (MBI) remain underrepresented in training. "Pseudodementia" is no longer a preferred term because depression contributes to cognitive decline that does not fully improve even after depression is treated. | Incorporate BPSD and MBI into curricula; prioritize multidisciplinary learning. Understand complex, bidirectional relationships between depression, cognitive symptoms, and dementia risk. |

## 5. Conclusion

Depression in neurocognitive disorders represents both a prevalent and consequential NCD-NPS and a potentially modifiable risk factor for dementia. Its bidirectional, heterogeneous, and stage-dependent relationship with neurodegeneration challenges traditional categorical distinctions between primary mood disorders and dementia-related affective syndromes. Depression in NCD varies across dementia subtype, illness stage, age of onset, symptom profile, apathy and anxiety overlap, vascular and inflammatory burden, sleep and circadian disruption, exposomic risk, caregiver context, and treatment responsiveness. This complexity underscores the need to move beyond generic symptom management toward biologically informed, person-centered, prevention-oriented, and stage-sensitive care.

Over the next decade, advancing the field will require harmonized NCD-specific nomenclature, multimodal biomarker integration, exposomic and life-course risk assessment, and development of targeted pharmacologic, psychosocial, neuromodulatory, sleep-focused, and caregiver-inclusive interventions. Equally important is embedding depression prevention into broader brain health strategies across the lifespan. Prevention must include universal strategies that promote healthy aging and brain health, selective approaches for individuals at elevated risk, indicated interventions for subthreshold or prodromal symptoms, and tertiary strategies to reduce relapse, disability, caregiver burden, and neuropsychiatric complications once depression and dementia are established.

The evidence reviewed in this white paper supports a shift from viewing depression in NCD solely as a symptom to be managed toward understanding it as a complex, multidimensional syndrome with implications for quality of life, function, caregiver well-being, suicide risk, and dementia prevention. Attention to sleep health, social connection, substance exposure, medical comorbidity, environmental adversity, and caregiver context broadens the clinical frame and identifies modifiable targets for intervention. At the same time, the modest and inconsistent efficacy of currently available pharmacologic treatments highlights the need for multimodal and precision approaches that are tailored to patient characteristics, underlying biology, disease stage, and care goals.

A coordinated international agenda—spanning regulatory agencies, clinicians, researchers, trainees, patients, carers, advocacy organizations, and policy makers—is essential to accelerate innovation and implementation. By integrating precision psychiatry, prevention science, exposomics, sleep health, scalable psychosocial care, and caregiver-inclusive models, the field can reduce the global burden of depression in NCD and contribute meaningfully to dementia risk reduction worldwide. These efforts are central to the IPA's next-decade roadmap and to improving outcomes for individuals living with neurocognitive disorders and those who care for them.

## CRediT authorship contribution statement

**Maria Paula Gastiazoro:** Writing – review & editing, Writing – original draft, Project administration, Conceptualization. **Jennifer Gatchel:** Writing – review & editing, Writing – original draft. **Lucia Crivelli:** Writing – review & editing, Writing – original draft. **Adriana Hermida:** Writing – review & editing. **Masaru Mimura:** Writing – review & editing, Writing – original draft, Conceptualization. **Richard Oude Voshaar:** Writing – review & editing, Writing – original draft, Conceptualization. **Marie Anne Gebara:** Writing – review & editing, Writing – original draft. **Melanie Gentry:** Writing – review & editing, Writing – original draft. **Maria Lapid:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Conceptualization. **Meryl Butters:** Writing – review & editing, Writing – original draft, Conceptualization. **Maarten Van Den Bossche:** Writing – review & editing. **Kristina Zdanys:** Writing – review & editing, Writing – original draft. **Jordan F. Karp:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Conceptualization.

## Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: **Maria I. Lapid** serves on the PurMinds Neuropharma Scientific Advisory Board with potential royalty interests. **Jennifer Gatchel** has served as a consultant for Eisai and Oliver Wyman. **Kristina Zdanys** receives royalties for the American Psychiatric Association Textbook of Geriatric Psychiatry, 6th Edition. **Jordan F. Karp** currently receives research support from Johnson and Johnson Neuroscience. Within the past two years he has provided scientific advising to Johnson and Johnson Neuroscience, Otsuka, and Biogen. He receives compensation for senior editorial service from American Journal of Geriatric Psychiatry and Journal of Clinical Psychiatry. The other authors have nothing to disclose.

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