

# Challenges in Alzheimer's Drug Development: Failures, Therapeutic Barriers and Clinical Translation

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**Abstract.** Alzheimer's disease (AD) continues to pose a significant challenge in pharmaceutical research, with drug development marked by high attrition rates despite decades of investigation. Numerous therapeutic candidates, particularly those targeting amyloid-beta and tau proteins, have shown promise in preclinical studies but failed to produce substantial clinical benefits. Most failures occur in late-stage trials, especially Phase II and III, due to limited therapeutic efficacy, unforeseen adverse effects, or inability to alter disease progression. The complex and multifactorial nature of AD pathology including neuroinflammation, synaptic degeneration, and metabolic disturbances makes developing a single curative treatment highly difficult. This review examines the underlying reasons for these setbacks, focusing on clinical trial outcomes and the limitations of previous pharmacological approaches. Examples of unsuccessful candidates underscore persistent gaps in understanding disease mechanisms and therapeutic targeting. Addressing these challenges requires a paradigm shift toward early diagnosis, patient-specific precision medicine, and combination therapy strategies. Additionally, advancing biomarker discovery, employing adaptive and innovative trial designs, and exploring novel molecular targets may improve the likelihood of clinical success. By integrating these approaches, future research holds the potential to overcome existing barriers and deliver effective interventions for AD.

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## 1. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder and one of the most pressing health challenges of the 21st century. Characterized by cognitive decline, memory impairment, and functional deterioration, AD places a substantial burden on patients, caregivers, and healthcare systems worldwide. Despite decades of intensive research and investment, effective disease-modifying therapies remain elusive, and most available treatments provide only symptomatic relief. The high rate of clinical trial failures underscores the complexity of the disease and the limitations of current therapeutic approaches.

Drug development for Alzheimer's disease is hindered by several factors, including an incomplete understanding of disease pathophysiology, the multifactorial nature of neurodegeneration, and difficulties in translating preclinical findings into clinical success. Biological barriers such as the blood-brain barrier further complicate drug delivery, while patient heterogeneity contributes to inconsistent therapeutic responses. Additionally, the long disease course and slow progression require extended clinical trials, which increase financial and logistical challenges. Given these obstacles, the field has shifted toward exploring novel therapeutic targets, biomarker-driven strategies, and precision-medicine approaches to improve translation from bench to bedside [1].

This review aims to critically examine the major challenges underlying Alzheimer's drug development, highlight reasons for past failures, and discuss strategies that may enhance the success of future therapeutic interventions. Affecting more than 55 million people globally, AD has become a major public health concern with profound implications for individuals and society. Its burden continues to rise with the aging population, representing a critical challenge for healthcare systems in both developed and developing countries. Despite decades of extensive research, there is still no definitive diagnostic tool or cure for AD, and the disease disrupts social and economic progress worldwide.

Recent advances in molecular tools and techniques for diagnostic and therapeutic interventions in AD particularly those in advanced stages of clinical development are receiving special attention. Contributions from our laboratory to the development of selective molecular tools targeting multifaceted toxicity in AD are also included. According to several large-scale investigations, more than 95% of AD drug candidates have failed in clinical trials, with a significant proportion discontinued during Phase II and III studies.

Historically, therapeutic targets have focused on the hallmark pathologies of AD: extracellular amyloid-beta ( $A\beta$ ) plaques and intracellular neurofibrillary tangles composed of hyperphosphorylated tau protein. Various therapeutic strategies including monoclonal antibodies, secretase inhibitors, tau aggregation inhibitors, and anti-inflammatory agents have been investigated. However, despite promising preclinical outcomes, most candidates have failed to produce significant cognitive improvement or disease-modifying effects in human trials [2].

Extracellular senile plaques of  $A\beta$  and intracellular neurofibrillary tangles of phosphorylated tau (pTau) are considered the primary pathophysiological hallmarks of AD. In an effort to explain the disease's complexity and multifactorial nature, several hypotheses have been proposed, including  $A\beta$  aggregation, tau accumulation, metal dyshomeostasis, oxidative stress, cholinergic dysfunction, inflammation, and impaired autophagy. However, none of these hypotheses independently accounts for all pathological features observed in AD. The interplay among these multiple pathways suggests that a single-target therapy is unlikely to halt or reverse disease progression.

Given the repeated failures of previous therapeutic candidates, there is growing consensus that traditional approaches to AD therapy need to be reconsidered. A deeper, more holistic understanding of the molecular mechanisms driving AD pathogenesis along

with the development of early biomarkers, precision-medicine strategies, and innovative clinical trial designs may improve the likelihood of therapeutic success.

This review aims to critically evaluate the reasons behind the repeated failures of AD drug candidates, with particular emphasis on clinical trial data, pharmacological limitations, and mechanistic shortcomings. By identifying the pitfalls of past strategies, this paper also outlines emerging directions that may guide future efforts in the search for effective Alzheimer's disease treatments [3].

## **2. Current Therapeutic Approaches for Alzheimer's Disease**

Over the past two decades, therapeutic strategies for Alzheimer's disease (AD) have largely focused on its characteristic pathologies, namely amyloid-beta ( $A\beta$ ) plaques and tau neurofibrillary tangles. However, as our understanding of AD pathology has expanded, additional targets such as neuroinflammation, mitochondrial dysfunction, synaptic loss, and metabolic impairments have gained attention. Despite these diverse approaches, the majority of drug candidates have failed to demonstrate clinical benefits, reflecting the complexity and heterogeneity of AD.

### **2.1 Amyloid-Targeting Therapies**

Amyloid-beta accumulation has long been considered a central driver of AD, forming the basis of the amyloid cascade hypothesis. This hypothesis describes the generation, misfolding, aggregation, and deposition of  $A\beta$  peptides as senile plaques in the brain, ultimately leading to neurodegeneration. Therapeutic strategies targeting this pathway aim to prevent  $A\beta$  production, inhibit its aggregation, or facilitate its clearance from the brain. These include monoclonal antibodies (mAbs) designed to bind  $A\beta$  and promote its removal through immune-mediated mechanisms (e.g., bapineuzumab, solanezumab). Secretase inhibitors also play an important role by blocking the enzymes responsible for  $A\beta$  generation. While these therapies have shown success in reducing amyloid plaque burden, they have consistently failed to improve cognitive outcomes [4].

### **2.2 Tau-Targeting Therapies**

Tau is a microtubule-associated protein (MAP) whose primary function is to modulate microtubule stability. It is predominantly found in the axons of neurons, where it interacts with axonal microtubules. Uncontrolled phosphorylation of tau leads to microtubule disintegration and the subsequent intracellular aggregation of phosphorylated tau (pTau) to form neurofibrillary tangles (NFTs), which constitute the pathological basis of the tau hypothesis of AD. Therapeutic strategies targeting tau include anti-tau monoclonal antibodies, which target extracellular tau to prevent its cell-to-cell spread. Tau aggregation inhibitors disrupt the formation of tau fibrils, while tau kinase inhibitors aim to reduce tau hyperphosphorylation. However, similar to amyloid-targeting therapies, tau-targeting drugs have also failed to demonstrate clinical efficacy due to the absence of significant cognitive benefit [5].

### **2.3 Neuroinflammation and Immune Modulation**

Neuroinflammation is a natural defense mechanism in living systems, in which the immune system recognizes pathogens, debris, misfolded proteins, and damaged cells and

initiates their degradation and clearance. Under AD conditions, amyloid deposits (senile plaques and neurofibrillary tangles) and damaged or dead neurons activate microglia, leading to an inflammatory response. Therapies such as nonsteroidal anti-inflammatory drugs (NSAIDs) and microglial inhibitors have been investigated to modulate immune pathways and reduce neuronal damage.[6]

## 2.4 Neuroprotection and Metabolic Modulation

Some drugs, such as neuroprotective agents (e.g., latrepirdine), insulin sensitizers (e.g., insulin, pioglitazone), cholinesterase inhibitors, and NMDA receptor antagonists (e.g., donepezil, rivastigmine, memantine), have targeted neuronal survival, synaptic function, and energy metabolism, as AD involves mitochondrial dysfunction and reduced cerebral glucose metabolism [7].

## 3. Case Studies: Clinical Failures of Major AD Drug Candidates

Despite the identification of multiple therapeutic targets in Alzheimer's disease, nearly all candidate drugs have failed to demonstrate efficacy in large-scale human trials. This section outlines representative examples of drugs from key therapeutic classes, detailing their mechanisms and the reasons for their clinical failure.

### 3.1 Amyloid-Targeting Therapies

They are monoclonal antibodies targeting aggregated A $\beta$ . Initially it failed in two Phase III trials (EMERGE and ENGAGE) due to lack of consistent cognitive benefit. Amyloid-Targeting Therapies and their drugs were approved by the FDA in 2021 via the Accelerated Approval pathway based on amyloid plaque reduction and not clinical efficacy. Widespread criticized due to high cost, unclear benefits, and risks of ARIA (amyloid-related imaging abnormalities).

#### 1. Aducanumab (Biogen)

This monoclonal antibody targets aggregated A $\beta$  but initially failed in two Phase III trials (EMERGE and ENGAGE) due to a lack of consistent cognitive benefit. Despite these setbacks, it was approved by the FDA in 2021 through the Accelerated Approval pathway, based solely on its ability to reduce amyloid plaque burden rather than demonstrated clinical efficacy. The approval generated widespread criticism because of its high cost, uncertain therapeutic benefits, and the associated risk of amyloid-related imaging abnormalities (ARIA).

#### 2. Solanezumab (Eli Lilly)

This therapeutic agent binds soluble monomeric A $\beta$  but failed in multiple Phase III trials (the EXPEDITION series), showing no significant improvement in cognition in patients with mild-to-moderate AD. Its lack of efficacy is attributed to targeting monomeric A $\beta$ , which may not represent the toxic species driving Alzheimer's pathology.

#### 3. Bapineuzumab (Pfizer, Johnson & Johnson)

Instrument: Detached immunotherapy focusing on A $\beta$  plaques.

Result: Fizzled Stage III due to need of clinical adequacy and expanded chance of vasogenic edema (ARIA-E), especially in APOE4 carriers.

#### 4. Semagacestat (Eli Lilly)

Component:  $\gamma$ -secretase inhibitor implied to decrease A $\beta$  generation.

Result: Ended in Stage III; declined cognition and caused unfavorable impacts counting skin cancer and diseases.

Reason for disappointment:  $\gamma$ -secretase too forms Indent and other basic proteins, driving to off-target harmfulness [8].

### 3.2 Tau-Targeting Therapies

Tau-targeting treatments aim to interfere with the abnormal aggregation and spread of tau proteins, which form neurofibrillary tangles in Alzheimer's disease. These tangles disrupt neuronal function and are closely associated with disease severity. Therapeutic strategies include anti-tau monoclonal antibodies that prevent the extracellular spread of tau between neurons, tau aggregation inhibitors that stop tau from forming toxic clumps, and kinase inhibitors that reduce tau hyperphosphorylation. Despite these promising mechanisms, most tau-targeting drugs have failed to demonstrate cognitive benefits in clinical trials. This lack of efficacy may be due to late intervention, poor brain penetration, or insufficient engagement of toxic tau species.

#### 1. Gosuranemab (Biogen)

Component: Monoclonal counter acting agent focusing on extracellular tau.

Result: Stage II trial (TAURIEL) fizzled; no impact on tau spread or clinical endpoints.

Reason for disappointment: Conceivable deficiently engagement of intracellular tau pathology and focusing on extracellular tau may be as well late in infection movement.

#### 2. Semorinemab (Genentech)

Instrument: Anti-tau monoclonal counter acting agent.

Result: Stage II fizzled to appear cognitive advantage despite a few biomarker changes.

Reason for disappointment: Destitute relationship between biomarker lessening and cognitive enhancement.

#### 3. TRx0237 (LMTX, TauRx)

Instrument: Tau accumulation inhibitor.

Result: Fizzled to illustrate critical advantage over fake treatment in Stage III.

Reason for disappointment: Conflicting comes about, with any watched advantage likely driven by unseemly control bunch comparisons [9].

### 3.3 Anti-Inflammatory Approaches

Anti-inflammatory approaches in Alzheimer's disease aim to reduce chronic neuroinflammation, which contributes to neuronal damage and disease progression. These strategies target activated microglia and astrocytes, which release pro-inflammatory cytokines in the AD brain. Some treatments involve the use of nonsteroidal anti-inflammatory drugs (NSAIDs), while others explore immune modulators, cytokine inhibitors, or drugs that regulate inflammatory signaling pathways. However, most clinical trials have failed, possibly due to late-stage intervention or the non-specific targeting of inflammation. It is also possible that some inflammatory responses are protective, making broad suppression counterproductive. Despite these setbacks, inflammation remains a promising adjunctive therapeutic target alongside amyloid- and tau-based treatments.

#### 1. Rofecoxib and Naproxen (NSAIDs)

Instrument: COX-2 inhibitors pointed at lessening neuroinflammation.

Result: Expansive trials like Adjust appeared no cognitive security, and long-term utilize indeed expanded unfavorable occasions.

Reason for disappointment: Timing; aggravation may be auxiliary or late-stage, and NSAIDs need brain specificity.

#### 2. Azeliragon

Component: Represses Seethe (receptor for progressed glycation end-products), thought to decrease aggravation and A $\beta$  transport.

Result: Fizzled in Stage III Undaunted trial; no distinction from fake treatment.

Reason for disappointment: Hazy instrument in people and destitute CNS entrance.[10]

### 3.4 Neuroprotective and Metabolic Modulators

Neuroprotective and metabolic modulators aim to preserve neuronal function and improve brain energy metabolism in Alzheimer’s disease. These therapies focus on enhancing mitochondrial health, regulating glucose utilization, reducing oxidative stress, and supporting synaptic function. Examples include latrepirdine (a neuroprotective agent), pioglitazone (an insulin sensitizer), and intranasal insulin, many of which were repurposed from drugs used in diabetes or psychiatric disorders. Despite promising hypotheses, most have failed in clinical trials due to limited efficacy, poor brain penetration, or uncertain relevance to AD pathology. Table 1 highlights major Alzheimer’s disease drug candidates and their reasons for clinical failure. Nevertheless, targeting metabolic dysfunction remains a promising strategy when used alongside other therapeutic approaches.

#### 1. Latrepirdine

Component: Antihistamine with proposed neuroprotective properties.

Result: Stage III trial (Association) appeared no enhancement in cognition or day by day work.

Reason for disappointment: Viability seen in prior Russian ponders might not be imitated; likely non-specific impacts.

#### 2. Pioglitazone

Component: PPAR- $\gamma$  agonist; pointed at moving forward affront affectability and lessening irritation.

Result: Fizzled in Stage III no delay in illness onset in high-risk people.

Reason for disappointment: Inadequately brain entrance, and Advertisement pathology may not be turned around by metabolic balance alone.

#### 3. Intranasal Affront

Component: Improves brain affront signaling to counter cognitive decay.

Result: Blended comes about; later bigger trials fizzled to illustrate factually critical cognitive benefits.

Reason for disappointment: Conveyance inconstancy and need of focused on dosing [11].

**Table 1.** Examples of Major Alzheimer’s Disease Drug Candidates and Reasons for clinical Failure.

| Drug Candidate | Target/Mechanism                                   | Clinical Phase            | Outcome   | Key Reason for Failure  |
|----------------|--|---------------------------|---|---|
| Aducanumab     | Monoclonal antibody targeting aggregated A $\beta$ | Phase III (EMERGE ENGAGE) | Approved via Accelerated Approval (2021) but with controversy | Reduced amyloid plaques without consistent cognitive benefit; high risk of ARIA |

|              |   |                            |   |   |
|--------------|---|----------------------------|---|---|
| Solanezumab  | Binds soluble monomeric A $\beta$               | Multiple Phase III Trials  | No significant cognitive improvement                | Targeted non-toxic A $\beta$ species          |
| Bapineuzumab | Passive immunotherapy against A $\beta$ plaques | Phase III                  | No clinical efficacy; ARIA-E Risk in APOE4 carriers | Safety concerns and lack of efficacy          |
| Semagacestat | $\gamma$ -secretase inhibitor                   | Phase III                  | Worsened cognition adverse effects                  | Off-target toxicity affecting Notch signaling |
| Gosuranemab  | Anti-tau monoclonal antibody                    | Phase II (TAURIEL)         | No impact on clinical endpoints                     | Ineffective engagement of tau pathology       |
| Pioglitazone | PPAR- $\gamma$ agonist (insulin sensitizer)     | Phase III (TOMORROW trial) | No delay in disease onset                           | Limited brain penetration                     |

### 3.5 Symptomatic Treatments (Endorsed Drugs)

Symptomatic medications for Alzheimer’s disease are approved drugs that help manage cognitive symptoms but do not alter the course of the disease. The main classes include cholinesterase inhibitors (donepezil, rivastigmine, galantamine), which increase acetylcholine levels to improve memory and attention, and the NMDA receptor antagonist memantine, which regulates glutamate activity to reduce excitotoxicity. These drugs provide modest, short-term improvements in cognition, behavior, and daily functioning, particularly in the early to moderate stages of AD. However, their effects diminish over time, and they do not address the underlying neurodegenerative processes. They are often used in combination to optimize symptom control. Figure 1 illustrates the different drugs and their respective failure rates.

#### 1. Donepezil, Rivastigmine, Galantamine

Instrument: Boost acetylcholine levels to move forward memory.

Result: Affirmed for symptomatic help but don't adjust infection movement.

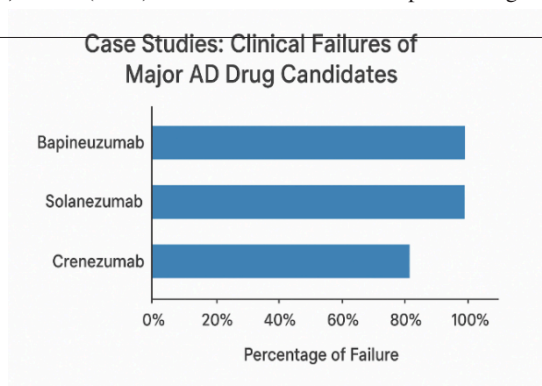
Restrictions: Give as it were brief and gentle cognitive advancement, frequently went with by gastrointestinal side impacts.

#### 2. Memantine (NMDA Receptor Enemy)

Component: Controls glutamate signaling to anticipate excitotoxicity.

Result: Unassuming advantage in moderate-to-severe Advertisement.

Restrictions: No effect on infection movement, utilized as it were as aide treatment [12].



**Fig 1.** Different drugs and failure ratio of the drugs.

## 4. Common Reasons for Alzheimer's Sedate Improvement Disappointments

Despite considerable investment and a pipeline rich in drug candidates, the success rate for Alzheimer's disease (AD) drug development remains alarmingly low. Numerous therapies that showed promise in preclinical and early-stage trials have failed in later phases, particularly in Phase II and III. A critical examination of these failures reveals a set of recurring and interconnected factors, reflecting both scientific and strategic limitations.

### 4.1 Late-Stage Intercession

One of the most significant challenges in AD clinical trials is the timing of therapeutic intervention. Most trials enroll patients who are already symptomatic, often in the mild cognitive impairment (MCI) or early dementia stages. However, accumulating evidence indicates that Alzheimer's pathology begins at least a decade before the onset of cognitive symptoms. Amyloid- $\beta$  deposition, tau hyperphosphorylation, and synaptic dysfunction can progress silently long before clinical diagnosis. Therefore, by the time a patient qualifies for a trial, irreversible neuronal damage may already have occurred, limiting the effectiveness of disease-modifying therapies. This temporal mismatch greatly reduces the likelihood of demonstrating therapeutic benefit, even if the drug successfully engages its intended target [13].

### 4.2 Heterogeneous Patient Populations

AD is not a uniform disease. Clinical presentation, rate of progression, genetic background (such as APOE4 carrier status), and the extent of pathology vary widely among patients. Unfortunately, most clinical trials still adopt a one-size-fits-all approach to enrollment, often overlooking this biological diversity. The result is increased variability in treatment responses and statistical noise that can obscure potential benefits in specific subgroups. This heterogeneity complicates data interpretation and may lead to the premature dismissal of therapeutics that might have been effective in genetically or pathologically defined subsets of patients [14].

### **4.3 Confinements of Preclinical Models**

Much of the drug discovery in AD relies on animal models, particularly genetically modified mice that express familial AD mutations. These models are valuable for studying specific pathological processes, such as amyloid plaque formation. However, they fall short of replicating the full spectrum of human AD, especially the sporadic forms, which account for more than 95% of cases. Rodent models often lack neurofibrillary tangle formation, extensive neuronal loss, and the complexity of human brain aging. Consequently, many drugs that show efficacy in animals fail to translate into clinical success, highlighting a critical gap in predictive validity [15].

### **4.4 Disengagement Between Biomarkers and Clinical Results**

An increasing number of trials have relied on biomarkers such as amyloid PET imaging, cerebrospinal fluid A $\beta$ 42 levels, or tau accumulation as surrogate endpoints to demonstrate biological activity. While these measures provide insight into target engagement and disease modification, their correlation with clinical outcomes remains inconsistent. Several drugs have successfully reduced amyloid burden yet failed to produce meaningful improvements in cognitive or functional scores. This disconnect raises questions about whether current biomarkers truly reflect therapeutic efficacy or merely represent isolated pathological features without addressing the multifactorial nature of AD [16].

### **4.5 Inadequate Understanding of Illness Instruments**

The dominant theories in AD research, particularly the amyloid cascade hypothesis, have guided drug development for decades. However, the repeated failure of amyloid-targeting therapies to produce cognitive benefits has prompted a reevaluation of this framework. Alzheimer's pathology involves not only amyloid and tau, but also neuroinflammation, mitochondrial dysfunction, oxidative stress, vascular impairment, and synaptic failure. Therapeutic strategies that narrowly focus on a single pathological component may therefore be inherently insufficient. The lack of integrated models that account for these diverse mechanisms contributes to the limited success of monotherapy approaches [17].

### **4.6 Security and Tolerability Issues**

Another major cause of clinical trial failure is drug-related toxicity. The central nervous system is particularly sensitive to adverse effects, and several promising agents have been discontinued due to safety concerns. For example,  $\gamma$ -secretase inhibitors such as Semagacestat were halted because they caused worsening cognition and an increased risk of skin cancer. Monoclonal antibodies like Bapineuzumab and Gantenerumab led to amyloid-related imaging abnormalities (ARIA), including edema and microhemorrhages. These outcomes highlight the delicate balance between achieving effective target engagement and maintaining acceptable safety profiles [18].

### **4.7 Imperfect Trial Plan and Endpoints**

Designing a successful Alzheimer's disease (AD) trial is inherently challenging. Most trials require long durations (12–18 months or more), which increases costs, dropout rates,

and logistical complexity. Additionally, primary endpoints such as the Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog) and the Clinical Dementia Rating–Sum of Boxes (CDR-SB) can lack sensitivity, particularly in the early stages of the disease. Variability in scoring, placebo effects, and rater biases further complicate outcome assessment. As a result, trials may fail to detect subtle but meaningful treatment effects, especially in early or prodromal populations [19].

#### **4.8 Financial and Administrative Limitations**

The tall steady loss rate in Advertisement trials has made considerable budgetary dangers, disheartening speculation by pharmaceutical companies. Each fizzled late-stage trial can take a toll hundreds of millions of dollars. Additionally, administrative pathways have been conflicting. The questionable endorsement of Aducanumab by the FDA beneath the quickened endorsement program despite uncertain clinical benefit illustrates the pressures between logical meticulousness, open weight, and administrative adaptability. Whereas such choices may energize proceeded advancement, they moreover chance dissolving certainty in endorsement benchmarks and may move center absent from genuinely successful medicines [20].

### **5. Future Headings for Alzheimer's Infection Sedate Improvement**

The rehashed disappointments in Alzheimer's infection (Advertisement) sedate advancement have lit up basic holes in both logical understanding and clinical procedure. As the worldwide burden of Advertisement proceeds to rise, there's a pressing ought to reframe current standards and seek after imaginative approaches that can upgrade the probability of restorative victory. Future advance will depend not as it were on focusing on fitting organic components but too on moving forward determination, refining clinical trial techniques, and personalizing treatments [21].

#### **5.1 Move Toward Early Conclusion and Mediation**

One of the most consistent lessons from failed trials is that intervention must occur earlier in the disease course. The pathological hallmarks of AD amyloid plaques, tau tangles, and neuroinflammation begin years before clinical symptoms appear. By the time cognitive decline becomes noticeable, significant and likely irreversible neuronal damage has already occurred. Therefore, future trials must prioritize the identification and enrollment of individuals in the preclinical or prodromal stages of AD. This can be facilitated by using advanced imaging techniques (e.g., amyloid PET, tau PET), cerebrospinal fluid biomarkers (e.g., A $\beta$ 42, p-tau), and blood-based biomarkers, which are increasingly gaining sensitivity and accessibility. Early detection not only expands the window for therapeutic intervention but also increases the likelihood of disease modification rather than providing minimal symptomatic relief [22].

#### **5.2 Advancement of Accuracy Pharmaceutical Approaches**

Given the heterogeneity of AD in terms of genetics, pathology, and clinical progression, a “one-size-fits-all” therapeutic model is no longer appropriate. Precision medicine tailoring treatment strategies to individual patient profiles holds great promise. Future clinical trials must incorporate stratification based on genetic risk factors (such as

APOE4 status), biomarker signatures, disease subtypes, and even co-existing pathologies. This could enable more targeted interventions, minimize adverse effects, and allow treatments to demonstrate clearer efficacy in selected populations. Furthermore, multi-omics data (including genomics, transcriptomics, and proteomics) may help identify novel therapeutic targets and predictive biomarkers, supporting more individualized treatment strategies [23].

### **5.3 Combination Treatments and Multi-Target Approaches**

Alzheimer's disease is a multifactorial disorder involving several components, including amyloid accumulation, tau pathology, neuroinflammation, oxidative stress, mitochondrial dysfunction, and impaired autophagy. As a result, it is increasingly recognized that no single-target therapy is likely to be effective in halting or reversing the disease. Instead, combination therapies similar to those used in cancer and HIV may be more successful. For example, a monoclonal antibody targeting amyloid could be used along with an anti-inflammatory agent or a tau aggregation inhibitor. Even within monotherapy, the development of multi-target small molecules that act on several pathological pathways simultaneously is being actively explored. Rationally designed combinations, supported by mechanistic insights and preclinical synergy data, represent a promising future direction [24].

### **5.4 Inventive Trial Plans and Versatile Strategies**

Conventional randomized controlled trial (RCT) designs, although considered the gold standard, may not be ideal for Alzheimer's drug testing due to the disease's slow progression and variability. Adaptive trial designs, such as platform trials or Bayesian models, allow for more flexible protocols, interim analyses, and modifications based on emerging data. This approach reduces trial costs and duration while improving the chances of identifying effective interventions. Furthermore, the use of digital biomarkers derived from wearable sensors, mobile apps, or cognitive performance tracking can provide continuous and objective data on disease progression, offering sensitive endpoints that traditional scales may miss [25].

### **5.5. Integration of Fake Insights and Machine Learning**

Counterfeit insights (AI) and machine learning (ML) have developing potential in Advertisement investigate. These apparatuses can help in early conclusion by analyzing huge datasets from imaging, genomics, and electronic wellbeing records. In sedate improvement, AI can offer assistance anticipate target-drug interactions, identify novel targets, and stratify patients based on multidimensional information. For clinical trials, ML calculations may optimize understanding enrollment, decrease whittling down, and personalize treatment arms based on real-time input. By moving forward, the proficiency and exactness of investigate forms, AI seem play a transformative part within the following era of Advertisement therapeutics [26].

### **5.6 Reexamination of Helpful Targets**

At last, the field is beginning to look beyond amyloid and tau as central therapeutic targets. While these proteins remain important, newer research is shedding light on the roles of neuroinflammation (e.g., microglial activation through TREM2), vascular

dysfunction, and insulin resistance in the brain (often referred to as “type 3 diabetes”), as well as the gut–brain axis. Targeting these lesser-explored pathways may offer novel therapeutic opportunities, especially as amyloid- and tau-focused strategies have plateaued in terms of clinical benefit. Drug repurposing using existing medications approved for other diseases, such as antidiabetics and antihypertensives also provides a faster, lower-risk avenue for investigating these emerging targets [27].

## **5.7 Limitations of Alzheimer infection**

Although this review provides a comprehensive overview of the major challenges, clinical failures, and barriers in Alzheimer’s drug development, certain limitations should be acknowledged [28-29]. First, due to the extensive and rapidly evolving nature of Alzheimer’s research, the review may not cover every emerging therapeutic strategy, clinical trial, or mechanistic insight published in the most recent literature. Some experimental approaches and early-stage findings may have been excluded due to limited or inconclusive evidence. Second, while the review synthesizes data from multiple clinical trials, it does not include a systematic quantitative analysis or meta-analysis; therefore, conclusions are based on qualitative interpretation rather than statistical comparisons [30]. Third, the complexity and heterogeneity of Alzheimer’s disease limit the ability to generalize findings across all patient populations, genetic subgroups, and disease stages [31]. Additionally, variations in trial design, biomarker use, and clinical endpoints across studies may introduce bias or inconsistencies that cannot be fully resolved within the scope of this narrative review. Finally, many insights rely on available published data, which may not fully represent unpublished negative outcomes or industry-held information, potentially affecting the completeness of the discussion [32].

## **6. Conclusion**

Alzheimer's illness proceeds to pose one of the foremost impressive challenges in neurodegenerative inquire about and medicate improvement. In spite of decades of seriously examination and significant money related venture, the victory rate of restorative candidates remains drearily moo. Most drugs have fizzled to illustrate clinical adequacy in stopping or turning around malady movement, especially in late-stage clinical trials. These disappointments have highlighted noteworthy limitations in our understanding of Advertisement pathophysiology and within the vital approaches utilized amid medicate improvement. Key reasons for disappointment incorporate an overreliance on the amyloid cascade speculation, insufficient infection modeling in preclinical thinks about, and the complexity of interpreting biomarker changes into important clinical advancements. Numerous candidates that effectively decreased amyloid or tau burden fizzled to appear critical cognitive or utilitarian benefits, uncovering a detach between neurotic clearance and clinical results. Moreover, unfavorable impacts and the failure to address the multifactorial nature of Advertisement have driven to the cessation of various promising operators. The investigation of past clinical trials underscores the significance of re-evaluating both restorative targets and trial plan techniques. It is clear that handling Advertisement requires a worldview shift one that moves past single-target approaches and grasps the complexities of malady heterogeneity. Early determination, stratification based on hereditary and biomarker profiles, and the selection of combination treatments must be prioritized. Moreover, coordination progressed apparatuses such as fake insights and versatile clinical trial models can streamline the revelation and assessment of future candidates. Whereas the travel toward a remedy remains full with challenges, the information picked up from past disappointments offers priceless experiences. Each unsuccessful trial includes to our

collective understanding and refines the way forward. By learning from these stumbles and grasping a more all-encompassing and personalized approach to treatment, there's recharged trust that compelling and disease-modifying treatments for Alzheimer's infection can be realized within the future.

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