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NEUROPSYCHIATRIC SYMPTOMS IN ALZHEIMER'S DISEASE - A NARRATIVE REVIEW

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ABSTRACT

Alzheimer's disease represents one of the major healthcare issues due to the aging global population and increased life expectancy. Neuropsychiatric symptoms are recognized as integral features of the disease. While previously believed to occur predominantly in the later stages, current evidence indicates that they frequently emerge during the earliest stages of the disease. Depression is associated with faster cognitive decline and increased disease burden. Although SSRIs are frequently used, their efficacy remains inconsistent. Apathy is one of the most prevalent neuropsychiatric symptoms in AD, arising from disruptions in motivation-related neural circuits and modulated by neuroinflammatory, genetic, and personality factors. Although no treatment is currently approved, catecholaminergic agents show the most consistent promise in reducing apathy. Psychosis, encompassing delusions, hallucinations, affects over half of patients. Agitation impairs patient's and caregiver's function. Aggression is linked to disruptions in serotonergic signaling, frontal lobe dysfunction, and psychotic features, with prevalence increasing as the disease progresses. Traditional antipsychotics pose safety risks, novel agents such as brexpiprazole, pimavanserin, and cannabinoids offer promising therapeutic approaches. Sleep disturbances such as reductions in slow-wave and REM sleep, as well as fragmented sleep architecture, are among the earliest symptoms and contribute to cognitive decline through impaired memory consolidation and altered clearance of neurotoxic proteins. Drugs such as suvorexant and melatonin show promising results. Despite extensive research over the years, effective therapy for neuropsychiatric symptoms remains elusive. In this review, current understanding of the neuropsychiatric symptoms and their therapy is highlighted.

KEYWORDS

Alzheimer's Disease, Neuropsychiatric Symptoms, Depression, Apathy, Psychosis, Agitation, Sleep Disturbances

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1. Introduction

Alzheimer's disease (AD) has been identified by the World Health Organization as a critical global public health concern[1]. It is currently estimated that approximately 6.9 million Americans aged 65 and older are living with AD. In the absence of significant medical advances aimed at preventing or curing the disease, this figure is projected to increase to 13.8 million by 2060[2]. The accumulation of amyloid-β (Aβ), neurofibrillary tangles, progressive synaptic loss and gliosis represent the core neuropathological features of Alzheimer's disease. However, the primary initiating mechanisms and drivers of disease progression remain incompletely understood[3]. A minority of AD cases are caused by autosomal dominant mutations in the APP, PSEN1, or PSEN2 genes, typically leading to early-onset AD. In contrast, most individuals develop late-onset Alzheimer's disease, which occurs later in life and arises sporadically[4]. Early manifestations of Alzheimer's disease may appear several years prior to diagnosis and include alterations in mood, increased anxiety, sleep disturbances, apathy, and social withdrawal. As AD progresses, cognitive and behavioral symptoms may emerge, such as impaired decision-making, disorientation, agitation, aggression, and neuropsychiatric features like delusions and hallucinations[5]. Neuropsychiatric symptoms (NPS) are recognized as integral features in patients with Alzheimer's disease, characterized by a diverse array of behavioral and psychological disturbances[6]. Studies indicate the importance of recognizing and managing the NPS as they are linked to a high risk of institutionalization, increased functional impairment in activities of daily living, decreased quality of life, and an accelerated progression to advanced stages of dementia[7]. Growing evidence suggests that neuropsychiatric symptoms may arise from dysfunction in specific neural circuits, particularly within prefrontal and subcortical regions exhibiting structural and functional abnormalities. The monoaminergic neurotransmitter systems—norepinephrine, serotonin, and dopamine—play crucial roles in modulating these circuits and are significantly affected by AD pathology[8]. Among neuropsychiatric symptoms, depression and apathy are the most commonly reported in individuals with mild cognitive impairment and early-stage Alzheimer's disease. However, elevated rates of agitation are also observed across all stages of AD. As the disease progresses, symptoms such as delusions, hallucinations, sleep disturbances, agitation and aggression tend to become more prevalent. Notably, apathy emerges as the most persistent neuropsychiatric symptom throughout the course of Alzheimer's disease[9].

Materials and methods: As a narrative review, we conducted a literature search to examine the most prevalent neuropsychiatric symptoms in individuals with Alzheimer's disease, their extensive impact on patients' daily functioning, and both current and emerging therapeutic approaches. Bibliographic research was performed in August 2025. The articles were selected using PubMed and open-access databases search, employing keywords related to neuropsychiatric symptoms in AD. A total of 45 articles were incorporated for the analysis.

2. Results - Neuropsychiatric symptoms in Alzheimer's disease

2.1 Depression

Depression represents one of the most common neuropsychiatric manifestations in Alzheimer's disease (AD), particularly during the early stages of the illness and in individuals with mild cognitive impairment (MCI). The presence of depressive symptoms in patients with MCI or early AD may serve as a significant indicator of disease progression, as evidence suggests that these individuals are more likely to experience accelerated cognitive decline over time. As the disease advances, depressive symptoms often diminish, while apathy emerges as a more persistent and prevalent feature across all stages of AD. Despite increasing recognition of the clinical relevance of depression in AD, the underlying mechanisms linking these conditions remain largely unclear and are likely associated with neurodegenerative changes characteristic of the disorder[9]. The prevalence of depression in Alzheimer's disease varies widely depending on diagnostic criteria and study design. Estimates range from approximately 13% based on DSM criteria to 42% using dementia-specific criteria, with population-based studies generally reporting lower rates than single-source studies. Patients with severe AD tend to show higher prevalence according to dementia-specific criteria, highlighting the need to consider both assessment methods and study settings when evaluating depression and planning interventions in this population[10]. Postmortem research indicates that major depressive disorder (MDD) may share underlying neuropathological features with Alzheimer's disease (AD), particularly involving disruptions in myelin and oligodendrocyte populations in the frontopolar cortex. Reductions in oligodendrocytes and their progenitors, along with altered fatty acid composition, may impair neural circuits critical for mood and cognition. As these cells also express AD-related proteins, such abnormalities could

contribute to increased susceptibility to AD later in life, suggesting that defective myelination might represent a common pathophysiological link between MDD and AD[11]. Microglia, the brain's resident immune cells, are central to the pathophysiology of neuroinflammation and play a critical role in Alzheimer's disease. Dysfunction of microglia may contribute to depressive symptoms in AD, as they act both as a source and a target of pro-inflammatory cytokines. Clinical and experimental evidence indicates that elevated levels of microglia-derived cytokines are associated with both depression and AD progression, suggesting that neuroinflammatory processes driven by microglia may link the pathogenesis of depression with neurodegeneration[12]. A Delphi study involving 53 Italian specialists in Alzheimer's disease highlighted that depression is a common and clinically significant symptom in AD, although its diagnosis remains challenging due to the lack of specific diagnostic criteria. Conventional DSM-5 criteria for major depressive disorder may not fully capture the unique presentation of depression in this population. Experts generally recommend the use of antidepressant medications, particularly SSRIs and multimodal agents, to minimize side effects, with vortioxetine emerging as a promising option due to its potential pro-cognitive effects. Consensus was reached in 86% of cases, reflecting a relatively consistent clinical approach to managing depression in AD despite the absence of formal guidelines[13]. The article by Shaobin Yang et al., published in Current Neuropharmacology in 2024, examines the bidirectional relationship between depression and Alzheimer's disease (AD), focusing on shared pathophysiological mechanisms associated with glucose metabolism abnormalities. The study highlights the role of the hypothalamic-pituitary-adrenal (HPA) axis, insulin resistance, glucose transporters, and oxidative stress as key elements in the pathogenesis of both disorders. Understanding these interactions opens new therapeutic opportunities, suggesting that improving glucose metabolism through lifestyle modifications, pharmacological interventions, or innovative therapeutic approaches may represent a promising strategy for the simultaneous treatment of both conditions[14]. Management of depression in Alzheimer's disease requires a careful, stepwise approach. Initial assessment should comprehensively evaluate the patient's mood, cognitive status, medical conditions, and environmental factors that might contribute to depressive symptoms. Non-pharmacological strategies, including structured daily routines, engagement in meaningful activities, and caregiver support and education, are recommended as the first line of intervention. When depressive symptoms are severe, persistent, or accompanied by suicidal ideation, pharmacological treatment may be warranted, typically beginning with low doses of selective serotonin reuptake inhibitors (SSRIs) due to their favorable safety profile. In cases where first-line agents are insufficient or poorly tolerated, alternative antidepressants targeting different neurotransmitter systems, or adjunctive therapies addressing agitation or psychotic features, may be considered. For refractory or high-risk cases, referral to a specialist in geriatric psychiatry or consideration of electroconvulsive therapy (ECT) may be appropriate. Treatment should be individualized, closely monitored, and adjusted based on both therapeutic response and tolerability[15]. According to the review by Madia Lozupone et al., treating depression in Alzheimer's disease remains a significant challenge due to its complex and potentially distinct underlying mechanisms. While SSRIs such as sertraline and citalopram have been the most frequently studied, their effectiveness is inconsistent, prompting the exploration of alternative therapies. Emerging treatments, including vortioxetine and ketamine metabolites (e.g., hydroxynorketamine), show promise by targeting glutamatergic signaling and synaptic plasticity, while personalized approaches considering genetic factors, including APOE status, may further improve treatment outcomes. Non-pharmacological interventions should continue as first-line strategies, and well-designed clinical trials are needed to establish safe and effective therapies for this population[16].

2.2 Apathy

Apathy represents a multidimensional syndrome in which individuals show a marked decline in spontaneous initiative, diminished pursuit of cognitive endeavors, and reduced emotional responsiveness. Within the spectrum of neuropsychiatric features in Alzheimer's disease, it consistently emerges as the most widespread. Estimates vary depending on the setting, with roughly half of patients in outpatient clinics exhibiting apathy, about one-third in community-based cohorts, and longitudinal data suggesting that more than 70% of patients experience it within five years[17]. Emerging evidence indicates that apathy arises from disruptions in frontal–subcortical loops, with the anterior cingulate cortex (ACC) serving as a key regulatory hub. Altered functioning within the ACC–striatal–thalamic pathway appears to undermine the ability to initiate and sustain goal-directed behavior. Rather than representing a purely emotional or cognitive deficit, apathy reflects a breakdown in the neural systems that integrate motivational drive with executive control. In Alzheimer's disease, as well as in other neuropsychiatric conditions, dysfunction of these circuits may help explain the pervasive difficulties patients face in translating intentions into purposeful actions[18]. Functional

imaging studies have demonstrated that the anterior cingulate cortex shows atypical patterns of activity, which are closely linked to diminished drive and reduced participation in everyday tasks. In parallel, neurochemical investigations point to disturbances in key transmitter systems—most notably dopaminergic and serotonergic pathways—that may further intensify apathetic features. From a cognitive standpoint, apathy in Alzheimer's disease is frequently characterized by deficits in higher-order executive abilities, difficulties in modulating affective responses, and compromised social processing, all of which interfere with the capacity to plan, initiate, and sustain purposeful actions[19]. In a study by Antonio L. Teixeira examining risk factors for apathy in Alzheimer's disease, 13,280 articles were screened, with 13 meeting inclusion criteria. The studies followed 2,012 participants for an average of 2.7 years, and most findings were based on single studies of moderate quality. Apathy onset was more likely in carriers of the T allele of the PRND gene and in individuals with elevated baseline IL-6 and TNFα levels. Progression of apathy was associated with thinner inferior temporal cortex, antidepressant use, ApoE ε4 carriage, longer disease duration, lower cognitive scores, higher initial apathy, premorbid personality traits (lower agreeableness, higher neuroticism), and greater midlife motivational capacity. Although limited by the small number of studies, the findings point to specific genetic, neurobiological, disease-related, and personality factors that may influence the development and worsening of apathy in Alzheimer's disease[20]. A large study by Myuri T. Ruthirakuhan et al., including 6,384 patients with Alzheimer's disease, provides important insights into pharmacological approaches for apathy. Across 21 randomized trials, methylphenidate emerged as the most promising intervention, showing potential to reduce apathetic symptoms and modestly improve cognition and daily functioning. Other agents, such as modafinil, cholinesterase inhibitors, antipsychotics, antidepressants, and valproate, demonstrated insufficient or inconsistent effects. However, the overall quality of evidence was limited due to small study numbers, methodological variability, and risk of bias. In many studies, apathy was assessed only as a secondary outcome, further limiting interpretability. These findings highlight the need for larger, long-term trials specifically targeting clinically significant apathy to better determine the efficacy of methylphenidate and other potential therapies[21]. Although no approved treatment currently exists, recent evidence points toward potential benefits of targeting catecholaminergic systems. Methylphenidate, the most extensively studied agent, appears to alleviate apathy by modulating both dopaminergic and noradrenergic signaling, thereby enhancing reward sensitivity and effort allocation. Noradrenergic involvement is particularly compelling given the role of the locus coeruleus in regulating motivation and its early degeneration in Alzheimer's and Parkinson's disease. While practical limitations restrict the use of methylphenidate in routine care, agents such as atomoxetine may provide alternative strategies, though further controlled studies are needed. Collectively, these findings suggest that repurposing drugs with established safety profiles offers a promising avenue for addressing apathy in neurodegenerative disorders[22].

2.3 Psychosis

Psychosis is characterized by the occurrence of delusions, hallucinations, and phenomena such as delusional misidentification. More than 50% of patients diagnosed with AD are expected to develop psychotic symptoms over the course of the disease. In the context of dementia, psychotic symptoms, once they emerge, tend to be long-lasting, with approximately 2/3 of affected individuals experiencing their persistence for a minimum duration of one year[23]. Neuroimaging evidence in AD patients with psychosis, particularly delusions, has revealed structural and functional alterations across key brain regions. Gray matter volume reductions are most observed in the frontal cortex, particularly the right frontal lobe, with additional involvement of medial temporal, parietal, and insular regions. Structural atrophy specifically affecting the parahippocampal and temporal cortices is associated with misidentification syndromes. SPECT and FDG-PET similarly indicate hypometabolism and hypoperfusion in neocortical areas, notably the frontal, orbitofrontal, insular, and temporal regions. Functional imaging thus converges on a model in which disruption of frontal-temporal circuitry and associated networks underlies the development of psychotic symptoms in AD[24]. In individuals with Alzheimer's disease, delusions and hallucinations have been linked to distinct clinical profiles. Delusions are more commonly associated with older age, depressive symptoms, and aggressive behavior, while hallucinations tend to correlate with increased dementia severity and longer disease duration[25]. Diagnosing psychotic symptoms in the context of cognitive decline presents significant clinical challenges. In AD, delusions are reported in approximately 35% of patients. Common themes include theft, persecution, infidelity, abandonment, and the belief that deceased individuals are still alive. Although, complex or systematized delusional content, such as erotomania, religious preoccupations, generalized suspiciousness such as fears of being harmed, has also been observed. Misidentification delusions including Capgras delusion (believing a familiar person has been replaced by an imposter), the phantom boarder delusion (believing strangers are living

in one's home), or misidentifying family members as unfamiliar[23,25]. Hallucinations are another core psychotic manifestation, with a median prevalence of 23% across studies. While they can involve multiple sensory modalities, visual hallucinations are the most common, whereas auditory ones are rare. Visual hallucinations most frequently involve the perception of people or animals, but may also include faces, deceased individuals, colors, inanimate objects, or vague, unstructured forms. Auditory hallucinations may encompass simple sounds as well as more elaborate experiences such as hearing full conversations[23,25]. However, no pharmacological treatments for psychosis in AD have received regulatory approval. In recent years, novel compounds have been investigated as potential therapeutic strategies[26]. Pimavanserin (a selective 5-hydroxytryptamine 2A inverse agonist) is the only antipsychotic drug approved for psychosis in Parkinson's disease. In AD, a phase 2 clinical trial conducted in nursing home residents demonstrated moderate efficacy of pimavanserin in reducing symptoms within the delusions and hallucinations domains with more pronounced effects observed among participants with more severe psychotic symptoms. However, in a subsequent phase 3 clinical trial involving individuals with various types of dementia, the statistically significant reduction in relapse risk was primarily driven by the PD subgroup, with no significant benefit observed in AD[27]. Atypical antipsychotics, such as risperidone, olanzapine, aripiprazole, quetiapine, remain the most commonly employed pharmacological agents for managing psychosis in AD, though their use is associated with modest efficacy and a heightened risk of adverse events, including cerebrovascular diseases, increased fall risk, cognitive deterioration, and elevated mortality. Among these agents, aripiprazole and risperidone have shown some therapeutic efficacy in meta-analyses, though tolerability—particularly for risperidone—remains a concern in the AD population[28]. This individual patient data meta-analysis demonstrates that cholinesterase inhibitors such as donepezil and rivastigmine, show modest but statistically significant reductions in psychotic symptoms such as delusions and hallucinations among patients with AD[29].

2.4 Agitation

Agitation and aggression are commonly observed in Alzheimer's disease and pose substantial challenges for patients, caregivers, and the healthcare system[30]. It is related to 45% of patients with AD[31]. Agitation is defined by excessive motor activity, verbal and physical aggression, such as shouting, cursing loudly, kicking, shoving, and hitting. Agitation contributes to functional impairment and cannot be fully explained by other conditions. This symptomatology is associated not only with accelerated cognitive decline, loss of functional independence, progression to advanced stages of AD, and increased mortality, but also with considerable caregiver burden. Additionally, agitation contributes to greater demands on clinical supervision, earlier institutionalization, and elevated healthcare expenditures[8,31]. Impairments in monoaminergic neurotransmitter systems may underlie agitation by altering the functional equilibrium between prefrontal and subcortical brain circuits essential for regulating behavior. Consequently, these systems represent promising therapeutic targets for alleviating agitation[8]. In 2023, brexpiprazole became the first therapy approved by the FDA for agitation associated with AD. Its therapeutic effects are believed to result from partial agonist activity at serotonin 5-HT1A and dopamine D2 receptors, combined with antagonist activity at serotonin 5-HT2A receptors[32]. Brexpiprazole is typically well tolerated, with frequently reported side effects including dizziness, headache, insomnia or drowsiness. Similar to other antipsychotic medications, brexpiprazole has been linked to an increased risk of mortality compared to placebo[32]. Nonetheless, in numerous other countries, no pharmacological agent has been officially approved for the treatment of agitation, leading to the widespread off-label use of medications that often lack evidence of efficacy and may present severe side effects[31]. Recent preclinical and early clinical studies have indicated interest in cannabinoids as potential therapeutic agents for agitation, given their anxiolytic, antidepressant, and anti-inflammatory functions. CBD and THC may help alleviate agitation by modulating neurotransmitter systems, addressing comorbid conditions, circadian disruptions, and enhancing cerebral blood flow. Cannabinoids may exert therapeutic effects in agitation by enhancing serotonergic tone through increased availability of tryptophan (serotonin precursor), potentially ameliorating mood and behavioral symptoms. Moreover, they inhibit glutamate release and reduce oxidative stress and tumor necrosis factor-α–mediated neuroinflammation, thereby modulating excitatory neurotransmission and inflammatory signaling[33]. Non-pharmacological interventions play a fundamental role in the management of agitation, focusing on increasing patients' quality of life. The strategies include structured daily routines to reduce confusion, modifying the environment to create a calm and safe setting, and training caregivers to recognize early signs of agitation. Additionally, music therapy, aromatherapy, and multisensory stimulation, have demonstrated efficacy in reducing agitation by regulating emotional and behavioral responses[34].

2.5 Aggression

Chemerinski and colleagues investigated the occurrence and clinical correlates of aggressive behavior in a cohort of 196 patients with Alzheimer's disease. They found that approximately 12% of participants exhibited aggression, with physical aggression observed in 7% and verbal aggression in 5% during the four weeks preceding psychiatric assessment. Physical aggression was predominantly associated with delusional ideation and heightened irritability, whereas verbal aggression correlated with a shorter disease duration. No significant differences were noted in overall cognitive decline or other psychiatric comorbidities, including depression, apathy, anxiety, emotional lability, or anosognosia, between aggressive and non-aggressive patients. The study highlights that aggressive outbursts in AD are frequently linked to irritability and psychotic symptoms, and emphasizes the importance of standardized assessment tools and longitudinal research to better understand the evolution and determinants of aggression in this population[35]. Agitation and aggression are common in Alzheimer's disease and are linked to poor clinical outcomes, yet their underlying neurobiology remains poorly characterized. Current evidence suggests associations with neuropathological changes, neuroimaging markers, neurotransmitter alterations, APOE genotype, inflammatory processes, and clusterin levels, although findings are often inconsistent, particularly regarding neuropathology and APOE status. Variability in assessment methods, symptom severity, and the heterogeneous nature of agitation likely contribute to these discrepancies. At present, no biomarker can be considered definitive for diagnosing or monitoring agitation/aggression. Identifying reliable biomarkers could facilitate early detection, patient stratification, and personalized interventions, highlighting the need for longitudinal studies to uncover predictive and prognostic indicators[36]. Impairment of the serotonergic system is a well-recognized feature in Alzheimer's disease and has been closely linked to the emergence of aggressive behaviors. Dysregulation of serotonin signaling may exacerbate irritability and impulsivity, contributing to both verbal and physical aggression in affected patients. Understanding the role of serotonergic dysfunction provides a critical rationale for exploring targeted pharmacological interventions aimed at mitigating aggression in AD, potentially improving both patient outcomes and caregiver burden[37].Criminal and antisocial behaviors, including aggression, can emerge in neurodegenerative disorders due to impairments in judgment, executive function, emotional regulation, and self-awareness. A retrospective review of over 2,300 patients with dementing illnesses found that such behaviors were relatively uncommon in Alzheimer's disease (≈8%), but considerably more frequent in behavioral variant frontotemporal dementia and semantic variant primary progressive aphasia. In Alzheimer's disease, these behaviors typically manifested as cognitive-related traffic violations, whereas in frontotemporal syndromes, they included theft, sexual misconduct, trespassing, and public urination. The findings suggest that new-onset aggressive or antisocial behavior in adults should prompt evaluation for frontal and anterior temporal lobe pathology and highlight the need for tailored clinical and legal approaches to these patients[38]. Rongqin Yu and colleagues conducted a comprehensive synthesis of primary studies to quantify the likelihood of aggressive behaviors in individuals with Alzheimer's disease (AD) and mild cognitive impairment (MCI). Their meta-analytic findings indicate that patients with AD exhibit a markedly elevated propensity for aggression compared to cognitively healthy peers, whereas the risk among those with MCI appears comparatively modest. Moreover, the comparative analysis between AD and MCI underscores a pronounced escalation of aggressive tendencies with disease progression. These observations highlight the clinical imperative for early identification and management of behavioral disturbances in AD and suggest that interventions targeting the prodromal stages may mitigate the evolution of aggression[39]. In recent years, significant research efforts have focused on developing novel antipsychotic therapies for the management of agitation and psychosis in Alzheimer's disease (AD), two behavioral and psychological symptoms of dementia (BPSD) closely associated with disease progression and cognitive decline. Conventional long-term administration of second-generation antipsychotics carries elevated risks of mortality and cerebrovascular complications, underscoring the urgent need for safer and more effective alternatives. Emerging pharmacologic options, such as brexpiprazole and pimavanserin, have demonstrated promising clinical potential. Brexpiprazole, a partial agonist at D2, D3, and 5-HT1A receptors and antagonist at 5-HT2A/B and adrenergic α1B/α2C receptors, has shown meaningful efficacy in controlling agitation in AD while exhibiting an improved tolerability and safety profile compared to traditional antipsychotics. Pimavanserin, a selective 5-HT2A/2C receptor antagonist already approved for Parkinson's disease psychosis, has shown preliminary efficacy in AD patients with severe psychotic manifestations. However, additional long-term studies are necessary to fully establish its therapeutic value and safety, particularly regarding cardiac effects such as QT interval prolongation[40]. Synthetic cannabinoids, including dronabinol and nabilone, offer a potential therapeutic alternative for managing agitation and aggression in Alzheimer's disease, with a potentially

improved safety profile compared to traditional antipsychotics. These agents act on CB1 and CB2 receptors, influencing neuroinflammatory pathways, pain, and other mechanisms relevant to AD symptomatology. Early clinical data indicate beneficial effects, though studies have been limited by small cohorts, brief treatment periods, and concomitant psychoactive medications. Importantly, severe adverse events commonly reported with cannabinoids in other populations appear minimal in AD, likely due to lower dosages. Future randomized controlled trials are needed to establish efficacy, long-term safety, and receptor-specific mechanisms, particularly targeting CB2-mediated modulation of inflammation and behavioral disturbances. Such research could expand pharmacological options for behavioral management in moderate-to-severe AD, where current treatments remain suboptimal[41].

2.6 Sleep disturbances

Sleep disturbances are typically defined by diminished sleep duration and quality, decreased sleep efficiency, heightened nocturnal awakenings, and elevated levels of daytime sleepiness. These conditions represent one of the earliest symptoms of AD and are associated with impaired memory consolidation, reduced clearance of metabolic waste products from synapses, including β-amyloid[42]. Individuals diagnosed with AD experience sleep disruptions, such as nocturnal awakenings, insomnia, hypersomnia, restless legs syndrome and circadian rhythm abnormalities resulting in a decreased total sleep time and efficiency. Several studies have identified sleep disturbances during the preclinical stages as potential predictors of dementia onset. Sleep disorders are present in roughly one-third of individuals with MCI[42,43]. Recent findings demonstrated that alterations in slow-wave sleep (SWS), indicated by reduced delta spectral power, were significantly associated with elevated amyloid-β (Aβ) levels, highlighting a potential regulatory role of SWS in the modulation of Aβ accumulation within the brain[44]. Other studies suggested that slow-wave EEG activity, particularly in the 1–2 Hz range, may serve as an early biomarker for tau pathology in preclinical or early AD. REM sleep plays a critical role in maintaining neuronal homeostasis, and its disruption has been linked to impaired neurogenesis and potential neurodegeneration. Researchers found that REM sleep disturbances were associated with elevated cerebrospinal fluid orexin levels in individuals with MCI. Increased orexin has been correlated with higher tau protein levels, indicating that orexinergic system dysregulation may reflect accelerated tau-related neurodegeneration in AD[44]. REM sleep disturbances are thought to result from cholinergic system dysfunction as the disease progresses. Degeneration of the basal forebrain in AD reduces cortical activation during REM sleep. Similarly, quantitative EEG analyses have revealed increased theta and delta power, along with decreased alpha and beta activity during REM sleep in individuals with AD[43]. Decreased amount of SWS and REM sleep is associated with decreased cognitive ability and may be promising targets for AD therapy. AD dementia is associated with reductions in characteristic features of N2 light sleep, including diminished sleep spindles and K-complexes with lower amplitude and frequency. These changes tend to intensify with dementia progression and differentiating between N1 and N2 stages becomes difficult. Some researchers refer to the indistinct sleep architecture observed in late-stage AD as indeterminate non-REM sleep[43]. There are multiple targets for sleep management in AD. The current research is focused on pharmacological and non-pharmacological treatment options. Suvorexant has shown the most promising results in individuals with mild AD. It prolonged total sleep time, increased sleep efficiency, and reduced night-time awakenings. However, these benefits were primarily evident in individuals with milder cognitive impairment (MMSE 21–26), with less effect observed in more advanced cases.Several trials suggest that melatonin may be effective in shortening sleep onset latency and decreasing nocturnal awakenings. It may enhance slow-wave activity, contributing to better sleep depth and stability. Nevertheless, the limited sample sizes constrain the generalizability of these findings[45]. AChEIs are commonly prescribed in early cognitive decline, however their role in sleep modulation remains uncertain. Early hypotheses linked acetylcholine with REM sleep regulation, yet clinical trials have not consistently demonstrated sleep benefits. Donepezil has been associated with side effects such as vivid dreaming and insomnia, and current evidence does not support its use for improving sleep. Continuous positive airway pressure therapy in individuals with cognitive impairment has demonstrated positive effects on sleep structure and quality[45].

3. Discussion:

Neuropsychiatric symptoms (NPS) are now widely acknowledged as a central and defining component of Alzheimer's disease (AD). Although cognitive decline remains the diagnostic cornerstone, it is increasingly evident that behavioral and psychiatric disturbances shape the lived experience of both patients and caregivers to an equal, if not greater, extent. Their frequency, variability across stages, and substantial impact on daily functioning argue strongly against viewing them as secondary complications. Rather, they should be regarded as core manifestations of the disease. The origins of NPS in AD are complex and multifactorial. Accumulating evidence suggests that neuropathological processes, particularly amyloid-β deposition and tau pathology, interact with disruptions in neurotransmitter systems, synaptic dysfunction, and neuroinflammatory mechanisms. Neuroimaging studies consistently highlight involvement of frontal, temporal, and limbic circuits, while post-mortem findings suggest selective vulnerability of fronto-striatal and cingulo-parietal networks. These biological mechanisms interact with psychosocial factors, such as social isolation or caregiver stress, producing the highly heterogeneous clinical picture observed in practice. This heterogeneity complicates both research and clinical management, as symptoms often fluctuate, overlap, and evolve with disease progression. Among the earliest NPS to emerge are depression and apathy. Depression has long been debated as either a prodrome of AD or an independent risk factor, and recent longitudinal studies suggest that persistent depressive symptoms may accelerate hippocampal atrophy and cortical thinning. Clinical trials, however, provide mixed results regarding whether treatment of depression alters the trajectory of cognitive decline. Apathy, by contrast, tends to be more stable and less responsive to intervention. Characterized by reduced motivation, diminished goal-directed behavior, and emotional blunting, apathy strongly predicts loss of independence and caregiver strain. Its resistance to current pharmacological approaches underscores the need for more targeted therapies. Psychotic manifestations, particularly delusions and hallucinations, are more common in moderate to advanced AD. Their presence is clinically significant because they are associated with faster cognitive deterioration, greater functional impairment, and earlier institutionalization. Neurobiological models implicate disruption of fronto-temporal connectivity and altered dopaminergic and serotonergic signaling, yet reliable biomarkers remain elusive. Treatment remains difficult: while atypical antipsychotics can provide symptomatic relief, they carry risks of sedation, cardiovascular events, and increased mortality. The recent approval of brexpiprazole and trials of pimavanserin represent important steps forward, though their long-term safety and efficacy in this population remain to be clarified. Agitation and aggression represent some of the most disruptive and burdensome NPS, often co-occurring with psychosis, depression, or anxiety. These behaviors not only endanger patients themselves but also contribute to caregiver burnout and crisis-driven institutionalization. Evidence indicates that non-pharmacological interventions—structured daily routines, environmental modifications, music therapy, or caregiver training—can reduce symptom severity and delay the need for pharmacological treatment. Nonetheless, in severe cases, medication is often unavoidable, highlighting the need for better-tolerated pharmacological options.Sleep disturbances, although sometimes overlooked, are emerging as both clinically and biologically important. Reduced slow-wave sleep and disrupted REM cycles have been linked to impaired clearance of amyloid-β through the glymphatic system. This suggests a bidirectional relationship: poor sleep may accelerate pathology, while pathological burden further disrupts sleep regulation. Clinically, this positions sleep disturbances as both early warning signs and potential therapeutic targets. Interventions such as light therapy, cognitive-behavioral approaches, or judicious use of sleep-promoting agents may therefore play a role not only in symptom management but also in modifying disease progression. Current pharmacological strategies for NPS are limited. Antidepressants, mood stabilizers, and antipsychotics provide only partial benefit and are associated with significant side effects in older adults. Emerging treatments targeting the glutamatergic and endocannabinoid systems are under investigation, and stimulants such as methylphenidate have shown some promise for apathy. However, most of these approaches remain experimental, and robust, long-term data are still lacking. This underscores the need for personalized treatment strategies that account for individual symptom profiles, comorbidities, and patient preferences. Non-pharmacological interventions remain essential, and their importance cannot be overstated. Tailored psychosocial programs, caregiver education, and environmental adaptations can significantly reduce symptom burden. Importantly, these approaches align with broader calls for person-centered dementia care, which seeks to preserve dignity and quality of life. Implementation, however, is uneven across healthcare systems, with barriers including lack of trained personnel, limited resources, and inadequate integration of psychosocial care into standard clinical practice.The implications of NPS extend far beyond individual patients. They are major drivers of healthcare utilization, institutionalization, and overall cost of dementia care. Caregivers of patients with prominent NPS experience higher rates of depression, anxiety, and physical illness, reflecting the

reciprocal burden of these symptoms on families and communities. From a health policy perspective, integrating NPS into dementia care planning, funding, and caregiver support programs is essential to address the societal impact of AD. Taken together, the available evidence underscores the centrality of NPS in Alzheimer's disease. Their biological underpinnings are multifaceted, their clinical presentations heterogeneous, and their management challenging. Progress will require a shift away from cognition-centric frameworks toward more comprehensive models that integrate behavioral, emotional, and psychosocial dimensions of the disease. Future research should prioritize biomarker discovery, targeted pharmacological innovation, and scalable non-pharmacological interventions. Only through such an integrative approach can the full complexity of AD be addressed, offering better outcomes for patients and their caregivers alike.

4. Conclusions

Neuropsychiatric symptoms in Alzheimer's disease are not ancillary features but a defining part of the clinical picture. They emerge in diverse forms—depression, apathy, psychosis, agitation, aggression, and sleep disturbances—at different points in the disease course. Their influence extends well beyond the patient, shaping daily life and often placing a disproportionate strain on caregivers. Despite notable advances in understanding their neurobiological foundations, therapeutic progress has been slow. Pharmacological treatments, while sometimes helpful, rarely provide robust or sustained benefits and frequently introduce new risks, particularly in frail older adults. Non-pharmacological interventions, on the other hand, are consistently safer and, in many cases, more acceptable to families. Still, their uptake is uneven, and in everyday practice they are too often applied late or inconsistently. Clinically, this highlights the importance of vigilance and early recognition. Symptoms such as apathy or subtle mood changes can be overlooked or misattributed, yet they carry prognostic weight and demand timely response. What seems most effective is not a single solution but rather a combination: pharmacological measures when strictly necessary, integrated with psychosocial support and caregiver guidance. This requires interdisciplinary collaboration and, crucially, flexibility, since symptom profiles vary widely between patients. From a research perspective, the field is still searching for reliable biomarkers and more precise therapeutic targets. The heterogeneity of symptom expression makes progress difficult, but it also underlines the need for approaches that can accommodate this variability rather than impose uniform solutions. On a broader scale, and perhaps less frequently acknowledged, is the challenge of system-level adaptation. Public health strategies, professional training, and long-term care planning should more explicitly recognize neuropsychiatric symptoms as core elements of Alzheimer's disease. Without such recognition, improvements at the clinical or research level risk being diluted by gaps in service delivery. Taken together, these points suggest a shift in perspective: Alzheimer's disease cannot be fully understood, nor adequately managed, if neuropsychiatric symptoms are treated as peripheral. Addressing them directly is essential if care is to become more humane, more sustainable, and ultimately more effective.

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