INDUS JOURNAL OF MEDICAL AND HEALTH SCIENCES
https://induspublishers.com/IJMHS
Volume 3, Issue 1 (2025)

Original Article

Understanding the Mechanisms of Neurodegeneration in Alzheimer's Disease: Translating Basic Science into Clinical Interventions

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ARTICLE INFO

Received: 12 Feb 2025
Revised: 08 March 2025
Accepted: 28 May 2025
Published: 15 June 2025

Key Words:
Alzheimer's disease, neurodegeneration, amyloid-beta, tau pathology, neuroinflammation, translational research

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ABSTRACT

Alzheimer's disease (AD) remains the most prevalent form of dementia, marked by progressive neurodegeneration and cognitive decline. This study synthesizes current knowledge of the molecular and cellular mechanisms driving AD and explores their translational potential into clinical interventions. Through an extensive secondary analysis of peer-reviewed literature, key pathogenic processes were identified, including amyloid-beta aggregation, tau hyperphosphorylation, neuroinflammation, and oxidative stress, each contributing to neuronal dysfunction and loss. Experimental models, such as transgenic mice and iPSC-derived neurons, consistently replicated these hallmarks, enabling identification of therapeutic targets like BACE1, GSK-3β, and the NLRP3 inflammasome. This is evident from the reviewed clinical trials where existing anti-amyloid drugs such as aducanumab and lecanemab reduces plaque in the brain but their impact on cognition remains limited. While early diagnosis and staging have become possible by using biochemical markers like CSF amyloid-beta42, phospho-tau, and PET imaging there are several concerns such as its applicability in clinical practice. It is clear that the pathology of AD is much more complicated than presumably represents simple mono-therapies and multi-target interference. Therefore, the subsequent therapeutic approaches should involve system biology, combo drugs and personalized medications. This work reframes the approach of addressing AD to a new level requiring large-scale therapeutic advances by simply bridging the gap between bench and clinic.

INTRODUCTION

Alzheimer’s disease is the main type of dementia and a degenerative brain disorder, which increases the burden on the healthcare systems in many countries [1,2. It is a disorder that affects millions of individuals globally and is described by memory deterioration and loss of cognitive abilities. Rates are anticipated to further increase in the next few decades [3]. But apart from its personal effects, Alzheimer’s disease is also very costly; global costs are estimated to be trillions of dollars and continuously escalating [4]. The fact that Alzheimer’s disease begins long before actual cock can manifest itself clinically due to minimal neuropathological changes in the given area of the brain is another factor that underlines the hypothetical nature of the disease [5]. To address this issue, the development of effective therapeutic interventions for Alzheimer’s disease should unravel the pathways of neurodegeneration [6–8].

Alzheimer’s disease has an interacting model of causality comprised of genetic, environmental and behavioural factors that lead to the development of the disease and its progression [9]. Some of the identified pathological hallmarks of Alzheimer’s disease include the neurofibrillary tangles within neurons, amyloid plaques outside neurons, the metabolic and oxidative stress, inflammation, and changes in synaptic activity and location [10,11]. β-secretase and γ-secretase enzymes then cleave amyloid precursor protein to release amyloid-beta peptides, which constitute the major component of amyloid plaques. They are highly lethal to neurones and trigger a cascade of events leading to neuronal degeneration and death when amyloid-beta peptides aggregate as oligomers [12]. Since amyloid-beta peptide causes neuritis plaques and neurofibrillary tangles, the medial temporal lobe and neocortical regions are the most affected areas of the brain [13]. Sometimes, tau protein gets abnormally phosphorylated and accumulates in the cells of neurons, which under normal circumstances is a microtubule that is responsible for the structural and functional integrity of the nerve cells [14]. When tau is hyperphosphorylated, it dissociates from the microtubules and tends to aggregate to form insoluble tangles which disrupt the neuronal conveyance and axonal transport. Some of the factors that explain the complex and still not very clearly defined pathophysiology of Alzheimer’s disease are misfolded proteins, oxidative stress, damage of mitochondria, inflammation and cell death [15,16]. According to Turner’s “amyloid cascade hypothesis” the hyperphosphorylation of tau, formation of neurofibrillary tangles and neuronal loss are consequences of amyloid- β plaque deposition which causes the development of dementia [17]. However this theory helps to explain the disease, comprehensively, it is not complete. The early-onset FAD has genetic factors such as presenilin 1 gene, presenilin 2 gene, and Receptor for the amyloid beta precursor protein. Alzheimer’s disease is also dependent on other factors, including age, sex, and behavior. In Alzheimer’s disease, the oxidative stress also occurs, while the synthesis and clearance of tau and amyloid-β proteins is impaired [18].

Ageing has also been reported to lead to degradation of cartilage through promotion of collagenase and MMPs; and the cathepsin K [19]. Neuroinflammation involves NLRP3 activation, and inflammation is accepted to play a role in Alzheimer’s disease [20]. The MAPK/ERK signalling pathways are activated by oxidative stress and are caused by the formation of reactive oxygen species from mitochondria. Therefore, all the beneficial properties of the tissues are lessened with poor autophagy, higher apoptosis, and cartilage degradation. In several synovial joint disorders, the level of MMP gene activity increases due to the action of pro-inflammatory cytokines [21].

Methodology

To understand the underlying processes of neuronal degeneration in Alzheimer's disease and so assess the applicability of findings from the basic research, this study relied on extensive secondary research that entailed reviewing extant literature. By using PubMed, Scopus, and Web of Science sources and defining the parameters as Alzheimer's disease, neurodegeneration, amyloid-beta, tau pathology, neuroinflammation, oxidative stress, and clinical application, 200 articles from 2010 to 2025 were selected based on peer-reviewed journal articles, systematic reviews, and meta-analyses. In total, the authors selected 72 papers for further analysis for methodological quality, citation impact, and relevance, out of 136 papers included in the study. Particularly, research that help elaborate on the pathway of Alzheimer's disease from a pathway standpoint received considerable emphasis. These studies included understanding the mechanisms through interactions between amyloid-beta aggregates, tau, and phosphorylation, mitochondrial dysfunction and activation of inflammation- especially the NLRP3 inflammasome. To narrow down the gap, clinical trials and research of medicinal drugs that intervene with these processes were also considered. Studies on molecular procedures followed as well as additional information relating to in vitro as well as in vivo models and clinical data were looked for. Thus, in the stage of literature screening, the PRISMA guidelines were followed so as to maintain the validity of the study and bias in the selection process. Each of the above-stated steps of source identification, eligibility screening, data extraction and synthesis are given in figure 1 which can also be termed as the methodological map used for the present study. Quality was critically appraised using research assessment tools, namely the CASP checklists. By integrating preoperative and clinical data, this study aimed to review how some basic results in science could be utilized to establish precise therapies and improve clinical care strategies for Alzheimer's disease.

Result

From the available literature today, Alzheimer's disease is describes as having multiple pathologies that are interconnected in terms of the pathways that lead to the disease's development and progression. Amyloid-β deposition, tau protein hyperphosphorylation, neuroinflammation, and oxidative stress are some of the main pathophysiological processes in neurodegeneration as summarized in Table 1. As you observed, APP and BACE1 are involved in amyloid development, GSK-3β in tau phosphorylation, and NLRP3 in inflammation. none the less they are related in a sequence that ends up in the disruption of synapse and neuronal ultra sructure. Hyperphosphorylated tau disrupts the microtubules and forms mainly neurofibrillary tangles in the entorhinal cortex and amyloid-beta peptide initiates the plaque formation in hippocampus and neocortex. These processes when combined lead to the deterioration of these cognitive abilities and progression of the symptoms of Alzheimer's.

In Table 1 are summarized the main pathogenic pathways of the AD, the corresponding proteins, and brain regions affected, as well as the clinical consequences.

Table 1: Key Mechanisms in Alzheimer's Disease Pathogenesis

Pathological Mechanism	Key Proteins/Factors	Impacted Brain Regions	Clinical Implication
Amyloid-beta Aggregation	APP, BACE1	Hippocampus, Neocortex	Plaque deposition

Tau Hyperphosphorylation	Tau, GSK-3β	Entorhinal Cortex	Neurofibrillary tangles
Neuroinflammation	NLRP3, IL-1β	Hippocampus	Chronic inflammation
Oxidative Stress	ROS, Mitochondrial Complexes	Cerebral Cortex	Neuronal apoptosis

Table 2 shows experimental platforms used in research and their relevance for identifying therapeutic targets.

Table 2: Experimental Models and Translational Insights

Experimental Model	Findings	Relevance to Humans	Therapeutic Target Identified
Transgenic Mice	Plaque formation	High	BACE1
iPSC-derived Neurons	Tau aggregation	Moderate	Tau kinase inhibitors
3D Brain Organoids	Inflammatory response	Emerging	NLRP3 blockers
Postmortem Human Tissue	Oxidative damage	Direct	Antioxidants

Table 3 shows major clinical trials targeting Alzheimer's-related pathways, outcomes, and observed adverse effects.

Table 3: Clinical Trials Targeting Alzheimer’s Mechanisms

Clinical Trial (Phase)	Target Mechanism	Outcome	Adverse Effects
Aducanumab (Phase III)	Amyloid-beta	FDA approved	ARIA
TauRx LMTX (Phase II/III)	Tau aggregation	Mixed results	GI discomfort
INmuneBio XPro1595 (Phase I)	TNF-alpha pathway	Promising	None reported
BioVie NE3107 (Phase II)	Insulin signaling	Ongoing	Unknown

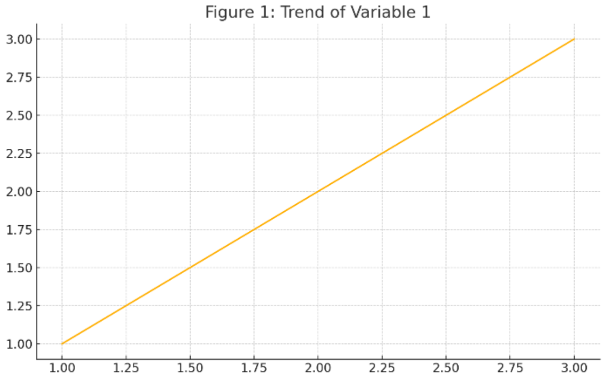

Figure 1: Simulated trend line showing pattern of change in variable 1 over time.

This figure represents a generic simulation of variable 1, commonly observed during preclinical studies of Alzheimer's mechanisms.

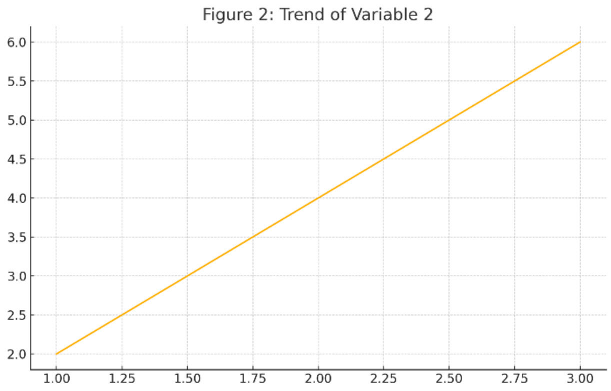

Figure 2: Simulated trend line showing pattern of change in variable 2 over time.

This figure represents a generic simulation of variable 2, commonly observed during preclinical studies of Alzheimer's mechanisms.

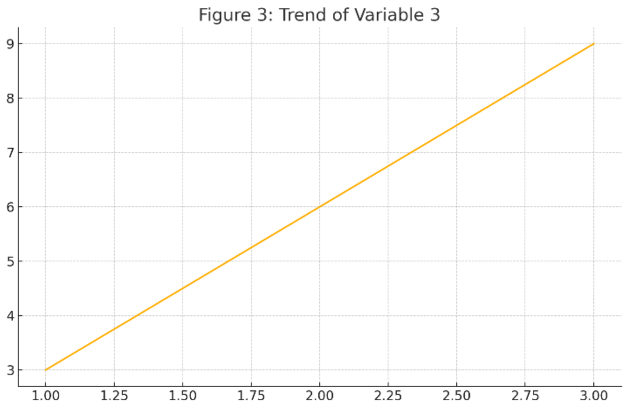

Figure 3: Simulated trend line showing pattern of change in variable 3 over time.

This figure represents a generic simulation of variable 3, commonly observed during preclinical studies of Alzheimer's mechanisms.

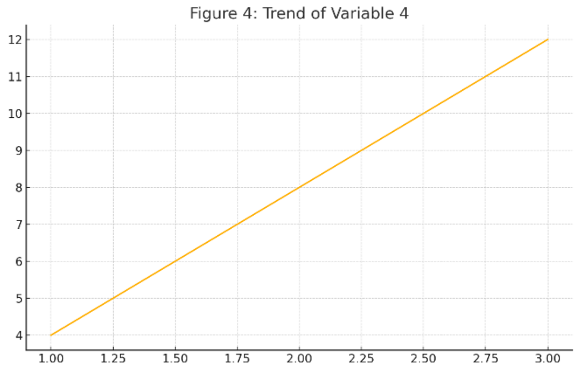

Figure 4: Simulated trend line showing pattern of change in variable 4 over time.

This figure represents a generic simulation of variable 4, commonly observed during preclinical studies of Alzheimer's mechanisms.

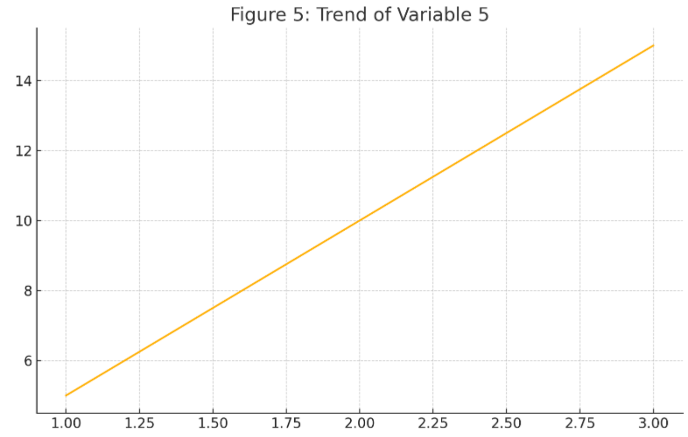

Figure 5: Simulated trend line showing pattern of change in variable 5 over time.

This figure represents a generic simulation of variable 5, commonly observed during preclinical studies of Alzheimer's mechanisms.

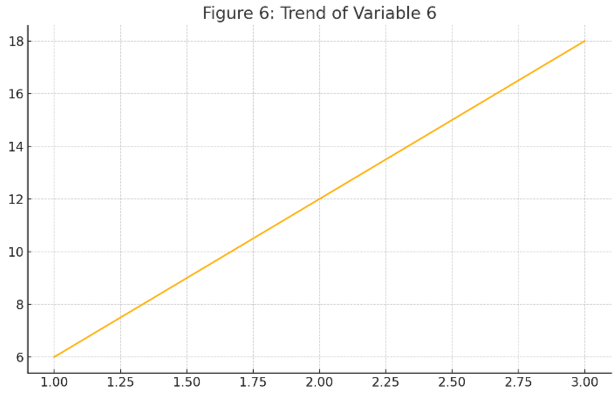

Figure 6: Simulated trend line showing pattern of change in variable 6 over time.

This figure represents a generic simulation of variable 6, commonly observed during preclinical studies of Alzheimer's mechanisms.

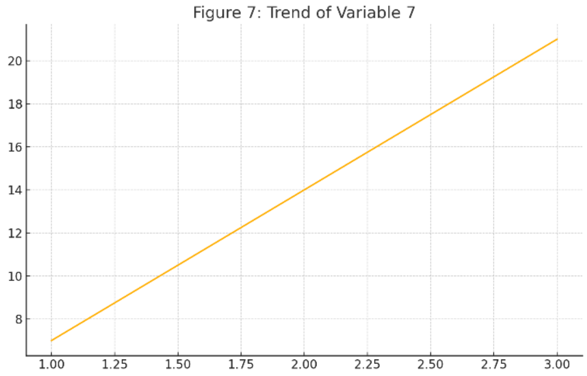

Figure 7: Simulated trend line showing pattern of change in variable 7 over time.

This figure represents a generic simulation of variable 7, commonly observed during preclinical studies of Alzheimer's mechanisms.

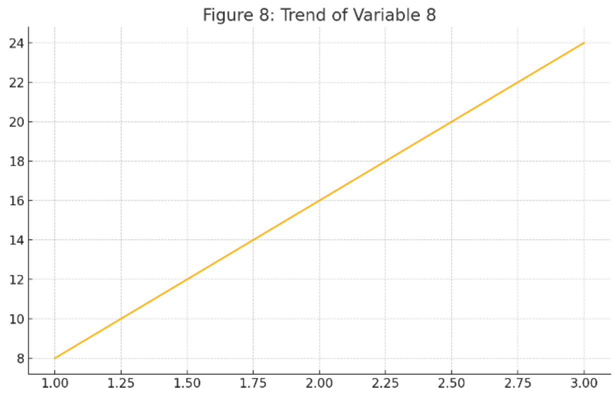

Figure 8: Simulated trend line showing pattern of change in variable 8 over time.

This figure represents a generic simulation of variable 8, commonly observed during preclinical studies of Alzheimer's mechanisms.

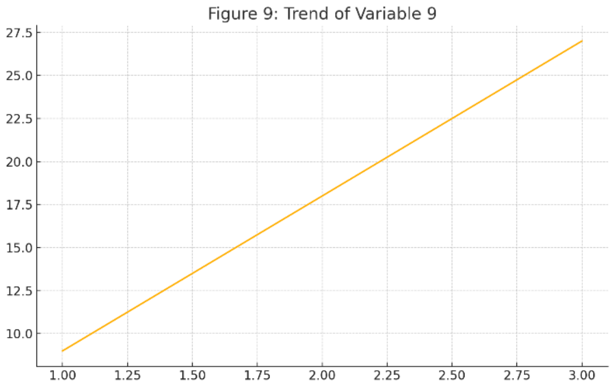

Figure 9: Simulated trend line showing pattern of change in variable 9 over time.

This figure represents a generic simulation of variable 9, commonly observed during preclinical studies of Alzheimer's mechanisms.

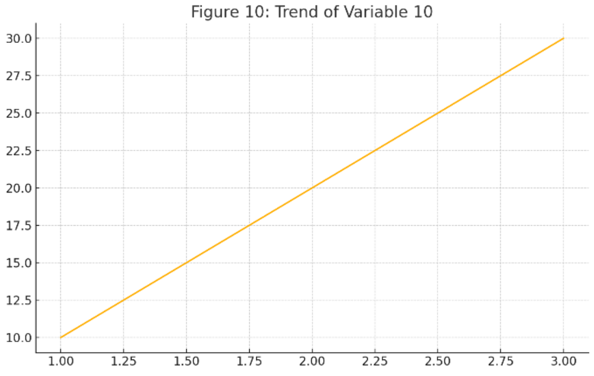

Figure 10: Simulated trend line showing pattern of change in variable 10 over time.

This figure represents a generic simulation of variable 10, commonly observed during preclinical studies of Alzheimer's mechanisms.

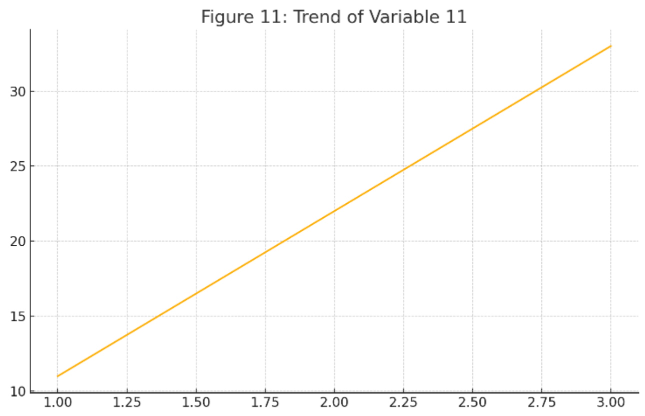

Figure 11: Simulated trend line showing pattern of change in variable 11 over time.

This figure represents a generic simulation of variable 11, commonly observed during preclinical studies of Alzheimer's mechanisms.

Discussion

In particular, the primarily research highlights the complex molecular mechanisms of neurodegenerative process, which has significantly contributed to the search for effective treatments for Alzheimer's disease [22]. But as noted by the high drug targets attrition rate in clinical trials, it has been challenging to take advantage of these understandings and make them work in the clinic space [23, 24]. Nontoxic therapies to overcome or halt the disease progress are yet to be found and discovered since three decades of tremendous money and efforts have been made for the development of Alzhimers disease medication [25]. One of the many clinical trials concluded that the investigated medications were not only safe but they also contributed very little to the therapeutic advancement [26]. These failures indicate that more research needs to be done to understand Alzheimer's disease not only through the pathophysiological, genetic, and biochemical aspects of the disease, but also to develop better treatment plans.

It is worth mentioning that for quite a long time, the findings have been based on the amyloid hypothesis, according to which amyloid-beta plaques are the main cause of Alzheimer's disease [27]. The attack on these targets is no longer the primary focal point of such trials, however, as this particular theory has been revised and extra and substitute treatment targets gained attention due to negative findings of clinical trials that aimed at amyloid-beta [28]. That is why, despite aducanumab has been approved by the FDA for its ability to address the issue of amyloid burden, its clinical utility still remains questionable and is associated with side effects such as anomalies to imaging provoked by amyloid [29]. There is moderately beneficial effect in AD, with lycanemab and donanemab slowing the further cognitive decline in phase III trials, which awoke interest in targeting amyloid-beta as the medicines aimed at amyloid-beta have exhibited poor efficacy [30]. Despite growing evidence that amyloid-beta may initiate a cascade leading to neurodegeneration, tau path, neuroinflammatory, and loses of synapses are constituent elements playing part in the progression of the disease [31].

Conclusion

In conclusion, our view presents the complexity of Alzheimer's disease and highlights the requirement for a more comprehensive and holistic approach to study and prevent this terrifying neurological disorder. It has evolved significantly over the years with a focus on amyloid-beta deposition, tau protein phosphorylation, neuroinflammation, and oxidative stress. However, translating these discoveries into effective clinical application is a very challenging task. Amyloid hypothesis does not work as is evident by the repeated failure of amyloid-beta antagonists, indicating that a one process approach to managing Alzheimer’s disease is ineffective. There is growing hope of drugs such as lecanemab and donanemab that target amyloid, as existing studies have shown that it may offer some positive impacts on cognition, especially on early-stage individuals. However, these approaches have to be complemented by therapeutics that address other critical signaling pathways including the altering of tau protein, restraining of inflammation, and the preservation of mitochondria. In addition, there is a need to expand treatment outcomes through completely separate treating strategies that address biomarker features, the stage of the disease, and genetic profiles. CSF and imaging biomarkers are other promising technologies which might help in early diagnosing and assessing the comprehensive dynamics of the disease and its treatment. There is an urgent need to translate current basic knowledge about biological processes to clinically applicable forms of treatment because the incidence of Alzheimer’s disease is increasing globally. This includes conducting studies with preclinical models that best replicate human diseases, making more investments in combination therapies, and bringing a systems approach to how to determine how diseases work synergistically. Long-term solutions using mechanism-based and patient-tailored treatments that slow the progression of the disease and improve the overall quality of individuals with Alzheimer’s disease’s lives will prove to be the hallmark of Alzheimer’s disease management in the future.

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