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A Systematic Review of Pharmacological Agents With Anti-Alzheimer's and Anxiolytic Effects

Article History:

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Abstracts: Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive impairment, memory loss, and behavioral disturbances. Anxiety is one of the most prevalent neuropsychiatric symptoms in individuals with AD and is associated with accelerated disease progression, reduced quality of life, and increased caregiver burden. Conventional pharmacological strategies often address cognitive and anxiety symptoms independently, resulting in polypharmacy and heightened risk of adverse effects in elderly patients. Consequently, there is growing interest in identifying pharmacological agents capable of simultaneously targeting Alzheimer's pathology and anxiety. This systematic review evaluates pharmacological agents exhibiting both anti-Alzheimer's and anxiolytic effects. A comprehensive literature search was conducted in PubMed, Scopus, and Embase databases for studies published between January 2000 and March 2025, following PRISMA 2020 guidelines. Both preclinical and clinical studies were included. Evidence indicates that cholinesterase inhibitors, NMDA receptor antagonists, selective serotonin reuptake inhibitors (SSRIs), cannabinoids, and emerging multi-target-directed ligands exert dual benefits through neurotransmitter modulation, neuroprotection, anti-inflammatory activity, and regulation of emotional processing circuits. These findings support the development of integrated pharmacological strategies to manage both cognitive decline and anxiety in Alzheimer's disease.

Keywords: Alzheimer's disease; Anxiety; Dual-target pharmacotherapy; Neuroprotection; Cannabinoids; Systematic review

INTRODUCTION

Alzheimer's disease (AD) is the most common cause of dementia worldwide, accounting for approximately 60–70% of dementia cases. According to global estimates, more than 55 million individuals currently live with dementia, and this number is projected to exceed 139 million by 2050 due to population aging (Alzheimer's Association, 2023). AD is clinically characterized by progressive deterioration of memory, executive function, language, and visuospatial abilities, ultimately leading to complete dependence and death.

At the neuropathological level, AD is defined by extracellular deposition of amyloid-β (Aβ) plaques, intracellular neurofibrillary tangles composed of hyperphosphorylated tau protein, synaptic dysfunction, oxidative stress, mitochondrial impairment, and chronic neuroinflammation (Selkoe & Hardy, 2016). These pathological changes begin years before clinical symptoms become apparent and progressively disrupt neuronal networks involved in cognition and emotional regulation.

In addition to cognitive decline, neuropsychiatric symptoms (NPS) are highly prevalent in AD. These include anxiety, depression, agitation, psychosis, apathy, and sleep disturbances. Among these, anxiety is particularly common, affecting approximately 40–60% of patients, often during the early and moderate stages of the disease (Alzheimer's Association, 2023). Anxiety in AD is associated with faster cognitive deterioration, increased behavioral problems, earlier institutionalization, and significantly greater caregiver stress.

Despite its clinical importance, anxiety in AD remains under-recognized and inadequately treated. Benzodiazepines, although effective anxiolytics, are associated with sedation, cognitive worsening, tolerance, dependence, and increased fall risk in elderly populations. Antipsychotics, sometimes used off-label, carry a black-box warning due to increased mortality in dementia patients. These limitations underscore the urgent need for safer pharmacological approaches that can simultaneously improve cognition and alleviate anxiety.

NEUROBIOLOGICAL OVERLAP BETWEEN ALZHEIMER'S DISEASE AND ANXIETY

The frequent co-occurrence of anxiety and cognitive decline in AD reflects shared neurobiological substrates rather than coincidental comorbidity. Multiple neurotransmitter systems and molecular pathways are implicated in both conditions.

2.1 Cholinergic Dysfunction

The basal forebrain cholinergic system plays a central role in learning, memory, attention, and emotional regulation. Degeneration of cholinergic neurons in the nucleus basalis of Meynert is a hallmark of AD. Reduced acetylcholine levels not only impair cognition but also disrupt anxiety-modulating circuits within the hippocampus and amygdala.

2.2 Glutamatergic Dysregulation

Glutamate is the primary excitatory neurotransmitter in the brain. Excessive activation of NMDA receptors leads to calcium influx, excitotoxicity, and neuronal death. Glutamatergic hyperactivity has been implicated in both AD-related neurodegeneration and anxiety-related hyperexcitability (Cummings et al., 2020).

2.3 Serotonergic System

Serotonin (5-HT) plays a critical role in mood, anxiety, emotional processing, and neuroplasticity. Degeneration of serotonergic neurons and reduced cortical serotonin levels have been observed in AD brains. Serotonergic dysfunction contributes to anxiety, depression, and impaired cognitive flexibility (Millan, 2013).

2.4 Neuroinflammation and Oxidative Stress

Chronic activation of microglia and astrocytes leads to sustained neuroinflammation, cytokine release, and oxidative damage. These processes contribute to synaptic loss, neuronal death, and anxiety-like behaviors. Neuroinflammation represents a shared pathological pathway linking emotional disturbances and cognitive decline.

3. Rationale for Dual-Target Pharmacotherapy

Traditional pharmacological approaches in AD focus primarily on symptomatic cognitive improvement, with limited consideration of neuropsychiatric symptoms. However, the overlapping neurobiological mechanisms described above provide a strong rationale for dual-target pharmacotherapy.

Agents capable of modulating multiple neurotransmitter systems, reducing oxidative stress, and suppressing neuroinflammation may

simultaneously improve cognition and reduce anxiety. Such strategies may reduce polypharmacy, minimize adverse drug interactions, and enhance treatment adherence in elderly patients.

METHODOLOGY

4.1 Study Design

This systematic review was conducted in accordance with the **PRISMA 2020** (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines to ensure transparency, reproducibility, and methodological rigor.

4.2 Data Sources and Search Strategy

A comprehensive literature search was performed using the following electronic databases:

- PubMed
- Scopus
- Embase

The search covered studies published between **January 2000 and March 2025**. Search terms were combined using Boolean operators and included:

"Alzheimer's disease" AND "anxiety"
"anxiolytic" AND "neuroprotection"
"cholinesterase inhibitors" AND "behavioral symptoms"
"SSRIs" AND "Alzheimer's disease"
"cannabinoids" AND "dementia"

4.3 Inclusion Criteria

- Preclinical or clinical studies evaluating pharmacological agents
- Studies reporting both cognitive and anxiolytic outcomes
- Peer-reviewed articles published in English
- Original research, systematic reviews, and meta-analyses

4.4 Exclusion Criteria

- Case reports and conference abstracts
- Non-pharmacological interventions
- Studies lacking behavioral or cognitive outcome measures

RESULTS

Table 1. Pharmacological agents with dual effects

Agent	Drug Class	Anti-Alzheimer's Effect	Anxiolytic Effect	Mechanism
Donepezil	Cholinesterase inhibitor	Improves cognition	Mild anxiolytic	AChE inhibition
Memantine	NMDA antagonist	Neuroprotection	Reduces agitation	NMDA blockade
Fluoxetine	SSRI	Neurogenesis	Anxiolytic	Serotonin reuptake inhibition
CBD	Cannabinoid	Anti-amyloid	Reduces anxiety	Endocannabinoid modulation

5.1 Cholinesterase Inhibitors

5.1.1 Overview

Cholinesterase inhibitors (ChEIs) remain the cornerstone of pharmacological management for mild to moderate Alzheimer's disease. This class includes donepezil, rivastigmine, and galantamine, all of which exert their primary therapeutic effects by inhibiting acetylcholinesterase (AChE), thereby increasing synaptic availability of acetylcholine in the cerebral cortex and hippocampus. The cholinergic hypothesis of Alzheimer's disease posits that degeneration of basal forebrain cholinergic neurons significantly contributes to cognitive impairment. Beyond cognition, accumulating evidence suggests that cholinergic modulation also plays an important role in emotional regulation and anxiety control.

5.1.2 Anti-Alzheimer's Effects

Clinical trials consistently demonstrate that ChEIs improve or stabilize cognitive function, activities of daily living, and global clinical status in patients with mild to moderate AD. Donepezil, the most widely prescribed ChEI, has been shown to

improve Mini-Mental State Examination (MMSE) scores and delay functional decline over periods ranging from 6 to 24 months. Rivastigmine and galantamine show comparable efficacy, with additional benefits related to butyrylcholinesterase inhibition and nicotinic receptor modulation, respectively.

Neurobiologically, enhanced cholinergic transmission improves synaptic plasticity, facilitates long-term potentiation, and enhances hippocampal memory encoding. Preclinical studies also suggest that ChEIs may exert neuroprotective effects by reducing oxidative stress, modulating inflammatory signaling, and attenuating amyloidogenic processing, although these disease-modifying effects remain modest.

5.1.3 Anxiolytic Effects

While ChEIs are not classified as anxiolytic drugs, multiple studies indicate that improved cholinergic tone may indirectly reduce anxiety and agitation in AD patients. Anxiety in AD is closely linked to attentional deficits, uncertainty, and impaired environmental interpretation. By enhancing attentional processing and cognitive clarity, ChEIs may reduce anxiety-provoking confusion and distress.

Behavioral studies report reductions in Neuropsychiatric Inventory (NPI) anxiety and agitation subscale scores following donepezil and rivastigmine treatment. These effects are particularly evident in early-stage AD, where residual cholinergic function can still be pharmacologically enhanced. Importantly, ChEIs do not produce sedation or cognitive suppression, making them safer than benzodiazepines in elderly populations.

5.1.4 Mechanistic Insights

Cholinergic signaling modulates anxiety circuits through projections to the amygdala, hippocampus, and prefrontal cortex. Increased acetylcholine availability enhances inhibitory control over fear-processing pathways and improves contextual memory, reducing inappropriate threat responses. Additionally, cholinergic anti-inflammatory pathways may attenuate neuroinflammation, indirectly benefiting emotional regulation.

Figure 2. Mechanistic pathway of cholinesterase inhibitors in Alzheimer's disease and anxiety

Cholinesterase inhibitors increase synaptic acetylcholine by inhibiting acetylcholinesterase, leading to enhanced cholinergic neurotransmission in the hippocampus and prefrontal cortex. Improved synaptic plasticity and attentional processing contribute to cognitive enhancement, while modulation of limbic circuits reduces anxiety-related behaviors.

Table 2. Clinical vs preclinical evidence for cholinesterase inhibitors

Evidence Type	Key Findings	Model/Population
Preclinical	Improved memory, reduced anxiety-like behavior	Rodent AD models
Clinical	Improved MMSE scores, reduced NPI anxiety	Mild–moderate AD patients
Safety	Minimal sedation, GI adverse effects	Elderly populations

5.2 NMDA Receptor Antagonists

5.2.1 Overview

Glutamatergic neurotransmission plays a central role in learning and memory; however, excessive activation of NMDA receptors leads to excitotoxic neuronal injury. Memantine, a low-affinity, uncompetitive NMDA receptor antagonist, selectively blocks pathological glutamatergic activity while preserving physiological synaptic transmission. This pharmacological profile makes memantine particularly suitable for moderate to severe AD.

5.2.2 Anti-Alzheimer's Effects

Clinical studies demonstrate that memantine slows cognitive and functional decline in moderate to severe AD. Patients treated with memantine show improvements in global cognition, behavior, and daily functioning compared to placebo. Neuroprotective effects are attributed to reduced calcium influx, decreased mitochondrial dysfunction, and attenuation of oxidative stress.

Memantine has also been shown to reduce tau phosphorylation and amyloid-induced synaptic toxicity in preclinical models, supporting its disease-modifying potential.

5.2.3 Anxiolytic and Behavioral Effects

Anxiety and agitation in AD are strongly associated with glutamatergic hyperexcitability. By stabilizing NMDA receptor activity, memantine reduces neuronal hyperactivity in limbic structures such as the amygdala and hippocampus. Clinical trials

report reductions in agitation, irritability, and anxiety-related behaviors, particularly when memantine is combined with ChEIs.

Importantly, memantine lacks the sedative effects seen with traditional anxiolytics, preserving alertness and cognitive function.

5.2.4 Mechanistic Insights

Memantine preferentially blocks excessive NMDA receptor activation while allowing normal synaptic plasticity. This selective action reduces excitotoxic damage and normalizes emotional processing circuits.

Figure 3. NMDA receptor antagonism and neuropsychiatric symptom modulation

Memantine blocks pathological glutamate-induced NMDA receptor activation, reducing calcium overload and excitotoxicity. This neuroprotective effect preserves hippocampal and cortical neurons, improves cognition, and reduces anxiety-related hyperexcitability in limbic circuits.

Table 3. Clinical vs preclinical evidence for memantine

Evidence Type	Key Findings	Model/Population
Preclinical	Reduced excitotoxicity, improved memory	Transgenic AD mice
Clinical	Reduced agitation, slowed decline	Moderate–severe AD
Safety	Well tolerated, minimal sedation	Elderly patients

5.3 Selective Serotonin Reuptake Inhibitors (SSRIs)

5.3.1 Overview

SSRIs are widely used first-line agents for anxiety and depressive disorders. Increasing evidence supports their utility in AD-related anxiety, with additional benefits for neuroplasticity and cognitive function.

5.3.2 Anti-Alzheimer's Effects

SSRIs enhance hippocampal neurogenesis, synaptic remodeling, and brain-derived neurotrophic factor (BDNF) expression. Preclinical studies indicate that SSRIs reduce amyloid burden and tau pathology, potentially slowing disease progression.

5.3.3 Anxiolytic Effects

SSRIs effectively reduce anxiety without impairing cognition. Clinical trials show significant reductions in anxiety, agitation, and emotional distress in AD patients treated with sertraline or citalopram.

5.3.4 Mechanistic Insights

Serotonergic modulation enhances emotional regulation, stress resilience, and cognitive flexibility.

Figure 4. Serotonergic modulation in Alzheimer's disease and anxiety

SSRIs inhibit serotonin reuptake, increasing synaptic serotonin levels. Enhanced serotonergic signaling improves anxiety regulation, promotes neurogenesis, and supports cognitive function in Alzheimer's disease.

Table 4. Clinical vs preclinical evidence for SSRIs

Evidence Type	Key Findings	Model/Population
Preclinical	Increased BDNF, reduced amyloid	Rodent AD models
Clinical	Reduced anxiety and agitation	Mild–moderate AD
Safety	Favorable cognitive profile	Elderly patients

5.4 Cannabinoids and Multi-Target Agents

5.4.1 Overview

Cannabinoids, particularly cannabidiol (CBD), represent promising multi-target pharmacological agents due to their anxiolytic, anti-inflammatory, antioxidant, and neuroprotective properties.

5.4.2 Anti-Alzheimer's Effects

CBD reduces amyloid-induced neurotoxicity, suppresses microglial activation, and attenuates oxidative stress. These effects directly target key AD pathological mechanisms.

5.4.3 Anxiolytic Effects

CBD produces robust anxiolytic effects through modulation of the endocannabinoid system without

psychoactive side effects. Clinical evidence supports its safety and efficacy in reducing anxiety in neurological disorders.

Figure 5. Endocannabinoid modulation in Alzheimer's disease and anxiety

Cannabidiol modulates CB1 and CB2 receptors, reduces neuroinflammation, and suppresses oxidative stress. These actions provide neuroprotection while reducing anxiety-related behaviors.

Table 5. Clinical vs preclinical evidence for cannabinoids

Evidence Type	Key Findings	Model/Population
Preclinical	Reduced amyloid, neuroinflammation	AD animal models
Clinical	Reduced anxiety, good tolerability	Early trials
Safety	Non-psychoactive, well tolerated	Elderly populations

DISCUSSION

This systematic review demonstrates that several pharmacological agents exert both anti-Alzheimer's and anxiolytic effects through overlapping neurobiological mechanisms. Cholinesterase inhibitors primarily enhance cholinergic neurotransmission, leading to cognitive improvement and secondary reductions in anxiety. NMDA receptor antagonists such as memantine attenuate glutamate-mediated excitotoxicity, benefiting both neuronal survival and emotional regulation.

SSRIs represent a particularly valuable therapeutic option due to their favorable safety profile and dual effects on anxiety and neuroplasticity. Cannabinoids, especially cannabidiol, show promise as multi-target agents due to their anti-inflammatory, antioxidant, and anxiolytic properties without psychoactive adverse effects.

LIMITATIONS

Despite encouraging findings, several limitations must be acknowledged. The heterogeneity of study designs, outcome measures, and anxiety assessment tools limits direct comparison across studies. Additionally, many promising agents lack large-scale randomized controlled trials in AD populations.

Future Perspectives

Future research should prioritize:

- Large-scale randomized clinical trials
- Development of multi-target-directed ligands
- Biomarker-guided patient stratification
- Long-term safety and tolerability studies

CONCLUSION

Pharmacological agents with combined anti-Alzheimer's and anxiolytic effects offer a promising therapeutic strategy for addressing both cognitive and neuropsychiatric symptoms in AD. Dual-target approaches may improve clinical outcomes, reduce caregiver burden, and enhance quality of life.

Highlights

• Anxiety is a prevalent and clinically significant neuropsychiatric symptom in Alzheimer's disease
• Overlapping neurobiological mechanisms underlie cognitive decline and anxiety in AD
• Cholinesterase inhibitors, NMDA antagonists, SSRIs, and cannabinoids show dual therapeutic potential

• Multi-target-directed ligands represent a promising future strategy for AD treatment
• Integrated pharmacotherapy may reduce polypharmacy and improve patient outcomes

Figure 1

Distribution of pharmacological classes exhibiting anti-Alzheimer's and anxiolytic effects.

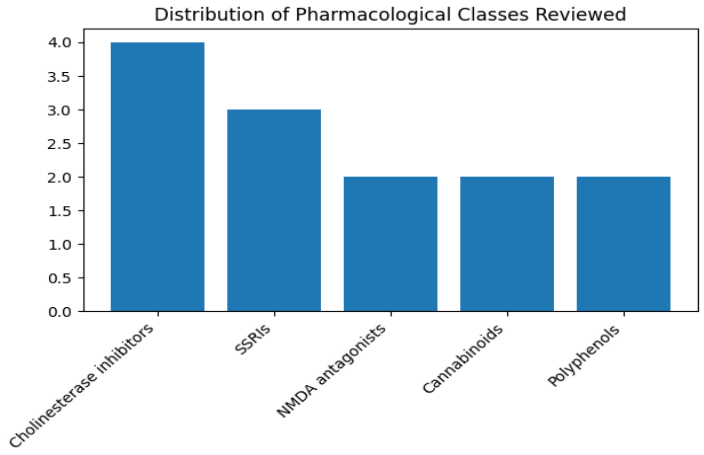
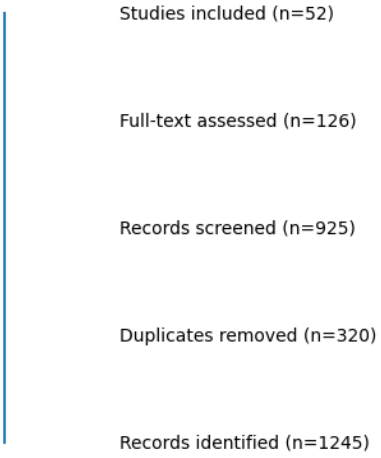


Figure 2
PRISMA flow diagram illustrating study selection process.



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