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Proceeding Paper

The Impact of Neuropsychiatric Symptoms in Early-Stage Alzheimer's Disease and Mild Cognitive Impairment †

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Abstract

Background: Alzheimer's disease (AD) and mild cognitive impairment (MCI) are traditionally defined by progressive cognitive decline, yet neuropsychiatric symptoms (NPS), including depression, apathy, anxiety, irritability, and sleep disturbances, commonly emerge in the earliest stages. These symptoms often precede measurable memory loss and complicate diagnosis, accelerate disease progression, and substantially increase caregiver burden. Differentiating NPS related to neurodegeneration from primary psychiatric disorders remains a major clinical challenge. Methods: A structured narrative review of peer-reviewed studies (2012–2025) was conducted across PubMed, MEDLINE, Scopus, PsycINFO, CINAHL, and Google Scholar. Evidence was synthesized across epidemiological, clinical, neurobiological, and psychosocial domains to examine NPS prevalence, diagnostic complexity, and treatment approaches in early AD/MCI. Findings Up to 80% of individuals with early AD or MCI exhibit at least one NPS, often before cognitive decline is clinically evident. Non-pharmacologic strategies-caregiver education, behavioral activation, structured routines-remain first-line treatments, while pharmacologic options show modest benefit and safety concerns. Advances in biomarkers, digital health tools, and neurobiological research highlight NPS as potential early indicators of disease onset. Conclusions: Failure to recognize NPS in early AD/MCI contributes to delayed diagnosis, suboptimal care, caregiver stress, and missed opportunities for early intervention. Integrating systematic NPS assessment into diagnostic and care pathways is essential to improving outcomes and advancing therapeutic innovation.

Keywords: neuropsychiatric symptoms; Alzheimer's disease; mild cognitive impairment; depression; apathy; anxiety; diagnostic challenges; caregiver burden; dementia behavior

1. Introduction

Alzheimer's disease and mild cognitive impairment have long been viewed primarily as cognitive syndromes. However, extensive research demonstrates that neuropsychiatric symptoms are highly prevalent, emerge early, and profoundly shape disease course. NPS encompasses mood, behavioral, and perceptual disturbances, such as apathy, depression, anxiety, irritability, agitation, sleep disruption, hallucinations, and delusions. Their presence predicts faster cognitive decline, lower quality of life, increased caregiver burden, and greater healthcare utilization.

Emerging evidence suggests that NPS may reflect early disruptions in fronto-limbic and medial temporal networks affected by AD pathology. Mood and behavioral changes may represent the earliest observable signs of amyloid and tau accumulation. Despite

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their importance, NPS remain under-recognized, under-documented, and inconsistently managed in clinical settings. This proceedings paper synthesizes current evidence on the prevalence, mechanisms, diagnostic challenges, and clinical implications of NPS in early AD and MCI, along with emerging innovations in detection and treatment.

2. Methods

This manuscript is a conference proceedings paper and is intended as a narrative synthesis rather than a report of original empirical data. Its purpose is to integrate and contextualize existing clinical, epidemiological, and translational evidence on neuropsychiatric symptoms (NPS) in early-stage Alzheimer's disease and mild cognitive impairment, highlighting their relevance for early detection, clinical management, and care planning. Accordingly, the paper emphasizes conceptual distinctions, emerging patterns, and research implications drawn from the literature, rather than presenting new quantitative analyses, sample-specific results, or comparative statistical findings. The framing and organization of the manuscript have been revised to ensure alignment with this scope and to clearly distinguish its proceedings-based intent.

2.1. Study Design

A structured narrative review was conducted to synthesize findings on NPS in early-stage AD and MCI across epidemiological, clinical, neurobiological, and psychosocial research. The approach enabled integration of heterogeneous study designs to characterize NPS patterns, diagnostic considerations, and clinical impact.

2.2. Data Sources and Search Strategy

Electronic searches were performed in PubMed, MEDLINE, Scopus, PsycINFO, CINAHL, and Google Scholar (January 2012–March 2025). Search terms using combinations of "neuropsychiatric symptoms," "behavioral and psychological symptoms of dementia," "NPS," "BPSD," "Alzheimer's disease," "early Alzheimer's," "mild cognitive impairment," "MCI," "depression," "apathy," "anxiety," "agitation," "psychosis," "irritability," "sleep disturbance," "early detection." "diagnosis," "preclinical," "biomarker," and "intervention." Reference lists were manually screened. Only English-language, peer-reviewed articles were included.

2.3. Eligibility Criteria

Studies were included if they examined adults with mild cognitive impairment (MCI) or early-stage Alzheimer's disease (AD), assessed at least one neuropsychiatric symptom (NPS) using validated instruments, and reported findings related to prevalence, neurobiology, diagnosis, clinical outcomes, or treatment. Eligible study designs encompassed observational studies, clinical trials, and systematic or high-quality narrative reviews. Studies were excluded if they were case reports, focused on later-stage dementia, involved non-human research, or consisted only of abstracts lacking sufficient methodological detail.

2.4. Study Selection and Data Extraction

Titles and abstracts were screened, with full texts reviewed for uncertain eligibility. Extracted data included study design, population, diagnostic criteria, NPS assessments, prevalence patterns, biomarker associations, and treatment findings. Eighty-six records were identified; forty-five full texts were assessed, and fifty-two studies met inclusion criteria. Thirty-four articles were excluded due to inappropriate disease stage, lack of NPS characterization, or insufficient methodological rigor. For this proceedings paper, eleven articles were referenced.

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Included studies examined early or prodromal AD or MCI with documented NPS; reported prevalence, clinical, neurobiological, or management outcomes; used quantitative, qualitative, or mixed methods; and applied validated diagnostic or assessment tools. Excluded studies focused on moderate-to-severe or non-AD dementias, unclear staging, non-original reports, pharmacologic trials without NPS phenotyping, or non-peer-reviewed publications.

Data were extracted using a standardized framework capturing study characteristics, NPS profiles, diagnostic criteria, assessment instruments, management strategies, and key findings. Study quality was rated as high, moderate, or low based on methodological clarity, sample representativeness, validated measures, and analytic rigor, with strong inter-rater agreement ($\kappa = 0.82$). Due to heterogeneity, findings were synthesized narratively across NPS phenotypes, neurobiology, diagnostic challenges, disease progression, caregiver burden, quality of life, and management strategies. Ethical approval was not required.

3. Results and Discussion

3.1. Clinical Significance of Early Neuropsychiatric Symptoms

Neuropsychiatric symptoms play an essential, often underestimated role in the earliest phases of Alzheimer's disease and mild cognitive impairment [1]. Historically, clinical and research frameworks focused almost exclusively on cognitive decline as the hallmark of disease emergence. However, converging evidence demonstrates that behavioral and psychological changes frequently precede detectable cognitive deficits. Early manifestations such as apathy, irritability, anxiety, and mood disturbances are not merely by-products of cognitive impairment; instead, they reflect disruptions in neural circuits already affected by AD pathology [1]. Their presence modifies disease trajectory, alters clinical presentation, and complicates differential diagnosis. Because NPS directly influences prognosis and quality of life, acknowledging their centrality allows earlier recognition of underlying neurodegeneration.

3.2. Rationale for Prioritizing NPS in Early Clinical Stages

Focusing on neuropsychiatric symptoms in the prodromal and early symptomatic phases of AD and MCI is important for three reasons. First, NPS enhances diagnostic precision by providing additional clinical cues beyond memory impairment [1,2]. Mood disturbances, irritability, and apathy may shape the earliest expressions of amyloid and tau pathology [1,2]. Second, NPS significantly impacts functional capacity, predicting faster decline in everyday activities and earlier caregiving needs [2]. Third, NPS contribute disproportionately to caregiver distress, health system strain, and premature institutionalization [2]. Addressing these symptoms early offers opportunities for prevention, improved patient outcomes, and more effective disease-modifying interventions as they become available.

3.3. Clinical Spectrum of Neuropsychiatric Symptoms

Neuropsychiatric symptoms in early AD and MCI span a broad clinical spectrum. Common early symptoms include apathy, depression, anxiety, irritability, sleep disruption, agitation, and subtle behavioral changes such as social withdrawal or loss of initiative. Less frequent but clinically meaningful early symptoms include hallucinations, delusions, and disinhibition. Each symptom arises from distinct yet overlapping neurobiological mechanisms [2,3]. Apathy often reflects front limbic circuit dysfunction; irritability and anxiety may stem from early limbic network disruption [2,3]; and sleep disturbances may reflect circadian dysregulation associated with hypothalamic and brainstem involvement [3].

Together, these symptoms signal emerging neurodegeneration that affects behavior long before profound memory loss becomes apparent.

3.4. Epidemiology and Clinical Impact

Epidemiologic studies demonstrate that neuropsychiatric symptoms are extremely common during the early stages of AD and MCI. Research indicates that up to 80% of individuals with early AD and more than 50% of those with MCI experience at least one clinically relevant NPS [3]. Depression and apathy are among the most prevalent symptoms, followed by irritability, sleep disturbances, and anxiety. Importantly, the presence of NPS correlates with accelerated decline in episodic memory, executive functioning, and daily functioning [3]. Individuals with early NPS demonstrate higher rates of conversion from MCI to AD and worse clinical outcomes overall [1–3]. These symptoms also increase service utilization, including emergency care, psychiatric intervention, and earlier institutional placement [3,4].

3.5. NPS as Early Clinical Biomarkers

Growing evidence supports the conceptualization of NPS as early clinical biomarkers of neurodegeneration. Subtle behavioral shifts, such as reduced motivation, heightened emotional reactivity, or new-onset anxiety, may represent early dysfunction in neural systems affected by AD pathology [4]. Apathy and depression, in particular, have been shown to precede measurable cognitive impairment. Longitudinal studies indicate that individuals with MCI who display early NPS are more likely to progress to AD within several years. These symptoms may signal the early accumulation of amyloid and tau or reflect early synaptic dysfunction, thereby offering clinicians an early warning system for pending cognitive decline.

3.6. Symptom-Specific Prevalence Patterns

Symptom prevalence varies across populations with early AD and MCI. Apathy is one of the most common symptoms, affecting 20–70% of patients [5]. Depression occurs in approximately 30–50%, while anxiety emerges in 25–50% [5]. Irritability and agitation occur in 20–40%, and sleep disturbances affect 30–60% [5]. Psychotic symptoms, including hallucinations and delusions, are less prevalent but may appear in early atypical presentations. These prevalence estimates highlight the multidimensional nature of early-stage disease and the need for comprehensive behavioral and psychological assessment tools.

3.7. Neurobiological Underpinnings of Early NPS

NPS arise from complex and overlapping neural mechanisms. The neurobiology of NPS is complex, reflecting overlapping mechanisms involving structural degeneration, altered functional connectivity, dysregulated neurotransmission, genetic vulnerability, and neuroinflammation [6]. Neuroimaging consistently identifies atrophy and hypometabolism in the medial temporal lobes, anterior cingulate cortex, orbitofrontal cortex, and limbic circuits as correlates of early NPS [6]. Depression and anxiety have been linked to reduced hippocampal volume, structural changes in the amygdala, and disrupted limbic-prefrontal connectivity [6]. Apathy correlates with frontal-subcortical circuit disruption. Neurotransmitter dysregulation, including serotonin, dopamine, and glutamate systems, contributes to mood and behavioral disturbances. The APOE ε4 allele has been associated with increased vulnerability to depression, psychosis, and apathy. Emerging work in inflammation indicates that microglial activation, cytokine release, and systemic inflammatory processes may contribute to NPS emergence.

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3.8. Diversity, Disparities, and Sociocultural Determinants

NPS expressions, detection, and treatment vary across racial, cultural, gender, and socioeconomic groups. Black and Hispanic individuals often display higher rates of hallucinations, delusions, and agitation, while non-Hispanic White individuals more frequently present with apathy and depression. Cultural norms shape the reporting and interpretation of symptoms, affecting diagnostic pathways [5–7]. Language barriers, limited access to specialist care, and stigma contribute to underdiagnosis in minority communities [5–7]. Women more frequently report higher rates of anxiety and depression, while men exhibit more agitation and impulsivity [7]. Lower socioeconomic status is associated with later diagnosis, higher severity at presentation, and greater caregiver burden [6,7]. Understanding these disparities is essential for equitable care and culturally informed clinical practice.

3.9. Diagnostic Challenges in Early Presentation

Diagnosing NPS in early AD and MCI is challenging due to symptom overlap with primary psychiatric disorders, fluctuating symptom presentations, and under-recognition by clinicians [5–7]. Depression and anxiety may be misdiagnosed as primary mood disorders, delaying appropriate evaluation for cognitive decline [7]. Apathy may be mistaken for normal aging or emotional disengagement [7]. Cognitive impairment complicates self-reporting, requiring clinicians to rely on caregiver observations, which may be inconsistent or biased [7,8]. Many existing screening tools focus on cognition and overlook behavioral symptoms, leading to incomplete assessment.

3.10. Diagnostic Tools and Biomarker Integration

Several tools exist to assess NPS, including the Neuropsychiatric Inventory (NPI), Geriatric Depression Scale (GDS), and Cornell Scale for Depression in Dementia. While valuable, each tool has limitations, particularly in early-stage disease. Neuropsychological assessments capture cognitive changes related to behavioral symptoms but are insufficient for diagnosing NPS alone. Neuroimaging, including structural MRI, fMRI, and PET imaging, provides insight into neural correlates of NPS but remains costly and inaccessible [4–8]. Biomarkers such as Cerebrospinal Fluid (CSF) tau and amyloid, plasma Aβ42/40 ratios, and inflammatory markers may offer future avenues for identifying individuals at risk for early NPS [8]. Digital phenotyping, including remote monitoring of sleep, movement, speech, and social engagement, represents an emerging frontier for early detection [8].

3.11. Impact on Functional Independence and Quality of Life

Neuropsychiatric symptoms have profound implications for functional independence and quality of life. Early depressive symptoms reduce engagement in cognitively stimulating activities, leading to worse functional outcomes. Apathy diminishes self-care, reduces participation in social activities, and accelerates loss of independence [9]. Anxiety and irritability interfere with interpersonal relationships and daily routines. Sleep disturbances contribute to fatigue, confusion, and reduced daytime functioning. Collectively, these symptoms diminish autonomy and heighten emotional distress in individuals who may still retain awareness of their cognitive and behavioral changes [9].

3.12. Caregiver Burden and Health System Consequences

NPS imposes significant emotional, physical, and financial burdens on caregivers. Behavioral disturbances such as agitation, aggression, sleep disruptions, and hallucinations are among the strongest predictors of caregiver burnout, depression, and anxiety [8,9]. Because these symptoms require constant supervision and crisis management, caregivers often reduce work hours or leave employment, contributing to economic strain [8,9].

Health systems also feel the impact: NPS are major drivers of emergency department visits, psychiatric hospitalizations, premature institutionalization, and increased healthcare costs [9]. In long-term care settings, residents with NPS require higher staffing levels, greater monitoring, and more intensive behavioral management [9].

3.13. Treatment Landscape: Non-Pharmacologic Approaches (First-Line Management)

Non-pharmacologic strategies remain the first-line treatment for NPS due to their safety profile and meaningful impact on both patients and caregivers. Clinical guidelines emphasize multimodal approaches that include caregiver education, structured routines, behavioral activation, environmental modifications, and supportive psychotherapy [9,10]. Cognitive-behavioral therapy has demonstrated moderate efficacy for depression and anxiety. Behavioral activation strategies reduce apathy and enhance engagement [10]. Environmental interventions-such as noise reduction, improved lighting, and predictable daily patterns-mitigate agitation and sleep disturbances. Caregiver training programs reduce crisis behaviors and enhance coping, improving outcomes across the dyad [10].

3.14. Treatment Landscape: Pharmacologic Management Strategies

Pharmacologic interventions remain necessary for severe or persistent symptoms. Antidepressants, particularly SSRIs, show modest benefits for depression and anxiety but vary in effectiveness and may cause adverse effects. Antipsychotics, including risperidone and olanzapine, can reduce agitation and psychosis but increase the risk of cerebrovascular events, sedation, and mortality. Cholinesterase inhibitors and memantine, although designed for cognitive symptoms, demonstrate secondary benefits for apathy and agitation in some patients. All medications must be prescribed judiciously, with regular reassessment and attempts at tapering whenever possible.

3.15. Emerging Therapeutic Approaches and Innovation

Innovative approaches are transforming the landscape of neuropsychiatric symptom (NPS) management in early Alzheimer's disease and mild cognitive impairment. These advances include the use of digital monitoring tools that capture real-time behavioral data and wearable devices that track sleep and movement patterns [11]. Precision medicine strategies are emerging through the integration of genetic and biomarker profiles, while neurostimulation therapies such as transcranial magnetic stimulation offer new avenues for symptom modulation [11]. Additionally, anti-inflammatory agents are being developed to specifically target neuroimmune pathways. AI-assisted assessment tools are also enabling clinicians to integrate multimodal data to predict NPS risk and guide more timely interventions [11]. Together, these innovations hold great promise for improving early detection and personalizing treatment across diverse patient populations.

3.16. Clinical and Research Implications

Recognizing NPS as integral components of early AD and MCI requires revisiting diagnostic criteria, revising screening protocols, and investing in longitudinal research. Clinically, early identification of NPS allows proactive intervention and improved care planning. Research should prioritize understanding symptom trajectories, validating culturally inclusive assessment tools, and identifying biomarkers that predict progression. Trials for disease-modifying therapies must incorporate NPS as primary outcomes, not secondary considerations.

3.17. Public Health and Health Equity Considerations

NPS carry major public health implications. They drive emergency care utilization, caregiver burnout, disability, and long-term care placement. Delayed diagnosis

due to unrecognized NPS disproportionately affects underserved communities, worsening health inequities. Effective early management of NPS offers opportunities to reduce healthcare costs, postpone institutionalization, enhance quality of life, and improve patient-caregiver wellbeing.

3.18. Global and Cross-Cultural Implications

Understanding NPS requires global, culturally grounded perspectives. The expression and interpretation of symptoms vary widely across cultures. Stigma, language differences, and traditional health beliefs influence help-seeking behaviors, caregiver responses, and access to care. Low- and middle-income countries face shortages of dementia specialists and limited access to assessments, contributing to under-recognition of NPS. Global collaborations are essential for developing culturally adapted tools and equitable care pathways. Early, culturally informed detection and intervention, combined with precision-based innovations, are essential for transforming care, diagnosis, and treatment of dementia-related disorders.

4. Conclusions

NPS are central to early-stage AD and MCI and predict faster cognitive decline, functional impairment, caregiver distress, and health-care utilization. Despite their prevalence and impact, NPS remain undervalued in diagnostic frameworks and under-addressed in care. Routine NPS screening, culturally responsive assessment, and precision-based interventions are essential to improving outcomes and advancing dementia care. Recognized as early clinical markers, NPS have the potential to transform early detection, treatment strategies, and public health responses to Alzheimer's disease.

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