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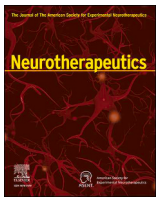

Review

Neuropsychiatric symptoms in Alzheimer's disease: Bridging mechanisms, management, and emerging innovations☆

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ABSTRACT

Neuropsychiatric symptoms (NPS) are among the most distressing and functionally disruptive features of Alzheimer's disease (AD), affecting the vast majority of individuals across the disease continuum. These symptoms, ranging from apathy and depression to agitation and psychosis, not only worsen quality of life but also predict faster decline, earlier institutionalization, and heightened caregiver burden. Yet, despite their clinical significance, NPS remain under-recognized and undertreated. This review synthesizes current understanding of the biological underpinnings of NPS in AD, highlighting network-level dysfunction, neurotransmitter imbalances, neuroinflammation, and emerging roles for tau pathology and circadian disruption. We critically examine current treatment paradigms, noting that pharmacologic interventions offer benefit but often carry significant risks. In contrast, non-pharmacological approaches, particularly those that integrate caregiver training, environmental design, and sensory engagement, hold promise but are inconsistently applied in routine care. Emerging innovations, including neuromodulation, repurposed agents (e.g., beta-blockers, cannabinoids), and digital therapeutics such as virtual reality and AI-enabled monitoring tools, offer new therapeutic avenues. We call for a paradigm shift toward person-centered, mechanistically-informed care that aligns intervention strategies with biological drivers of NPS. Future progress hinges on inclusive clinical trials, implementation of first-line behavioral strategies, and development of biomarker-guided, precision approaches to symptom management. Effective care for NPS in AD demands integration, not substitution, of pharmacologic and non-pharmacologic strategies, grounded in a deeper understanding of both disease biology and lived patient experience.

Introduction

Alzheimer's disease (AD) is the most prevalent neurodegenerative disorder worldwide [1]. Its clinical phase is characterized by both progressive cognitive decline and a spectrum of neuropsychiatric symptoms (NPS) that significantly impact patient quality of life, caregiver burden, and healthcare costs [1]. These symptoms, which range from agitation, aggression, and psychosis to apathy and depression, affect at least 90 % of individuals with AD dementia at some point during the disease course ([2]). NPS profoundly impact patients and caregivers [3]. Left unmanaged, NPS contribute to earlier institutionalization, increased morbidity, and greater functional impairment [3].

This review uses the term neuropsychiatric symptoms (NPS) in alignment with the existing literature, but it is important to acknowledge that this term may not fully capture the context-dependent nature of many dementia-related behaviors. Increasingly, clinicians and researchers advocate for framing such behaviors as responsive behaviors, which are expressions of unmet needs or distress rather than direct manifestations of neurobiological dysfunction alone [4,5]. For example, irritability in a person with dementia may reflect hunger, discomfort, or environmental overstimulation, but the individual may lack the cognitive, linguistic, or executive capacity to communicate their needs effectively. From this perspective, NPS arise at the intersection of neurodegenerative vulnerability, caregiver interpretation, and environmental context. This ecopsychosocial framework encourages a more holistic and compassionate approach to symptom management, reduces inappropriate medication use, and promotes non-pharmacologic interventions that address root causes. International guidelines often

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prefer the term behavioral and psychological symptoms of dementia (BPSD) for this reason, but we retain the term NPS in this manuscript for consistency with contemporary research.

Despite their clinical significance, NPS are underdiagnosed and undertreated, often overshadowed by a focus on cognitive decline, with current management strategies facing multiple limitations [6]. This is, in part, due to the heterogeneous presentations of NPS, which can vary widely between patients in terms of severity, symptom clustering, and progression over time. Pharmacological interventions, such as antipsychotics, antidepressants, and anticonvulsants, have shown modest efficacy and are often accompanied by side effects, including a "black box" warning for antipsychotics about increased mortality risk [7]. The U.S. Food and Drug Administration (FDA) approved brexpiprazole in May 2023 for agitation in AD dementia [7], but its long-term safety and real-world effectiveness remain under investigation, and its use requires careful risk-benefit consideration [8]. Another limitation of pharmacologic therapies is the incomplete understanding of the neurobiology underlying NPS, which hampers the development of targeted treatments. Other pharmacological treatments, such as lithium [9] or serotonin-targeting drugs [10], are used off-label (discussed in Section III).

Non-pharmacological approaches, such as cognitive-behavioral therapies, caregiver interventions, and structured environmental modifications, are effective in managing multiple NPS in AD dementia (e.g., agitation, depression, and apathy), but are inconsistently implemented in routine clinical practice [11]. Virtual reality (VR)-based therapies are being explored for reducing agitation and anxiety by creating immersive, calming environments tailored to patient experiences, potentially improving emotional regulation and engagement [12–14]. Other technologies include transcranial magnetic stimulation (TMS), which is being investigated as a neuromodulatory intervention targeting disrupted networks in the prefrontal cortex, with early evidence suggesting benefits in alleviating depression, apathy, and impulsivity [15]. However, barriers to widespread adoption persist, including high equipment costs, lack of standardized protocols, limited insurance coverage, and insufficient evidence from large-scale, long-term, controlled studies. Compounding these challenges is a misconception among general practitioners and specialists not trained in cognitive neurology and neuropsychiatry that agitation and behavioral disturbances in AD dementia are solely psychiatric in nature, leading to an overreliance on pharmacological approaches rather than patient-centered, integrated care approaches [6].

Given the urgent need for more effective and patient-centered interventions, this review provides an important perspective on current treatment paradigms, emerging therapeutics, and the translational challenges of integrating mechanistically informed strategies into real-world AD care.

Clinical relevance of neuropsychiatric symptoms (NPS) of Alzheimer's disease (AD) dementia and biological foundations

While this review focuses on NPS in the context of AD dementia, it is important to note that NPS often emerge earlier along the disease continuum. Mild Behavioral Impairment (MBI), a diagnostic construct that is a prodromal stage of dementia, captures later-life emergence of persistent NPS that may precede mild cognitive impairment (MCI) and signal elevated dementia risk [16]. Nearly half of individuals who eventually develop dementia exhibit neuropsychiatric symptoms before reaching the stage of MCI [17]. Thus, it is important to recognize these symptoms as potential early clinical indicators rather than only as consequences of advanced cognitive decline [17].

NPS in AD dementia are increasingly recognized as core features of the disease that influence patient outcomes, caregiver burden, and healthcare utilization [3]. These symptoms, including apathy, depression, anxiety, agitation, and psychosis, are prevalent across all stages of the illness and often predict functional decline, institutionalization, and mortality [3,18]more strongly than cognitive severity alone [19–21]. Caregiver response to NPS also plays an important role in impacting outcomes. High levels of caregiver distress have been associated with increased institutionalization risk and worsened patient trajectories [22–24]. Indeed, early identification and intervention for NPS, including both neurobiologically-driven symptoms and contextually-mediated behaviors, may mitigate later cognitive and functional deterioration, as well as improve caregiver well-being [25,26].

The same NPS that accelerate disease progression also represent some of the most challenging and consequential aspects of dementia care in real-world settings. Because approximately 70 % of people with dementia live in the community, a great deal of NPS management falls to family caregivers [27]. NPS are major drivers of care decisions, including increased utilization of paid home caregivers and premature institutionalization [3,28]. These increase the already high out-of-pocket costs of dementia care, exceeding that for any other condition [29]. Given the common use of privately hired informal companions and the standard practice of add-on fees at long-term care facilities, the out-of-pocket costs for NPS are likely greatly underestimated. Coping with these behaviorally and emotionally taxing symptoms is the main driver of stress among dementia caregivers [30], leading to disproportionately worse physical and mental health outcomes among dementia caregivers compared to those caring for individuals with other chronic illnesses [3,27]. Hospitalized patients with dementia are particularly vulnerable to NPS exacerbation and often face care environments ill-equipped to address their behavioral needs, which further complicates management and contributes to poor outcomes for this population [31].

Syndrome-based diagnostic criteria for NPS in Alzheimer's disease

Provisional consensus criteria have been developed to improve the characterization of neuropsychiatric syndromes in Alzheimer's disease and other cognitive disorders. The International Psychogeriatric Association guidelines propose diagnostic criteria for agitation, defined by the presence of emotional distress accompanied by excessive motor activity, verbal or physical aggression, or disinhibition, which represents a clinically significant change from baseline and persisting for at least two weeks [32]. These symptoms must cause functional impairment, be observed across multiple settings, and not be solely attributable to another psychiatric disorder or delirium. In parallel, provisional criteria for depression in AD have been proposed and emphasize symptoms such as pervasive sadness, loss of interest, and social withdrawal, while accounting for overlap with cognitive decline [33].

Symptomatology

NPS in AD do not occur in isolation. They frequently present as dynamic and overlapping symptom clusters that fluctuate over time and across disease stages. Depression is common, tends to emerge early in the disease course, and usually manifests with dysphoria, irritability, anxiety, social withdrawal, disrupted sleep, appetite changes (including weight loss), diminished energy, psychomotor slowing, difficulty concentrating, and a profound loss of interest or pleasure in previously enjoyed activities ("anhedonia") [34]. Depression before the onset of AD depression increases risk for later dementia; however, it may be underdiagnosed due to overshadowing by cognitive symptoms [35]. Apathy is also one of the most common and under-recognized symptoms, and is frequently mistaken for depression, but is distinct in its hallmark features: profound loss of motivation, diminished initiation of conversation or activity, social withdrawal, reduced emotional expression, and disengagement from previously enjoyed pursuits [36]. Agitation, one of the most distressing NPS for caregivers, can manifest as verbal outbursts (shouting, cursing, repetitive questioning), physical aggression (hitting, grabbing, pushing), pacing, restlessness, exit-seeking, and emotional lability such as sudden crying or anger [32].

This cluster of behaviors tends to peak in the moderate to severe stages of AD and often arises unpredictably in response to environmental triggers or internal distress, as one's ability to communicate needs becomes increasingly impaired [37]. Psychosis, though less common than other NPS, is highly disruptive when present and is characterized by delusions (false, fixed beliefs such as theft, infidelity, or misidentification of people) and hallucinations (most often visual, such as seeing people or animals who are not there) [32]. Psychotic symptoms in AD are strongly associated with agitation and portend accelerated cognitive decline, increased functional impairment, and heightened care needs [38].

Neurobiological and contextual drivers of neuropsychiatric symptoms

The neurobiology of NPS in AD involves distributed dysfunction across multiple brain systems and is not limited to classic Alzheimer's pathologies such as neuritic amyloid plaques or tau tangles. Alterations, such as imbalances in neurotransmitter systems, including cholinergic, serotonergic, glutamatergic, and dopaminergic pathways, contribute to behavioral dysregulation [39]. For instance, agitation and psychosis have been linked to dysregulation in serotonergic transmission and prefrontal-limbic circuit dysfunction, while apathy correlates with structural and functional disruption in the anterior cingulate cortex [40]. The literature also implicates tau pathology as a key driver of neuropsychiatric symptoms. Tau accumulation may contribute to MBI by disrupting the functional integrity of the salience network, which plays a critical role in emotional processing and network coordination [41].

Neuroinflammation [42,43] and circadian rhythm disturbances [44] have also been identified as contributors to the development or exacerbation of NPS in AD dementia, driving behavioral dysregulation through effects on neurotransmitter systems, stress responses, and sleep-wake cycles. Occult seizure activity, including subclinical epileptiform discharges, has also been implicated in worsening NPS [45]. New-onset epilepsy in AD dementia may represent an overlapping but distinct phenotype, sharing common neurobiological substrates with NPS [45]. In addition, co-pathologies such as cerebrovascular and subcortical disease further contribute to the emergence of NPS, particularly in mixed dementia presentations, where small vessel disease and white matter changes are common [46].

These pathophysiological insights are important for advancing precision therapeutics (e.g., pharmacologic and neuromodulation strategies), but the expression of NPS are also impacted by interpersonal, caregiver, and environmental dynamics. They are also impacted by interpersonal, caregiver, and environmental dynamics. Behaviors such as wandering, repetitive questioning, or verbal outbursts may arise not only from network-level neurodegeneration but also in response to unmet needs, caregiver distress, or environmental overstimulation. An ecopsychosocial model provides a broader framework that accounts for biological, psychological, and social-contextual factors.

Psychosocial and environmental contributors to neuropsychiatric symptoms

In addition to biological underpinnings, psychosocial and environmental mechanisms play a significant role in the development and maintenance of NPS. These symptoms often arise within interpersonal and ecological contexts that are misaligned with the person's needs. For instance, agitation and aggression have been associated with unmet physical or emotional needs, such as discomfort, loneliness, or fear, which the person with dementia may not be able to express verbally due to progressive aphasia or executive dysfunction [4,47,48]. Apathy and withdrawal may occur if environments lack stimulation or social engagement [49]. The quality of caregiver-patient relationships also influences symptom severity. High caregiver burden and poor emotional attunement are associated with more frequent behavioral disturbances, especially when caregivers misinterpret behaviors as intentional rather than disease-driven [47]. Behavioral symptoms should be understood not only as neurodegenerative sequelae, but as expressions of distress influenced by psychosocial dynamics and caregiving interactions.

Current therapies for neuropsychiatric symptoms in Alzheimer's disease

Pharmacological management of NPS in AD remains both a cornerstone of care and a source of ongoing controversy due to modest efficacy and notable safety concerns. There is guideline emphasis on non-pharmacologic strategies as first-line interventions [48], but, rightfully so, medications are frequently utilized, particularly in cases of moderate to severe agitation or psychosis that are distressing to patients or caregivers and difficult to manage [50].

Non-pharmacological interventions

Non-pharmacological approaches are endorsed as first-line treatments for NPS in all major guidelines, especially in community-dwelling individuals [48]. Structured behavioral interventions, such as the DICE model (Describe, Investigate, Create, Evaluate), identify antecedents to behavior and tailor interventions accordingly [51]. Although group-level benefits were not observed in a memory clinic trial, individuals with higher baseline NPS and caregiver distress appeared to benefit from the approach, indicating it may be most effective when targeted to people with AD dementia who have high-need cases [51]. Programs such as MIND at Home [52] and the recently launched GUIDE model [53,54] focus on interdisciplinary care management to prevent the escalation of NPS. Reminiscence therapy, activity-based engagement, and music therapy have also shown promise in reducing apathy, agitation, and depression [55].

In addition to these psychosocial and activity-based interventions, addressing sensory impairments, particularly hearing loss, offers a promising non-pharmacological avenue to reduce NPS [56]. A cross-sectional study of older adults with cognitive impairment reported that hearing aid use was independently associated with significantly fewer NPS, less dysphoria, and reduced symptom severity, even after controlling for cognitive function and medication use [56]. On average, hearing aid users had two fewer NPS and nearly four points lower total Neuropsychiatric Inventory-Questionnaire (NPI-Q) severity scores than non-users, as well as three points lower scores on the Cornell Scale for Depression in Dementia [56].

Training caregivers to respond to distress behaviors using communication techniques, structured routines, and emotional validation can also significantly reduce symptom severity and improve caregiver well-being [57]. Interventions such as REACH (Resources for Enhancing Alzheimer's Caregiver Health) [58] and the Savvy Caregiver [59] have led to improved coping, reduced stress, and delayed nursing home placement. Cognitive Behavioral Therapy (CBT) is another approach primarily studied for MCI and early-stage AD dementia, but modified forms have been piloted to treat comorbid depression and anxiety in persons with dementia [60]. Emerging practices combine CBT with caregiver involvement or deliver therapy via digital platforms to increase accessibility [60]. Music-based therapeutic interventions have also demonstrated benefits in reducing depressive symptoms [61]. Other promising modalities include environmental design changes, sensory interventions, and structured social engagement [62].

Cholinesterase inhibitors and memantine

Cholinesterase inhibitors (ChEIs; donepezil, rivastigmine, galantamine) and the NMDA receptor antagonist memantine are approved for cognitive symptoms in AD but may have favorable effects on NPS [63]. These agents likely mediate behavioral effects through enhancement of frontal-subcortical cholinergic circuits (ChEIs) and modulation of glutamatergic neurotransmission (memantine), influencing neural systems

involved in emotional regulation and motivational drive [64]. A meta-analysis demonstrated small but statistically significant improvements in global NPS scores with ChEIs, particularly in mild AD dementia (reduction of 1.38 points on the NPI), though the clinical significance of these modest effects is debatable [63]. Cholinergic therapies in particular may ameliorate NPS, particularly apathy, agitation, disinhibition, and psychosis, by enhancing cholinergic neurotransmission in frontal and temporal brain regions [65].

Importantly, clinical trials in more advanced AD populations provide evidence of behavioral benefit. In a randomized controlled trial of donepezil in patients with severe AD, treatment led to significantly greater improvements on the Severe Impairment Battery, a cognitive scale developed for advanced dementia that assesses attention, orientation, language, memory, praxis, visuospatial ability, and social interaction, and on the Clinician's Interview-Based Impression of Change Plus Caregiver Input, a global rating that integrates clinician observations with caregiver reports of cognitive, functional, and behavioral changes [66]. While there was a trend toward improvement in total NPI scores, changes in individual neuropsychiatric symptom domains did not reach statistical significance [66]. Rivastigmine was associated with significant reductions in eight of twelve NPI-Nursing Home domains, including delusions, hallucinations, agitation, apathy, irritability, aberrant motor behavior, nighttime disturbances, and appetite changes, among nursing home residents with moderate to severe AD who had NPS at baseline; nearly half experienced clinically meaningful (>30 %) improvements [67]. Furthermore, in a 24-week RCT of memantine added to donepezil in moderate to severe AD, combination therapy significantly outperformed placebo on all measured outcomes, including cognition, function, global clinical status, care dependency, and behavior, as measured by NPI total (−0.1 vs + 3.7 points; P = .002) [68].

Antidepressants: SSRIs and SNRIs

Depression in the context of early AD dementia or MCI should be approached similarly to later-life depression in general, with attention to overall psychiatric symptom burden, treatment tolerability, and patient preferences rather than assuming dementia-specific pharmacologic strategies are always necessary [69]. Selective serotonin reuptake inhibitors (SSRIs) are often prescribed for depression, anxiety, and agitation in AD. When agitation is the predominant symptom, SSRIs are generally preferred as first-line agents due to their more favorable safety profile compared to antipsychotics [32]. Notably, the Citalopram for Agitation in Alzheimer's Disease (CitAD) trial found that citalopram not only reduced agitation but also showed some benefit in reducing psychosis symptoms associated with agitation [70]. However, although citalopram showed modest efficacy for agitation in the CitAD trial, concerns about QT prolongation (though this risk is overstated) [71] and cognitive side effects limit enthusiasm for its widespread use [72]. Conversely, escitalopram yielded null results in a randomized controlled phase 3 trial [73]. Despite concerns about side effect profile, the CitAD trial has heavily influenced real-world clinical practice, where SSRIs, particularly citalopram or escitalopram, have been widely adopted as first-line pharmacologic treatments for agitation, even if psychotic symptoms are present, due to their relative tolerability and clinicians' familiarity with them [32]. SNRIs such as venlafaxine and duloxetine have been less studied in AD populations but may offer benefits in cases where comorbid depression contributes to behavioral disturbance [32].

Sertraline, one of the most prescribed SSRIs in dementia populations, has been extensively studied for depression in AD dementia, but its efficacy for behavioral symptoms such as agitation and irritability is unclear. Large studies, such as the randomized Health Technology Assessment - Study of Antidepressants for Depression in Dementia (HTA-SADD) trial, failed to demonstrate significant improvements in sertraline or mirtazapine over placebo for depression in AD dementia, with no meaningful difference in depression scores at 13 or 39 weeks for either drug [74]. Furthermore, both medications were associated with a higher incidence of adverse reactions compared to placebo [74]. The DIADS-2 trial similarly reported no benefit of sertraline over placebo [75]. As a result, sertraline is not routinely recommended as a first-line agent for agitation or depression in AD, but it remains a favorable option for comorbid depression and anxiety in clinical practice due to its relatively favorable safety profile, particularly regarding cardiac risk compared to other SSRIs.

Mirtazapine, a noradrenergic and specific serotonergic antidepressant, was also evaluated in the HTA-SADD trial with similar findings: no significant benefit over placebo for depression and a higher incidence of adverse effects [74]. The SYMBAD trial, which evaluated mirtazapine for agitation in AD, likewise did not show therapeutic benefit and actually demonstrated a concerning signal for increased mortality in the mirtazapine group [76].

Anti-anxiety medications and anticonvulsant "mood stabilizers"

Benzodiazepines are sometimes prescribed for acute anxiety, agitation, or insomnia in AD dementia, particularly in crises or inpatient settings. Their use is discouraged in dementia care due to a well-established association with adverse outcomes in older adults, such as falls, sedation, cognitive worsening, delirium [77] or paradoxical disinhibition, whereby agitation or aggression may intensify following administration [78]. In addition, long-term benzodiazepine use has been associated with faster cognitive decline in observational studies [79], raising concerns about their safety beyond short-term or very targeted use. For example, in a prospective, population-based cohort study involving over 3400 community-dwelling older adults, Gray et al. reported that higher cumulative exposure to benzodiazepines was associated with greater risk of cognitive decline and dementia [79]. While short-term or intermittent use did not significantly elevate risk, extended exposure, particularly at higher doses, was linked to measurable declines in cognitive performance over time, reinforcing caution against chronic use in this vulnerable population [79].

Anticonvulsant "mood stabilizers" have also been explored for NPS in AD, though with limited success. In a 16-week retrospective open-label study, Suzuki and Inoue compared valproic acid (mean dose 215.0 ± 122.6 mg/day) and lamotrigine (mean dose 48.0 ± 27.6 mg/day) in 45 inpatients with severe AD dementia and prominent behavioral symptoms [80]. Valproic acid reduced NPI agitation scores by 3.3 ± 2.5 points, while lamotrigine produced a greater reduction of 4.0 ± 2.2 points; however, this between-group difference was not statistically significant (p = .30) [80]. Despite these benefits, valproic acid was associated with adverse effects in 30 % of patients, including somnolence, body tilt, and dizziness, underlining its limited tolerability in this population [80]. Interestingly, carbamazepine, an older and extensively cross-reactive drug, demonstrated significant improvements in agitation, aggression, and hostility in small studies, though adverse events occurred in 59 % of 51 patients in a nursing home trial [81] and 44 % of 21 patients in an outpatient study [82], including falls, gastrointestinal distress, and sedation.

Lithium is an under-studied option, which has emerged based on its neuroprotective properties, anti-impulsivity effects, and potential to modulate aggression and mood lability. A case series reported that when lithium was used as an adjunct to antipsychotic treatment in patients with AD dementia and frontotemporal dementia, several symptoms improved, including auditory and visual hallucinations, paranoia, anxiety, anger/aggression, agitation, impulsivity, and physical violence [83]. However, in a multicenter, randomized, placebo-controlled, double-blind, parallel group trial of 77 patients with AD dementia, lithium did not differ from placebo in improving agitation/aggression [84]. Lithium remains an off-label and cautiously used agent in this population due to its narrow therapeutic index, requirement for regular serum monitoring, and vulnerability to toxicity in the context of renal impairment or dehydration, which are common in advanced age and dementia [63].

Antipsychotics

When non-pharmacological strategies fail to adequately manage symptoms, particularly in cases of severe distress or danger to self or others, pharmacologic treatment may become necessary. In such situations, medications should be used judiciously and tailored to the specific neuropsychiatric presentation, with careful consideration of the risks and benefits of each option. Psychosis and agitation frequently co-occur in AD, and the clinical context often determines the choice of treatment.

Antipsychotics such as risperidone, olanzapine, and quetiapine have long been used off-label for the management of agitation (verbal and physical), aggression, and psychosis in AD [85]. Risperidone is the only antipsychotic with regulatory approval for short-term use in certain countries (e.g., Canada, Europe), but its use is challenging due to safety concerns [86]. The FDA's approval in May 2023 of an atypical antipsychotic, brexpiprazole (Rexulti), for agitation in AD is the first such approval in the US, but it does not eliminate long-standing concerns regarding class-wide risks [87]. Notably, the brexpiprazole trials showed greater efficacy at Eastern European trial sites, which enrolled participants with limited racial and ethnic diversity, and they did not demonstrate significant benefit when analyses were restricted to US sites [8]. This raises important questions about the generalizability of the findings. In addition, risperidone showed superior efficacy in earlier studies but was never granted FDA approval for agitation in AD [88].

All antipsychotics, including brexpiprazole, carry box warnings for increased mortality in elderly patients with dementia [89] with adverse effects including cerebrovascular events, sedation, and falls [90]. The CATIE-AD trial, a large, multi-center randomized controlled trial, found no statistically significant advantage of atypical antipsychotics over placebo on clinician-rated global improvement [88]. However, numerically higher rates of clinical improvement at 12 weeks were observed with olanzapine and risperidone compared to placebo, suggesting a possible therapeutic signal in some patients [88]. These modest benefits were often offset by adverse effects, including extrapyramidal symptoms, sedation, and confusion, which led to high discontinuation rates [88]. As some have noted, when patients are carefully selected and closely monitored, the balance between efficacy and safety may become more favorable. Antipsychotics should therefore be reserved for cases of severe distress or risk, used judiciously, and always considered after behavioral and environmental interventions have failed.

Cannabinoids

Cannabinoids are emerging as a pharmacological alternative for agitation in AD. A randomized controlled trial of nabilone demonstrated a significant reduction in agitation scores over six weeks compared to placebo, with modest but notable adverse effects such as sedation, lethargy, and delirium [91]. In addition, a randomized controlled trial of dronabinol (synthetic THC) is investigating its efficacy for severe agitation in AD across inpatient, assisted living, and nursing home settings [92]. This three-week study involving 80 participants has shown early feasibility and good tolerability, intending to determine if targeting the cannabinoid system offers a safe and effective approach to treating advanced-stage behavioral disturbances [92].

Emerging therapeutics

There is growing momentum toward the development of novel, targeted, and safer interventions for NPS in AD, which include pharmacological innovation, neuromodulation technologies, biomarker-guided precision approaches, and digital health solutions.

Repurposed drugs

Several medications, listed below, are being re-evaluated or have the potential to be evaluated for NPS. This repurposing allows for rapid clinical testing due to known safety profiles but requires rigorous study to confirm therapeutic specificity in AD.

- Dextromethorphan-quinidine was originally approved for pseudobulbar affect. It acts as an NMDA receptor antagonist and sigma-1 receptor agonist, modulating glutamate signaling and reducing excitotoxicity [93]. These mechanisms are thought to contribute to agitation in dementia. In a randomized controlled trial, dextromethorphan-quinidine significantly reduced agitation in patients with AD dementia compared to placebo [93].
- Beta-blockers (e.g., propranolol) have shown potential in reducing aggression and agitation, likely through modulation of peripheral and central noradrenergic signaling, a pathway implicated in stress-related behaviors [94]. In a randomized controlled trial of nursing home residents with probable or possible AD dementia, propranolol (mean dose 106 mg/day) significantly improved agitation/aggression and overall NPS on the Clinical Global Impression of Change compared to placebo, and was well tolerated [95]. In addition, a 2022 review concluded that propranolol may be effective for managing agitation and aggression in dementia and may be trialed in refractory cases, particularly when antipsychotics have failed or are contraindicated [94]. Its favorable safety profile includes the absence of extrapyramidal symptoms, minimal sedation, and a well-established cardiovascular safety record when used with appropriate monitoring for hypotension or bradycardia [94].

Newer antidepressants

Esketamine, a non-competitive NMDA receptor antagonist delivered intranasally, represents a novel and rapid-acting antidepressant with a distinct mechanism involving both glutamatergic modulation and neurotrophic signaling. While currently approved for treatment-resistant depression, emerging evidence suggests it may also confer neuroprotective, anti-inflammatory, and pro-cognitive benefits, making it a potential candidate for managing depression in AD, especially in cases characterized by apathy, anhedonia, or SSRI resistance [96].

Other newer antidepressants on the market include Auvelity, a combination of dextromethorphan and bupropion, which acts as an NMDA receptor antagonist and sigma-1 receptor agonist. It is approved by the FDA for major depressive disorder and has gained attention for its potential to treat affective symptoms in AD [97]. In a phase 3 trial of patients with AD and agitation, treatment with Auvelity significantly reduced the risk of relapse compared to placebo, with a relapse rate of 7.5% versus 25.9% and a hazard ratio of 0.275 ($P = .014$) [97]. The medication was well tolerated, with no evidence of sedation, cognitive worsening, or cardiovascular instability [97]. Vortioxetine, another multimodal antidepressant with serotonin receptor modulation properties, has demonstrated improvements in both cognitive function and mood in patients with major depressive disorder [98]. Although participants in the meta-analyzed trials were not screened for a primary diagnosis of AD, subsequent research has shown that vortioxetine can produce meaningful improvements in depressive symptoms in patients with AD [99].

Agomelatine, approved in Europe, acts as a melatonin receptor (MT1/MT2) agonist and 5-HT2C antagonist, promoting circadian rhythm regulation and enhancing frontal dopamine and norepinephrine release [100]. While originally developed for major depressive and

anxiety disorders, emerging evidence shows that agomelatine may also improve depressive symptoms, anxiety, and sleep disturbances in patients with AD, with a favorable tolerability profile and no significant adverse effects on cognition [101,102].

Experimental agents

Other experimental agents, including psychedelic compounds (e.g., psilocybin), are being explored for their potential to modulate mood, enhance neuroplasticity, and reduce neuroinflammation, which are mechanisms relevant to both depression and neurodegenerative disease progression [103]. At the time of this writing, an ongoing clinical trial (*NCT04123314*) is investigating the effects of psilocybin-assisted therapy on depression in individuals with MCI or early AD [104]. It is examining if psilocybin can alleviate depressive symptoms and improve emotional well-being in this population by potentially enhancing resilience and coping through its influence on mood regulation and neuroplasticity [104].

Advances in neuromodulation: transcranial magnetic stimulation, transcranial direct current stimulation, electroconvulsive therapy, and deep brain stimulation

Neuromodulation techniques are effective treatments for neuropsychiatric conditions, including depression and obsessive-compulsive disorder [105–107]. These act by modulating nodes within distributed brain networks, particularly fronto-limbic and fronto-striatal circuits, with therapeutic effects arising from changes in functional connectivity between stimulation sites and broader disease-relevant networks [108]. Based on this success, there is interest in applying neuromodulation to AD dementia. While preliminary studies using TMS and DBS in AD have shown improvements in cognition and neural connectivity, their effects on NPS (e.g., agitation, apathy, and depression) are mostly unexplored and not yet supported by consistent clinical data [109,110].

Repetitive transcranial magnetic stimulation (rTMS), particularly when applied to the dorsolateral prefrontal cortex, has shown efficacy in reducing apathy and cognitive slowing in cognitively impaired populations [111,112]. However, the clinical effects of rTMS in mood disorders are often short-lived, typically requiring maintenance treatments, which raises questions about the durability of benefit in the context of NPS in AD, where symptoms often recur over longer timeframes. Transcranial direct current stimulation (tDCS) is an emerging technique that delivers low-intensity electrical currents to modulate cortical excitability. Anodal tDCS over the dorsolateral prefrontal cortex has potential to enhance mood, motivation, and executive function in AD dementia, but findings are preliminary [15,113]. Compared to other neuromodulation modalities, tDCS is relatively inexpensive, portable, and well-tolerated, typically associated with only minor and transient side effects [15]. A pilot study demonstrated that combining tDCS with rTMS yielded improvements in cognition, NPS, and sleep in moderate AD dementia, suggesting possible synergistic effects between modalities [113]. While conventional rTMS is limited to superficial cortical targets such as the prefrontal cortex, “deep” TMS may impact deeper brain regions, such limbic circuits that are more directly implicated in affective and behavioral dysregulation. Still, the use of tDCS for NPS in AD dementia is unproven, necessitating further validation in larger randomized controlled trials. Therapeutic outcomes have been inconsistent across studies, likely due to variation in stimulation parameters and small sample sizes.

Electroconvulsive therapy (ECT) is a highly effective treatment for severe, refractory depression in the elderly, and newer protocols are focusing on ultra-brief pulse widths to minimize cognitive side effects [105,114,115]. There is a positive pilot trial of ECT to treat severe agitation in AD [116], building on promising results from case series [117,118]. Deep brain stimulation (DBS), although still investigational for AD dementia, is being explored for both cognitive improvement and NPS such as agitation, with targets including the fornix and nucleus basalis of Meynert [119,120]. Experimental closed-loop DBS systems, which adapt stimulation based on real-time neural feedback, are conceptually supported by efforts to personalize brain stimulation parameters in AD dementia [120]. Although studies in AD dementia are still limited, the rationale stems from their success in circuit modulation for other neuropsychiatric conditions, and growing interest in targeting AD-related circuit dysfunction with precision-guided neuromodulation [119].

Biomarker-driven therapeutic approaches

Biomarkers such as plasma phosphorylated tau, neurofilament light chain (NfL), and PET imaging of amyloid and tau pathology allow for stratification of patients by disease stage and molecular subtype [121]. The advent of fluid and imaging biomarkers in AD is reshaping how NPS are conceptualized within the broader pathophysiology of dementia. However, findings are mixed. For example, a prospective longitudinal study of 236 individuals followed over eight years reported no significant relationship between core AD biomarkers and the development of NPS during the transition from cognitively unimpaired status to MCI [122]. In contrast, a systematic review of 19 cross-sectional and longitudinal studies found that higher amyloid-beta burden was associated with depression and anxiety [123].

Peripheral inflammatory markers, including interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and C-reactive protein (CRP), were associated with increased risk and severity of psychotic symptoms across psychiatric and neurodegenerative disorders. In AD dementia, microglial activation in anterior cingulate cortex and temporal regions, measured by the PET ligand binding of [^{11}C]PBR28, was associated with more severe NPS (particularly irritability, nighttime disturbances, and agitation) [42]. Ongoing studies are characterizing network-based biomarkers, such as resting-state fMRI connectivity, in cognitively impaired individuals with NPS; however, their utility in predicting response to neuromodulation is untested [124–126]. Integration of biomarkers into clinical trials for NPS in AD dementia may enhance patient selection and provide surrogate outcome measures for early therapeutic efficacy [127].

Virtual reality technologies

Artificial intelligence (AI) and immersive technologies such as virtual reality (VR) are being assessed to detect, monitor, and even intervene upon NPS in AD [13,14,128,129]. AI-driven speech analysis and natural language processing tools, for example, can detect early affective changes predictive of depression and anxiety [130,131]. Wearable sensors and home-based monitoring systems use machine learning algorithms to detect agitation episodes and predict behavioral escalation [132,133]. VR therapies have been employed to create calming, personalized environments that reduce anxiety and agitation in dementia patients, particularly in care home settings [13,129]. A recent mixed-methods study from Cyprus reported that VR exposure led to notable reductions in apathy, aggression, and depression among institutionalized individuals with dementia, with improvements confirmed through both physiological (heart rate) and behavioral data [13]. To date, no trials have specifically evaluated the effects of virtual reality immersion on emotional regulation and social engagement in individuals with AD–related cognitive impairment. However, smaller studies have suggested that these digital innovations have the potential to generate rich behavioral data streams that can be integrated into future AI-driven therapeutic models [13,129].

Given the multifactorial nature of NPS in AD, combination approaches of integrating pharmacologic and nonpharmacologic (e.g., digital, behavioral, neuromodulatory) therapies, are gaining momentum as a future standard. Future research must not only validate these

strategies through rigorous randomized controlled trials but also address health disparities in access and implementation.

Future directions

As NPS become increasingly recognized as core features of AD dementia, the future of effective NPS management depends not only on advancing technology and integrative care models but, perhaps more critically, on deepening our understanding of the heterogeneity of symptom clusters and their underlying biological mechanisms. While AI tools, digital health platforms, and wearable sensors offer powerful solutions for detecting, monitoring, and managing NPS, their transformative potential hinges on being grounded in mechanistic insights. For example, passive sensing technologies can track behavioral patterns, sleep disruptions, apathy-related inactivity, and agitation episodes in real time, enabling earlier intervention and personalized care plans [133]. Yet, such tools must be informed by research that elucidates the key pathophysiological contributors to NPS in AD, including neuroinflammation [42,43], neurotransmitter dysregulation [39], disrupted functional connectivity [126], and aberrant stress and circadian signaling [44]. A more mechanistically informed approach may facilitate biologically meaningful subtyping of NPS and support precision medicine strategies. Advances in pharmacogenomics, polygenic risk scores, and multimodal biomarker integration hold promise for tailoring treatments to an individual's biological profile, ultimately enhancing efficacy, safety, and quality of life [134].

Given the multifactorial complexity of neuropsychiatric symptoms in Alzheimer's disease, strengthening the evidence base for combined diagnostic and therapeutic strategies is essential. Current clinical trials frequently exclude individuals with severe behavioral symptoms, limiting generalizability and real-world applicability. Moving forward, future studies must prioritize inclusive recruitment and adopt transdiagnostic frameworks that capture the multidimensional, fluctuating nature of behavioral symptoms across the dementia continuum. Equally important is the integration of structured, first-line non-pharmacologic strategies such as the Describe-Investigate-Create-Evaluate (DICE) approach and other ecopsychosocial interventions into both research and clinical care paradigms. These strategies can help prevent the inappropriate use of medications for symptoms that may arise from unmet needs, environmental stressors, or caregiver misunderstanding, conceptualized as the “indirect pathway” of symptom expression [135]. Designing trials that rigorously evaluate these multicomponent interventions alongside or before pharmacological agents will help ensure that medications are reserved for cases of true neurobiological disturbance rather than contextual or relational distress. This shift toward integrative, mechanism-informed, and person-centered care models offers the greatest promise for improving outcomes for both patients and caregivers.

Conclusion

NPS are among the most disabling and complex features of AD that profoundly shape quality of life, clinical outcomes, caregiver burden, and healthcare utilization. Pharmacological approaches traditionally adapted from treatments for DSM-defined psychiatric syndromes, such as major depressive disorder or schizophrenia, have limited efficacy in AD populations and often overlook the multifactorial roots of NPS, which span neurobiological changes, psychosocial stressors, caregiver dynamics, and environmental triggers. The DSM framework, while clinically useful, may not adequately capture the phenomenology or pathophysiology of NPS in the context of neurodegenerative disease. Thus, advances in neuromodulation, biomarker discovery, and digital therapeutics offer new pathways for intervention. Much of the current evidence base, however, is limited by small sample sizes, inconsistent outcome measures, and lack of real-world applicability. Nonetheless, non-pharmacologic interventions continue to hold promise but require broader implementation and integration into standard care models.

A precision medicine framework, rooted in individualized symptom profiles, biological signatures, psychosocial context, and caregiving environment is essential to align treatment with the underlying pathophysiology of NPS. Limitations such as the high cost of emerging technologies, uneven access across care settings, and variability in workforce training must be acknowledged and proactively addressed. Moving forward, sustained investment in multidisciplinary, translational research is urgently needed to develop and evaluate targeted and ethically grounded strategies. The future of NPS management in AD dementia depends on a paradigm shift that bridges neurobiology, behavioral science, implementation science, and social ecology to deliver truly person-centered dementia care.

Authors Contributions

Deborah K. Rose, MD: Conceptualization; Writing: Original Draft; Writing: Review & Editing; Literature Review; Project Administration.

Constantine G. Lyketsos, MD, MHS: Conceptualization; Supervision; Writing: Review & Editing; Methodological Guidance; Clinical Oversight.

Paul B. Rosenberg, MD: Supervision; Writing – Review & Editing; Critical Revisions; Validation of Content.

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