

# ***Multifactorial Mechanisms and Emerging Strategies in Alzheimer's Disease Pathology, Diagnosis, and Treatment***

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**Abstract.** Alzheimer's disease (AD) is one of the most common neurodegenerative diseases. Its high incidence and severe cognitive decline impose a heavy burden on society. Exploring its pathogenic mechanisms and diagnosis/treatment strategies is a current research focus. This review systematically elaborates on the core pathological mechanisms of AD. These include senile plaques formed by the abnormal deposition of  $\beta$ -amyloid protein ( $A\beta$ ), neurofibrillary tangles caused by hyperphosphorylation of tau protein, and the regulatory roles of endoplasmic reticulum stress and autophagy dysfunction in neuronal damage. It also reveals the interconnections between these multiple mechanisms. It summarizes the latest advances in AD diagnosis, focusing on the shift in NIA-AA diagnostic criteria, as well as the application value of cerebrospinal fluid biomarkers, PET imaging, and blood biomarkers in early diagnosis. In addition, it reviews existing treatment strategies, including non-pharmacological methods such as cognitive training and lifestyle interventions. It also covers the current status and challenges in developing disease-modifying therapies, such as those targeting  $A\beta$  clearance and tau aggregation inhibition. By integrating key advances in AD's pathological mechanisms, diagnostic criteria, and treatment methods, this paper provides a theoretical reference for early AD identification, optimization of treatment strategies, and exploration of new intervention targets.

**Keywords:** Alzheimer's Disease, Pathology, Diagnosis, Therapeutic Strategies

## **1. Introduction**

Alzheimer's disease (AD) is a progressive, irreversible neurodegenerative disorder which represents the leading cause of dementia in the elderly, accounting for 60-80% of all dementia cases [1]. Its core feature is a progressive decline in cognitive function, ultimately severely impairing patients' activities of daily living, social functioning, and personality [2]. This imposes a substantial burden on patients, families, and society. Understanding the nature of AD, exploring its complex pathological mechanisms, identifying diagnostic biomarkers, and discovering effective prevention and treatment strategies remain one of the most pressing challenges in contemporary neuroscience and biomedical research.

This review aims to systematically synthesize the latest research advances in the field of AD. It conducts an in-depth exploration of AD's complex multifactorial pathological mechanisms, characterizes the clinical progression from preclinical stages to severe dementia, provides a critical

review of the current applications and future prospects of various diagnostic tools, and analyzes currently available or investigational therapies in clinical trials. By offering a comprehensive overview of the current AD research landscape, it seeks to establish a robust theoretical foundation for understanding the disease's essence and developing effective prevention and treatment strategies.

## 2. The disease essence and pathological core

The widely accepted core neuropathological features of AD are extracellular  $\beta$ -amyloid ( $A\beta$ ) deposits forming senile plaques and intracellular hyperphosphorylated tau protein aggregates forming neurofibrillary tangles (NFTs). However, in contrast to amyloid plaques, neurofibrillary tangles show lower specificity for AD and can be observed in a broader range of neurodegenerative diseases, such as progressive supranuclear palsy, corticobasal degeneration, and subtypes of frontotemporal dementia [3]. These pathological alterations do not occur randomly but follow specific spatiotemporal spreading patterns:  $A\beta$  deposition typically begins in the neocortex, whereas tau pathology originates in the entorhinal cortex and medial temporal lobe. As the disease progresses, they spread to the hippocampus, association cortices, and eventually the whole brain. This process closely parallels the trajectory of clinical cognitive decline. In recent years, the understanding of AD's pathological mechanisms has evolved beyond the simplistic “amyloid cascade hypothesis” towards a more complex, multifactorial model of interacting “pathogenic cascades”.

### 2.1. Amyloid- $\beta$ cascade hypothesis

$A\beta$  is a transmembrane peptide derived from amyloid precursor protein (APP), normally involved in synaptic formation and neuronal repair. Under physiological conditions, APP is sequentially cleaved by  $\alpha$ -secretase (such as ADAM10) and  $\gamma$ -secretase, generating the soluble  $sAPP\alpha$  fragment with neuroprotective properties. However, in AD, the proteolytic cleavage of APP may be altered by genetic mutations such as those in PSEN1 (presenilin-1) and PSEN2 (presenilin-2) [4]. First, APP is cleaved by  $\beta$ -secretase (BACE1) to release  $sAPP\beta$ , leaving a C-terminal fragment (C99), which is further processed by  $\gamma$ -secretase to generate  $A\beta$  peptides of different lengths (e.g.,  $A\beta_{40}$  and  $A\beta_{42}$ ). The  $A\beta$  subtype most associated with AD is  $A\beta_{42}$ , accounting for 5-10% of total  $A\beta$  production [5].

$A\beta$  aggregation begins intracellularly. Its monomers self-assemble into soluble oligomers through hydrophobic interactions and hydrogen bonding—these oligomers are the most neurotoxic form [6]. They further aggregate into insoluble protofibrils, eventually maturing into  $\beta$ -sheet-rich amyloid fibers that deposit as extracellular plaques. Studies show that  $A\beta$  aggregates can self-propagate, exhibiting prion-like self-replicating ability [7]. For a long time, AD research has focused on the extracellular plaques mentioned above. Traditional views hold that  $A\beta$  plaques initiate cell death by physically compressing neurons, triggering microglial activation and inflammation, or inducing oxidative stress. However, growing evidence—such as human autopsy studies—shows that neuronal loss and synaptic damage can occur years before plaques appear, suggesting that plaques may be a result rather than a cause of disease progression [8]. Additionally, focal plaques have been found to correlate with neuroinflammation and cognitive decline, while diffuse plaques show no significant association with pathological changes. This heterogeneity indicates that not all plaques are equally toxic, warranting a re-evaluation of plaques as therapeutic targets [9].

## 2.2. Tau pathology

Tau protein is a microtubule-associated protein that plays a key role in stabilizing microtubule structures and maintaining axonal transport. In AD, excessive activation of kinases leads to hyperphosphorylation of tau at serine/threonine residues. Specifically, glycogen synthase kinase-3 $\beta$  (GSK-3 $\beta$ ) phosphorylates tau by recognizing Ser/Thr-Pro motifs (such as Ser202/Thr205 and Ser396/Ser404), with its activity significantly elevated in AD. This process is inhibited by the Wnt/ $\beta$ -catenin pathway or activated by A $\beta$  oligomers [10]. Recent studies have shown that GSK-3 $\beta$  accelerates pathological spread by promoting tau release into extracellular vesicles through phosphorylation (Ibid). For cyclin-dependent kinase 5 (CDK5), its mechanism involves abnormal activation upon binding to p25. CDK5 primarily acts on the N-terminus of tau (e.g., Ser199/Ser202) and the microtubule-binding domain (e.g., Ser262/Ser356), leading to tau dissociation from microtubules [11]. Particularly, the activation of CDK5-p25 complex negatively correlates with tau phosphorylation levels, suggesting it may regulate pathological progression through other mechanisms. Other contributing kinases include the MARK family and tyrosine kinase (TYK2). MARK1/2/4 specifically phosphorylate the KXGS motifs of tau (e.g., Ser262/Ser356), disrupting microtubule binding and promoting tau aggregation. A recent *Drosophila* model study showed that MARK4 exacerbates tau toxicity by enhancing Ser396 phosphorylation, while MARK1/2 primarily regulate Ser262/356 sites [12]. TYK2 phosphorylates tau at Tyr29, inhibiting autophagic degradation and promoting pathological aggregation. Studies have confirmed that knocking down TYK2 reduces brain tau levels and alleviates neuroinflammation in mice [13]. Concurrently, reduced phosphatase activity in AD impairs dephosphorylation capacity, triggering tau dysfunction. For example, protein phosphatase 2A (PP2A), the main tau phosphatase, shows decreased activity in AD due to methylation or inhibitory proteins (e.g., SET), leading to insufficient tau dephosphorylation. The interaction between the catalytic subunit of PP2A (PP2Ac) and regulatory subunits (e.g., PR55 $\alpha$ ) is modulated by tau phosphorylation sites (e.g., Thr231), forming a negative feedback loop [14]. Following activation of kinases and phosphatases, hyperphosphorylated tau loses its ability to bind microtubules, disrupting axonal transport. Pathological tau self-aggregates into soluble oligomers (the main toxic species), which further assemble into paired helical filaments (PHFs) via  $\beta$ -sheet structures. These PHFs converge into intracellular neurofibrillary tangles (NFTs), ultimately causing neuronal structural collapse. Phosphorylated tau spreads between neurons via exosomes or prion-like mechanisms, with its seeding activity dependent on specific phosphorylation patterns (e.g., Ser262/356) [10].

Additionally, tau is a lysine-rich protein, particularly in regions spanning the microtubule-binding domain (MBD). Acetylation of specific lysine residues in tau has been linked to AD pathology in the brains of patients [15]. For instance, acetylation at K174 may prolong tau's half-life by disrupting its ubiquitination degradation pathway (e.g., inhibiting CHIP-mediated ubiquitination), thus promoting pathological aggregation (Ibid). K281, located in the KXGS motif of the microtubule-binding region (MTBR), when acetylated, inhibits tau-microtubule binding, reduces complex stability, and promotes tau dissociation from microtubules to form fibrils [16]. Acetylation at K274 and K321 influences tau aggregation behavior by modulating its conformational dynamics.

The relationship between tau acetylation and phosphorylation has been deeply studied. Acetylation can regulate phosphorylation sites via steric hindrance. For example, acetylation of K321 in tau inhibits downstream phosphorylation of Ser324, forming an "acetylation-phosphorylation switch" that directly regulates tau's microtubule-binding capacity and aggregation tendency through conformational changes [16]. This occurs because acetylation directly inhibits phosphorylation at adjacent sites by blocking kinase (e.g., GSK-3 $\beta$ ) binding sites or altering local

charge environments. Acetylation can also indirectly promote phosphorylation via kinase activation—studies have shown that acetylation stabilizes GSK-3 $\beta$  and enhances its catalytic activity, thereby facilitating pathological tau phosphorylation. However, acetylation does not always promote phosphorylation: for instance, acetylation of K280 in tau (catalyzed by p300) specifically enhances phosphorylation of Ser202/Thr205, Thr231, and Ser422, but has no effect on Ser396 [17]. Figure 1 illustrates the interconnected molecular mechanisms underlying tau pathology, including key elements such as neurofibrillary tangles, A $\beta$ -degrading enzymes, and associated signaling pathways.

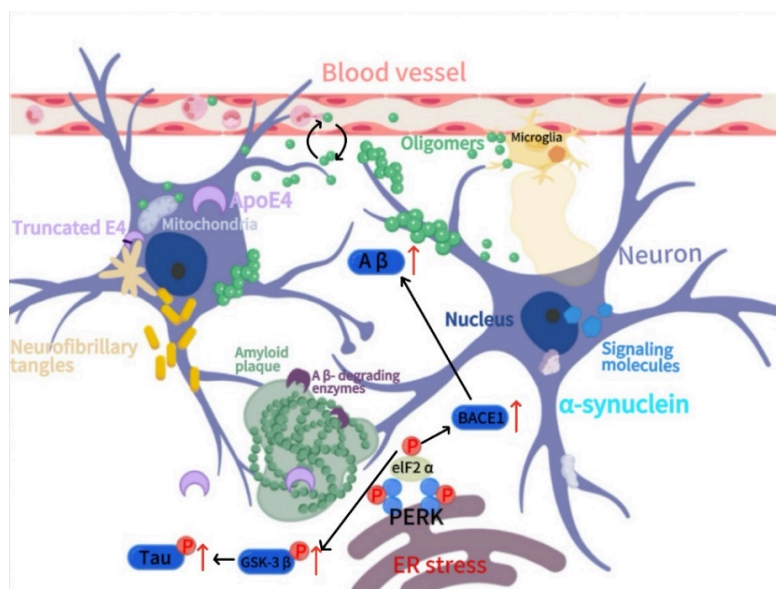


Figure 1. Key pathological components and their interactions in AD

### 2.3. ER stress

The endoplasmic reticulum (ER) is a key organelle involved in protein synthesis, folding, and calcium storage. In AD, certain factors can cause the demand for protein folding in the ER to exceed its processing capacity. This prompts cells to initiate the unfolded protein response (UPR), also known as the endoplasmic reticulum stress response. The triggering factors may involve a “triple hit” of A $\beta$ , tau, and calcium homeostasis imbalance. Upon UPR initiation, three pathways attempt to restore protein homeostasis. These branches are composed of protein kinase R-like endoplasmic reticulum kinase (PERK), inositol-requiring enzyme 1 (IRE1), and activating transcription factor 6 (ATF6) [18]. Mouse experiments with PERK, IRE1, and ATF6 gene knockouts have demonstrated their specific roles in both pathological and physiological endoplasmic reticulum stress responses. Normally, these three sensors remain inactive by binding to the chaperone BiP. However, when misfolded proteins accumulate in the ER lumen, BiP dissociates from PERK, IRE1, and ATF6, leading to their activation [19]. Activation of these three pathways induces recruitment and activation of immunosuppressive cells. This process exacerbates neuroinflammation and immune imbalance in AD, forming a vicious cycle of “ER stress-immunosuppression-neurodegeneration” [20]. Sustained or excessive ER stress ultimately induces apoptosis.

However, current research in this field involves several controversies. First, there is debate about whether ER stress is a triggering factor or a secondary effect. Some studies using animal models have found that ER stress can precede A $\beta$  deposition and tau pathology. For example, ER calcium leakage caused by PS1 mutations directly activates UPR, promoting A $\beta$  production and tau phosphorylation [21]. Conversely, some argue that A $\beta$  oligomers indirectly induce ER stress by

disrupting ER calcium homeostasis and protein folding environment, meaning ER stress is a downstream result of AD pathology. Second, the UPR pathway is considered to have a dual role. It has short-term protective effects: the PERK pathway relieves ER burden by inhibiting global protein synthesis and promoting molecular chaperone expression, while the IRE1 $\alpha$ -XBP1s pathway enhances protein folding capacity [22]. Additionally, it has long-term damaging effects: the persistently activated PERK-ATF4 pathway induces the pro-apoptotic factor CHOP, and IRE1 $\alpha$  exacerbates neuroinflammation via the TRAF2-NF- $\kappa$ B pathway while ATF6 dysfunction weakens anti-apoptotic signals [23].

## 2.4. Autophagy

Autophagy is a process in which cells form double-membrane autophagosomes to encapsulate damaged organelles, misfolded proteins, or pathogens. These autophagosomes then fuse with lysosomes to form autolysosomes, ultimately degrading the encapsulated components. Its core functions include clearing protein aggregates, maintaining organelle homeostasis, and providing energy stress adaptation. Functional autophagy is crucial for A $\beta$  peptide clearance and tau protein regulation in the mammalian brain. However, during AD progression, autophagic dysregulation exacerbates amyloidosis and tau pathology. First, A $\beta$  oligomers, particularly A $\beta$ 42, inhibit autophagosome-lysosome fusion, disrupting autophagic flux. For example, studies in mouse models have found that A $\beta$  binds to the lysosomal membrane protein LAMP1, impairing lysosomal acidification and preventing autophagosomes from completing degradation [24]. This leads to intracellular accumulation of A $\beta$ , forming a vicious cycle. Second, under normal conditions, tau proteins are degraded via autophagy and the ubiquitin-proteasome system (UPS). In AD, however, autophagic dysfunction prevents effective tau degradation. Hyperphosphorylated tau proteins aggregate into tangles, further inhibiting the autophagic pathway. For instance, tau can bind to the autophagic receptor protein p62, blocking p62-mediated autophagic degradation [25].

Throughout AD progression, autophagy's role evolves. Initially, neurons attempt to mitigate A $\beta$  and tau accumulation via autophagy, but regulatory dysfunction often renders this effort ineffective, potentially harming neurons due to overactivation. During AD progression, abnormal expression or post-translational modifications of autophagy-related genes (such as ATG5, Beclin-1) can impair autophagosome formation. For example, Beclin 1 deficiency causes A $\beta$  deposition, which weakens autophagy and promotes AD pathology [26]. However, in the study of Russel et al. (2013), activated mTORC1 can inhibit autophagy by regulating the Beclin1-VPS34 complex [27]. Moreover, drugs like rapamycin or activators of AMP-activated protein kinase (AMPK) can inhibit the mTOR pathway, potentially promoting autophagy [28].

Furthermore, mitochondrial dysfunction can trigger mitophagy, but this process is often inhibited in pathological conditions. For example, PINK1/Parkin is a key regulatory pathway for mitophagy. In AD, downregulation of PINK1 expression or abnormal ubiquitination of Parkin prevents the recognition and clearance of damaged mitochondria, leading to the release of reactive oxygen species (ROS). ROS exacerbate A $\beta$  deposition and tau phosphorylation. ROS from mitochondrial dysfunction damage autophagy-related proteins, further inhibiting autophagic flux and creating a vicious cycle [29].

### 3. Diagnosis

#### 3.1. Diagnostic criteria and framework

The NIA-AA research framework was jointly released by the National Institute on Aging (NIA) and the Alzheimer's Association (AA) [30]. Its core goal is to define AD based on biology, regard AD as a continuum from asymptomatic pathological accumulation to clinical symptoms, and objectively reflect disease progression through biomarkers. Notably, this framework mainly applies to research settings, not clinical diagnosis.

In 2018, the framework introduced the ATN classification system, which divides biomarkers into three categories [31]. Among them, A refers to A $\beta$  deposition, such as A $\beta$ -PET and cerebrospinal fluid (CSF) A $\beta$ 42/A $\beta$ 40 ratio; T represents pathological tau protein, such as tau-PET and CSF p-tau181/p-tau217; N refers to neurodegeneration, such as reduced FDG-PET metabolism and MRI brain atrophy (Ibid). The system emphasizes that the A+T+ combination is a specific marker of AD. While N-type biomarkers are common in AD, they have low specificity and may be caused by other diseases [32].

The NIA-AA framework divides AD into asymptomatic and symptomatic stages, and refines them by combining ATN biomarkers with cognitive performance [33]. Preclinical AD has three stages. Stage 1 involves only A $\beta$  deposition, no cognitive impairment, showing A+. Stage 2 is still asymptomatic, showing A+ and N+. By stage 3, there is A+, N+ and mild cognitive decline. Besides, Symptomatic AD has two types. The milder one is MCI due to AD: showing A+ and T+, with cognitive impairment but not meeting dementia criteria. The severe one is AD dementia: A+, T+ with significant cognitive and functional impairment.

#### 3.2. Biomarkers

The diagnosis of AD relies on the detection of biomarkers for its core pathological features, including A $\beta$  deposition, hyperphosphorylation of tau protein, and neurodegeneration. As mentioned earlier, a reduced A $\beta$ 42/A $\beta$ 40 ratio is a key early sign of AD, reflecting the formation of amyloid plaques. There are many methods to detect A $\beta$  currently. One is CSF analysis. This method obtains CSF through lumbar puncture to detect the A $\beta$ 42/A $\beta$ 40 ratio. Another method is PET imaging. Specifically, tracers such as Florbetapir, Florbetaben, or Flutemetamol are used to directly visualize amyloid plaques in the brain via positron emission tomography (PET). Studies have reported that the consistency between CSF A $\beta$ 42/A $\beta$ 40 ratio and amyloid PET imaging exceeds 90% [34]. Simple methods, such as a robust direct manufacturing process for multi-chamber paper devices using wax printing, can detect amyloid A $\beta$ 42 via copper-enhanced gold nanoprobe colorimetric immunoblotting. This improves sensing performance and saves time and cost. In addition, blood-based biomarkers (BBM) are increasingly used in clinical practice to support AD diagnosis. Compared to the traditional diagnostic methods mentioned above, BBM offers a more accessible and cost-effective alternative for AD biomarker detection and proves valuable in early AD diagnosis [35]. Some newly identified blood biomarkers such as A $\beta$ 42/A $\beta$ 43, p-tau 181, and A $\beta$ 42/APP669-711 can also be used for early AD detection [36].

Moreover, total tau (t-tau) and phosphorylated tau (p-tau181, p-tau217) are specific biomarkers for AD, and their presence can be detected in various ways. Lai et al. (2024)'s research has shown that CSF p-tau217 has a diagnostic specificity for AD as high as 98% [37]. PET imaging is also applicable to tau detection. New tau tracers such as MK-6240 (18F-MK-6240) can specifically show the distribution of AD-related tau pathology by targeting tau filaments. Similarly, in study of Lai et

al. (2024), blood p-tau217 exhibits excellent diagnostic efficacy, and its correlation with tau PET is better than that of other p-tau subtypes [37].

In addition, neurodegenerative markers reflect neuronal loss and synaptic dysfunction, including brain atrophy and reduced glucose metabolism, and can be used as one of the detection criteria. Among them, miRNA can be preserved as a diagnostic biomarker or therapeutic agent in these diseases [38]. Structural MRI can be used to assess the degree of atrophy in regions such as the hippocampus and medial temporal lobe, which is significantly related to AD progression [34]. Furthermore, fluorodeoxyglucose (FDG-PET) can show reduced glucose metabolism in the parietal and temporal lobes of the brain, so it can be used as an auxiliary method to diagnose AD and monitor disease progression. Additionally, the integration of FDG-PET with structural MRI improves the accuracy of brain age prediction, which may introduce a new approach for related multimodal brain age prediction research [39]. It is not difficult to see that CSF detection remains the main method for biomarker identification, but it requires a high-risk and uncomfortable sampling method. Therefore, people have been looking for new biomarkers that can be identified from other body fluids or tissues. Rajendran & Krishnan (2024) proposes that body fluids such as sweat, serum, saliva, mucosa, tears, and urine may serve as alternative sources of biomarkers helpful for early disease detection [40]. Notably, emerging studies have shown that artificial intelligence (AI) can enhance these imaging methods by improving the accuracy and efficiency of image analysis in the aforementioned neuroimaging techniques [41]. This enables earlier and more accurate detection of AD-related changes. Specifically, AI algorithms can identify AD biomarkers by analyzing genetic and proteomic data, aiding in early diagnosis.

## 4. Current therapeutic strategies

### 4.1. Non-pharmacological intervention

Non-pharmacological intervention is the core of comprehensive AD management. It can reduce behavioral symptoms, maintain functional independence, and synergize with medications. First, patients with AD can use cognitive training to maintain cognitive function. It mainly strengthens residual cognitive abilities through targeted tasks such as memory strategies and logical reasoning. Multi-domain cognitive training (CT) may delay structural brain decline in amnesic mild cognitive impairment (aMCI), thereby delaying the onset of AD [42]. A method similar to CT, repetitive transcranial magnetic stimulation (rTMS), has also been found to specifically improve global cognitive function, language performance, and memory in people with AD (pwAD), especially in the mild or early stages of the disease [43]. Furthermore, studies have found that rTMS combined with CT is more effective than rTMS alone in improving cognitive abilities in patients with AD [44-45].

Second, moderate physical activity (PA), as one protective factor, can delay cognitive decline in individuals with AD [46]. The association between PA and cognitive health in older adults may occur through regulating core pathophysiological changes related to the disease. Currently, PA has been proven to be a core contributor to healthy functional aging and can positively affect aging-related biology [47]. Regular physical activity, higher cardiorespiratory fitness, or a combination of both can significantly reduce cognitive impairment and lower the risk of AD.

In addition, behavioral interventions have been found to reduce neuropsychiatric symptoms. Through environmental adjustments (e.g., placement of familiar items) and structured activities (e.g., music therapy), symptoms such as agitation and depression in patients can be alleviated [48].

## 4.2. Pharmacological intervention

In the field of drug therapy for AD, besides the widely used cholinesterase inhibitors (such as donepezil, rivastigmine, galantamine) and NMDA receptor antagonists (such as memantine), research in recent years has continuously expanded new therapeutic strategies. For example, Lecanemab, a monoclonal antibody drug targeting amyloid deposition, works by clearing amyloid plaques in the brain to achieve disease-modifying effects [49]. Phase III clinical trials confirmed that intravenous infusion every two weeks significantly slows the rate of cognitive decline in patients with early AD. Another similar drug, Donanemab, targets glutamate-modified A $\beta$  and specifically binds to plaques [50]. Monthly infusions can effectively clear amyloid, and about 70% of patients can stop treatment after meeting the plaque clearance criteria within 18 months (Ibid). However, the therapeutic effects of such drugs may be affected by misunderstandings and statistical biases, and their safety and long-term efficacy need further improvement.

In terms of combination therapy, the combination of memantine and donepezil has been confirmed to have a synergistic effect in patients with moderate-to-severe AD [51]. Meta-analysis shows that the combination regimen is significantly superior to monotherapy in improving the Severe Impairment Battery (SIB) score. The remission rate of neuropsychiatric symptoms increases to 40%, with safety comparable to monotherapy [52]. This synergistic effect comes from the complementary mechanisms: memantine blocks glutamate excitotoxicity, and donepezil enhances cholinergic transmission.

For common neuropsychiatric symptoms in AD patients, such as agitation and hallucinations, Brexpiprazole is the first drug approved by the FDA for treatment. It improves agitation by regulating serotonin and dopamine receptors [53]. In addition, the new combination drug AXS-05 (dextromethorphan + bupropion) significantly delays the recurrence of agitation symptoms in Phase III trials [54]. Another innovative therapy, TTCM2 antibody, targeting both amyloid and tau protein pathology, can cross the blood-brain barrier via nasal spray delivery. It specifically binds to toxic tau oligomers, reduces neurofibrillary tangles, and improves cognitive function in animal models [55].

At the forefront of drug development, new breakthroughs in BACE inhibitors are noteworthy. The Tat-BACE1 peptide developed by the team from Chongqing Medical University reduces  $\beta$ -amyloid production by blocking BAG3 protein's stabilization of BACE1 enzyme [56]. It significantly improves synaptic function and spatial memory in AD model mice. Such strategies targeting protein interactions provide a new direction for AD treatment. In addition, drugs such as Xanomeline-trospium and dexmedetomidine have shown potential in alleviating AD-related psychosis and agitation in clinical trials [57]. The former improves cognition by selectively activating muscarinic receptors, and the latter reduces aggressive behavior by regulating the central noradrenergic system.

Also, inducing autophagy is a promising approach to treating neurodegenerative diseases. Among these, trehalose is an autophagy inducer with negligible adverse effects. It has been approved for human use by the FDA. Trehalose shows therapeutic effects in various experimental disease models. It can induce mTOR-independent autophagy. It also exerts chaperone-like effects on proteins, endowing them with their natural spatial structure. Thus, it can reduce the accumulation of neurotoxic abnormal/misfolded proteins [58].

It is worth noting that the use of all drugs should consider the patient's pathological stage and genetic characteristics. For example, APOE  $\epsilon$ 4 carriers respond better to the combination of memantine and donepezil, with a 20% higher cognitive improvement than non-carriers [59]. Amyloid-targeting drugs require confirmation of plaque load via PET imaging and vigilance against the risk of amyloid-related imaging abnormalities. Currently, AD drug therapy is evolving from

single symptom control to multi-target intervention. The comprehensive management model combining drug therapy and non-drug intervention has become the core strategy to delay disease progression and improve patients' quality of life.

## 5. Conclusion

This report systematically reviews parts of AD's core pathological mechanisms, diagnostic systems, and existing interventions. It offers an integrated perspective for understanding the disease's nature and guides clinical practice. However, given the pathological complexity and therapeutic challenges of AD, a limitation is that this report cannot comprehensively summarize all aspects of its pathology and treatment methods. Nonetheless, the complexity of AD implies the importance of interdisciplinary research. For pathological intervention, we should not focus solely on specific pathologies. Instead, we need to explore approaches like dual regulation of A $\beta$  and tau, or synergistic repair of endoplasmic reticulum stress and autophagic balance. In terms of diagnostics, efforts should be directed toward promoting the clinical translation of non-invasive biomarkers. Coupled with optimized multimodal imaging technologies, these efforts may accelerate the shift toward a "biomarker-driven" precision diagnosis paradigm. In the realm of therapeutic technologies, we must deepen research on the targeting and safety of innovative therapies. Combining intelligent non-pharmacological interventions will enable personalized treatment for patients. Importantly, with AI, we can integrate multi-omics data, optimize clinical trial design and translation pathways, and drive breakthroughs from symptom management to etiological treatment. Finally, biomarker-driven precision medicine and technology integration might bring new hope of earlier intervention and better efficacy to AD patients.

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