Computational Modeling of Alzheimer's Disease Progression Through Beta-Amyloid Dynamics, Cholinergic Dysfunction, and Therapeutic Intervention

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Abstract

Alzheimer's disease is a progressive neurodegenerative disorder associated with memory loss, cognitive decline, and neuronal dysfunction. Several biological processes contribute to its progression, including beta-amyloid accumulation, tau pathology, cholinergic dysfunction, neuroinflammation, and oxidative stress. This study developed a computational model to examine how these processes interact and how different therapeutic interventions influence simulated cognitive outcomes over time. The model was implemented in Python and simulated disease progression over 420 months under six conditions: control, donepezil, lecanemab, hypothetical anti-tau treatment, hypothetical anti-inflammatory treatment, and combination treatment. The results showed that the combination treatment produced the highest final cognitive function score of 0.9537, compared with 0.8888 in the control condition. It also produced lower modeled tau pathology, inflammation, and oxidative stress. A sensitivity analysis found that changes in amyloid production and clearance had notable effects on the difference between combination treatment and control. However, the model used simplified biological relationships and illustrative parameter values that were not validated against clinical data. Its cognitive function score represents a simulated index rather than a clinical measurement. These findings demonstrate how computational modeling can be used to explore interactions between disease-related processes and generate hypotheses about potential treatment strategies for Alzheimer's disease.

Introduction

Alzheimer's disease is the most common neurodegenerative disorder and the leading cause of dementia worldwide. The disease is characterized by progressive memory loss, impaired cognitive function, and the gradual deterioration of a person's ability to perform daily activities. As populations continue to age, the prevalence of Alzheimer's disease is expected to increase significantly, creating major social, economic, and healthcare challenges. Despite decades of research, current treatments provide only limited symptomatic relief and are unable to completely halt or reverse disease progression. Understanding the biological mechanisms that drive Alzheimer's disease remains one of the most important challenges in modern neuroscience.

Several interconnected pathological processes contribute to the development and progression of Alzheimer's disease. One of the most widely studied mechanisms is the accumulation of beta-amyloid protein in the brain. Beta-amyloid originates from the cleavage of amyloid precursor protein (APP), which is a protein found in neuronal cell membranes. Under pathological conditions, enzymes known as beta-secretase and gamma-secretase produce beta-amyloid fragments that can aggregate into oligomers and eventually form extracellular plaques. These plaques disrupt communication between neurons, impair synaptic function, and contribute to neuronal death. The amyloid cascade hypothesis proposes that beta-amyloid accumulation initiates a series of downstream events that ultimately lead to cognitive decline and neurodegeneration.

In addition to beta-amyloid pathology, cholinergic dysfunction plays a significant role in the symptoms observed in Alzheimer's disease. The cholinergic system relies on the

neurotransmitter acetylcholine, which is essential for learning, attention, and memory formation. Acetylcholine-producing neurons located within the basal forebrain project to memory-related structures such as the hippocampus and cerebral cortex. As Alzheimer's disease progresses, many of these neurons degenerate, resulting in reduced acetylcholine availability and impaired neural communication. This loss of cholinergic signaling is strongly associated with deficits in memory encoding and recall. Consequently, several commonly prescribed Alzheimer's medications aim to increase acetylcholine levels by inhibiting the enzyme acetylcholinesterase, which normally breaks down the neurotransmitter after its release.

Recent research has demonstrated that Alzheimer's disease cannot be explained by a single pathological pathway. Additional factors such as neuroinflammation, oxidative stress, mitochondrial dysfunction, and impaired protein clearance contribute to disease progression. Activated microglia and astrocytes release inflammatory molecules that may further damage neurons, while oxidative stress can impair cellular function and accelerate neurodegeneration. Furthermore, evidence suggests that disruptions in the brain's glymphatic system may reduce the clearance of beta-amyloid and other toxic proteins, potentially increasing the risk of plaque accumulation over time. These findings highlight the complex and multifactorial nature of Alzheimer's disease.

Because Alzheimer's disease involves numerous interacting biological systems, computational modeling offers a valuable approach for investigating disease progression. Computational simulations allow researchers to represent biological processes mathematically and examine how changes in specific variables influence long-term outcomes. Such models can be used to simulate beta-amyloid accumulation, cholinergic decline, therapeutic intervention, and cognitive deterioration over time. By integrating multiple disease mechanisms into a single

framework, computational approaches provide an opportunity to explore relationships that may be difficult to observe directly through laboratory experiments alone.

The purpose of this study is to develop a computational model that simulates the interactions between beta-amyloid accumulation, cholinergic dysfunction, and therapeutic intervention in Alzheimer's disease. By incorporating established biological mechanisms into a dynamic simulation, this research seeks to evaluate how variations in amyloid clearance, acetylcholine availability, and treatment timing influence cognitive outcomes. The resulting model may provide insight into the complex processes underlying Alzheimer's disease and demonstrate the potential of computational methods as tools for studying neurodegenerative disorders and evaluating future treatment strategies. Beta-amyloid is produced through the enzymatic cleavage of APP, a transmembrane protein found throughout the brain. Under normal physiological conditions, APP is processed in a manner that does not generate harmful protein fragments. When APP is cleaved by beta-secretase and gamma-secretase enzymes, beta-amyloid peptides are produced. These peptides can aggregate into soluble oligomers and eventually form insoluble extracellular plaques.

Literature Review

Beta Amyloid Pathology

Alzheimer's disease has been the subject of extensive research for several decades, yet its underlying mechanisms remain incompletely understood. Numerous hypotheses have been proposed to explain the onset and progression of the disease, with the amyloid cascade hypothesis and the cholinergic hypothesis emerging as two of the most influential frameworks. More recently, researchers have recognized the importance of additional factors, including neuroinflammation, oxidative stress, mitochondrial dysfunction, and impaired protein clearance. Together, these mechanisms contribute to the complex and multifactorial nature of Alzheimer's disease and provide the foundation for current therapeutic strategies and computational modeling efforts.

One of the most studied theories of Alzheimer's disease is the amyloid cascade hypothesis, which proposes that accumulation of beta-amyloid protein initiates a sequence of pathological events leading to neurodegeneration and cognitive decline. The accumulation of beta-amyloid is believed to be one of the earliest pathological events in Alzheimer's disease, resulting from an imbalance between the production and clearance of Aβ42 and related beta-amyloid peptides (Selkoe & Hardy, 2016). As beta-amyloid levels increase, soluble oligomers can interfere with synaptic signaling, reduce synapse density, and impair long-term potentiation, a process critical for learning and memory (Selkoe & Hardy, 2016). Furthermore, the deposition of beta-amyloid has been associated with the development of neurofibrillary tangles, neuronal death, and progressive cognitive decline, supporting its role as a major

contributor to disease progression (Reitz, 2012). Although the precise sequence of pathological events remains debated, substantial evidence suggests that disruptions in beta-amyloid homeostasis play a central role in the onset and advancement of Alzheimer's disease (Reitz, 2012; Selkoe & Hardy, 2016). Beyond the direct effects of beta-amyloid accumulation, Alzheimer's disease is also characterized by the formation of neurofibrillary tangles composed of hyperphosphorylated tau protein (Weller & Budson, 2018). Evidence suggests that beta-amyloid deposition may occur years before the onset of clinical symptoms and can promote tau phosphorylation, leading to neuronal dysfunction and cell death (Weller & Budson, 2018). The interaction between beta-amyloid and tau pathology highlights the complex nature of Alzheimer's disease and suggests that multiple pathological pathways contribute to cognitive decline.

Recent evidence suggests that soluble beta-amyloid oligomers may contribute more directly to cognitive impairment than mature amyloid plaques. Small oligomeric forms of beta-amyloid have been shown to disrupt synaptic function by interfering with neuronal communication, ultimately impairing the brain's ability to encode and retrieve memories (Nimmrich & Ebert, 2009). As synaptic dysfunction progresses, the loss of functional connections between neurons contributes to the decline in cognitive performance observed in Alzheimer's disease.

Furthermore, research has demonstrated that soluble beta-amyloid oligomers can impair synaptic plasticity, particularly within the hippocampus, a brain region essential for learning and memory (Li & Selkoe, 2020). Long-term potentiation, a cellular mechanism underlying memory formation, is consistently disrupted by beta-amyloid oligomers before significant neuronal death occurs (Li & Selkoe, 2020). These findings suggest that cognitive decline may begin at the

synaptic level long before extensive plaque deposition becomes apparent.

As well as disrupting synaptic communication, beta-amyloid accumulation has been associated with downstream pathological processes including tau hyperphosphorylation and neurofibrillary tangle formation (Weller & Budson, 2018). Evidence indicates that beta-amyloid deposition may precede clinical symptoms by many years and initiate a cascade of neurodegenerative events that ultimately result in neuronal dysfunction and cell death (Weller & Budson, 2018). Collectively, these findings support the hypothesis that beta-amyloid plays a central role in Alzheimer's disease progression through its effects on synaptic function, memory-related neural pathways, and the development of secondary pathological mechanisms.

Cholinergic Dysfunction

In addition to beta-amyloid pathology, cholinergic dysfunction is widely recognized as a major contributor to the cognitive decline observed in Alzheimer's disease. The cholinergic hypothesis proposes that degeneration of cholinergic neurons and the resulting reduction in acetylcholine neurotransmission play a central role in memory impairment and other cognitive deficits associated with the disease (Francis et al., 1999). Acetylcholine is an essential neurotransmitter involved in attention, learning, memory formation, and synaptic plasticity. Consequently, disruptions in cholinergic signaling can significantly impair cognitive function.

The basal forebrain cholinergic system is particularly vulnerable to degeneration in Alzheimer's disease. This region provides extensive cholinergic projections to the hippocampus and cerebral cortex, areas critical for learning, memory, and higher cognitive processing (Auld et al., 2002). Studies have demonstrated that the loss of cholinergic neurons within the basal forebrain is strongly associated with the severity of cognitive impairment observed in Alzheimer's patients (Auld et al., 2002). Furthermore, evidence suggests that beta-amyloid

peptides may directly contribute to cholinergic dysfunction by disrupting neuronal signaling and promoting neurodegeneration within cholinergic pathways (Auld et al., 2002).

As cholinergic neurons degenerate, levels of acetylcholine within the brain decline, leading to impairments in communication between neurons and reduced synaptic efficiency (Terry & Buccafusco, 2003). This reduction in neurotransmitter availability has been linked to deficits in memory formation, attention, and executive functioning. In addition, decreased cholinergic activity may further exacerbate the effects of beta-amyloid pathology by reducing the brain's ability to compensate for ongoing neurodegenerative processes (Ferreira-Vieira et al., 2016).

Given the significant role of acetylcholine in cognition, many current Alzheimer's treatments focus on enhancing cholinergic neurotransmission. Cholinesterase inhibitors such as donepezil, rivastigmine, and galantamine function by inhibiting acetylcholinesterase, the enzyme responsible for breaking down acetylcholine within the synaptic cleft (Ferreira-Vieira et al., 2016). By increasing acetylcholine availability, these medications can temporarily improve cognitive function and quality of life for some patients, although they do not halt disease progression. Recent research has also highlighted the importance of the basal forebrain cholinergic system as a potential target for future therapeutic interventions aimed at preserving cognitive function and slowing neurodegeneration (Berry & Harrison, 2023).

Current Therapeutic Interventions

Given the significant role of cholinergic dysfunction in Alzheimer's disease, many current treatment strategies focus on improving neurotransmitter signaling and reducing cognitive symptoms. Cholinesterase inhibitors, including donepezil, rivastigmine, and galantamine, function by inhibiting acetylcholinesterase, the enzyme responsible for breaking down

acetylcholine within the synaptic cleft. By increasing acetylcholine availability, these medications enhance cholinergic neurotransmission and can produce modest improvements in cognition, memory, and daily functioning (Rabins & Lyketsos, 2006; Weller & Budson, 2018). However, these therapies do not prevent neuronal degeneration or alter the underlying progression of the disease.

Another commonly prescribed treatment is memantine, an N-methyl-D-aspartate (NMDA) receptor antagonist that helps regulate glutamatergic signaling within the brain. Excessive glutamate activity may contribute to excitotoxicity, a process that damages neurons through prolonged stimulation. By reducing this abnormal activity, memantine may improve cognition and functional outcomes in patients with moderate to severe Alzheimer's disease (Weller & Budson, 2018; Clinical Practice Guidelines for Dementia, 2025).

Despite their widespread use, current pharmacological therapies provide primarily symptomatic benefits. Multiple reviews and meta-analyses have reported that cholinesterase inhibitors and memantine can improve cognitive performance and global functioning, but their effects are generally modest and do not halt disease progression (Qiu et al., 2018; Raina et al., 2008). As a result, increasing attention has shifted toward disease-modifying therapies that target the underlying pathological mechanisms of Alzheimer's disease.

Recent therapeutic developments have focused on reducing beta-amyloid burden through monoclonal antibody therapies and inhibitors of amyloid production. These approaches aim to remove existing amyloid deposits or prevent their formation by targeting proteins involved in beta-amyloid generation. Although some therapies have demonstrated reductions in amyloid accumulation, their effects on long-term cognitive outcomes remain an active area of

investigation, highlighting the need for improved approaches capable of addressing multiple disease pathways simultaneously (Weller & Budson, 2018).

Computational Models of Alzheimer's Disease

The complexity of Alzheimer's disease presents a significant challenge for researchers attempting to understand the interactions among beta-amyloid pathology, neurotransmitter dysfunction, neuroinflammation, and cognitive decline. Because these processes occur across multiple biological scales and progress over many years, computational modeling has emerged as an important tool for integrating existing knowledge and evaluating potential therapeutic strategies (Geerts et al., 2017). Computational approaches allow researchers to simulate disease progression and examine how changes in individual variables influence overall outcomes.

Modern computational models incorporate biological mechanisms ranging from molecular interactions and neuronal signaling to large-scale neural networks. These models provide a framework for examining causal relationships between pathological processes that may be difficult to isolate experimentally. Rather than relying solely on observational correlations, computational simulations can evaluate how multiple disease mechanisms interact over time and predict the effects of potential interventions before clinical testing occurs (Geerts et al., 2017).

Although numerous computational models have examined individual aspects of Alzheimer's disease, many focus primarily on beta-amyloid accumulation or other isolated pathological mechanisms. Existing models often do not simultaneously incorporate amyloid burden, cholinergic dysfunction, and therapeutic intervention within a single framework. Consequently, there remains a need for computational approaches capable of integrating multiple biological pathways while evaluating how treatment timing and efficacy influence cognitive

outcomes. Such models may improve understanding of disease progression and provide a valuable platform for investigating future therapeutic strategies (Geerts et al., 2017).

Methodology

Computational Model Design

This study used a computational simulation written in Python to examine relationships between amyloid accumulation, tau pathology, cholinergic dysfunction, and cognitive decline in Alzheimer's disease. The simulation ran for 420 months, equivalent to 35 years, with treatment beginning at month 120 in the intervention scenarios. Six conditions were compared: control, donepezil, lecanemab, hypothetical anti-tau treatment, hypothetical anti-inflammatory treatment, and combination treatment.

Model Variables and Parameters

The model tracked amyloid burden, tau pathology, inflammation, oxidative stress, cholinergic function, and cognitive function. Mathematical equations represented changes in these variables over time based on production, clearance, and treatment effects. The initial values were 0.08 for amyloid, 0.03 for tau, 0.04 for inflammation, 0.04 for oxidative stress, and 0.98 for cholinergic function. All variables were normalized between 0 and 1. The cognitive function score was a model-generated index rather than a validated clinical measurement.

Treatment Comparison and Sensitivity Analysis

Each treatment scenario used different assumptions to represent its effects on the modeled biological processes. Donepezil increased the effective cholinergic signal used in the cognitive calculation, while lecanemab increased modeled amyloid clearance. The hypothetical anti-tau and anti-inflammatory treatments increased the clearance of their respective targets. The combination condition applied these modeled effects together.

Python was used to record the results and generate graphs comparing cognitive function, amyloid burden, tau pathology, inflammation, oxidative stress, and cholinergic function. A sensitivity analysis tested the effects of changing selected parameters to 75% and 125% of their original values. The resulting differences between the combination and control conditions were compared to evaluate how parameter changes influenced the model's predictions.

Limitations

The model used simplified biological relationships and illustrative parameter values that were not calibrated or validated against clinical data. Its treatment effects and cognitive function scores therefore represent simulated outcomes rather than evidence of clinical effectiveness. The results are intended to explore possible relationships between disease processes and generate hypotheses for future research, not to predict individual disease progression or determine the best treatment for patients.

Results

Treatment Comparison

The computational simulation was run over 420 months to examine changes in amyloid burden, tau pathology, inflammation, oxidative stress, cholinergic function, and cognitive function under six treatment conditions. Treatment began at month 120 in the five intervention scenarios, while the control condition continued without treatment. All variables were represented using normalized values between 0 and 1, with the cognition score serving as a model-generated index rather than a validated clinical measure.

At the end of the simulation, the control condition produced a cognition score of 0.8888. The donepezil scenario produced a score of 0.9128, while lecanemab produced a score of 0.9259. The hypothetical anti-tau and anti-inflammatory scenarios produced scores of 0.8983 and 0.8933, respectively. The combination scenario produced the highest final score, at 0.9537.

The combination scenario had a final cognition score 0.0649 points higher than the control condition. This difference reflected the treatment effects built into the model and should not be interpreted as a measured improvement in patients. The combination scenario also produced the lowest final values for tau pathology, inflammation, and oxidative stress among the six conditions.

Figure 1. Cognitive Function Over Time

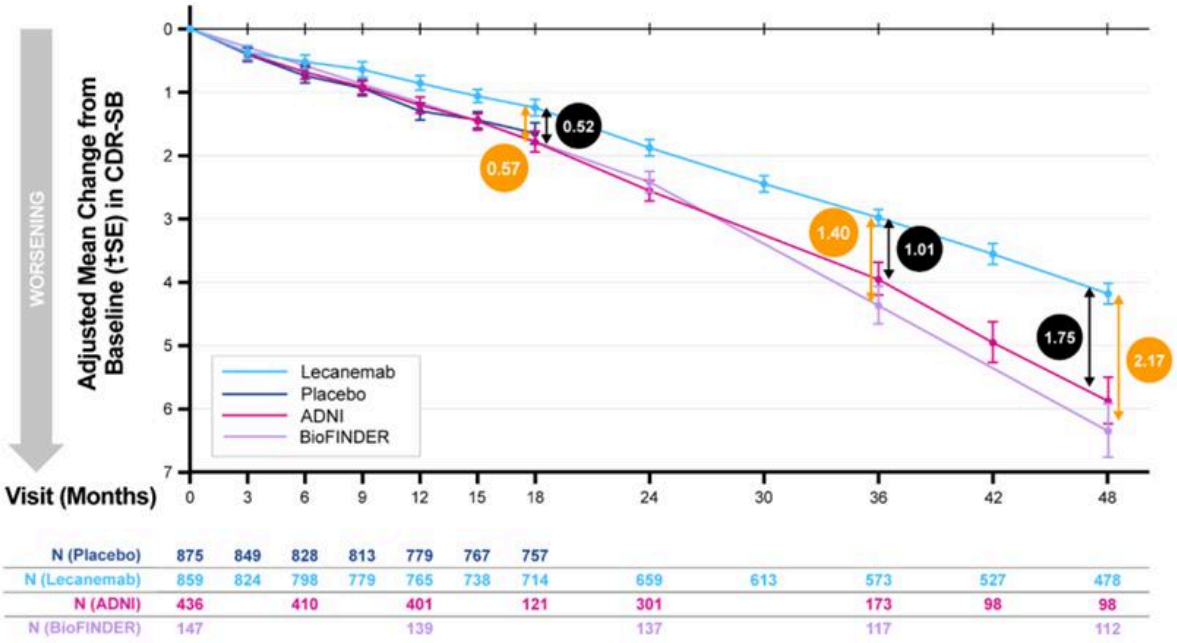

Table 1. Final Treatment Comparison

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Treatment	Cognition score	Amyloid burden	Tau burden	Inflammation	Oxidative stress	Cholinergic function
Control	0.8888	0.2036	0.0783	0.0496	0.0265	0.8804
Donepezil	0.9128	0.2036	0.0783	0.0496	0.0265	0.8804
Lecanemab	0.9259	0.1237	0.0538	0.0325	0.0176	0.9049
Anti-Tau (hypothetical)	0.8983	0.2035	0.0482	0.0469	0.0261	0.8873
Anti-Inflammation (hypothetical)	0.8933	0.2020	0.0776	0.0284	0.0224	0.8812
Combination	0.9537	0.1229	0.0309	0.0166	0.0143	0.9115

Note. Values are normalized model outputs, not clinical measurements.

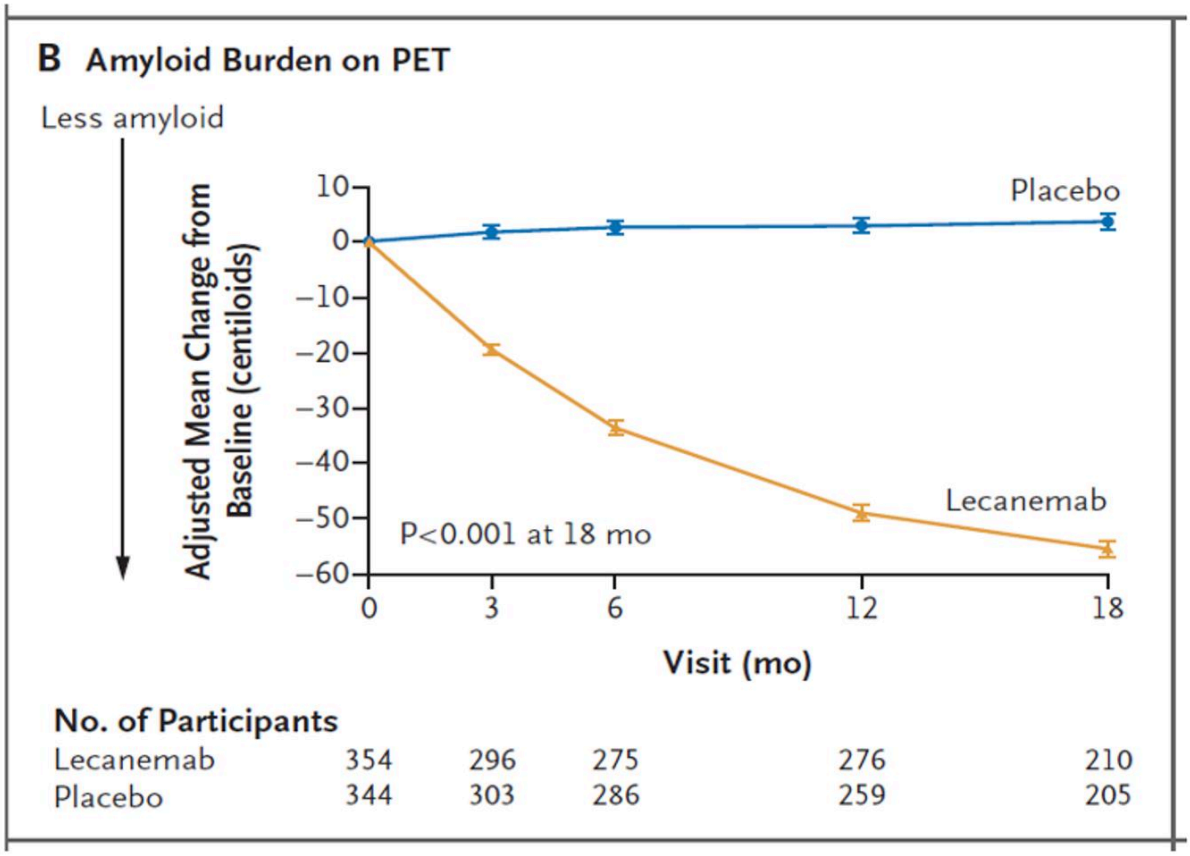
Changes in Amyloid Burden

The amyloid burden graph compared the control, lecanemab, and combination scenarios. At the end of the simulation, the control condition had an amyloid burden of 0.2036. The lecanemab condition had a value of 0.1237, while the combination condition had a value of 0.1229.

These results indicate that the model produced lower final amyloid burden in the two scenarios that included lecanemab. The combination scenario had a slightly lower final amyloid value than lecanemab alone. This pattern followed the model's assumption that lecanemab increases amyloid clearance.

The difference between the control and treatment scenarios was generated by the equations and parameter values used in the simulation. It does not independently establish the magnitude of amyloid reduction that would occur in a clinical setting.

Figure 2. Modeled Amyloid Burden



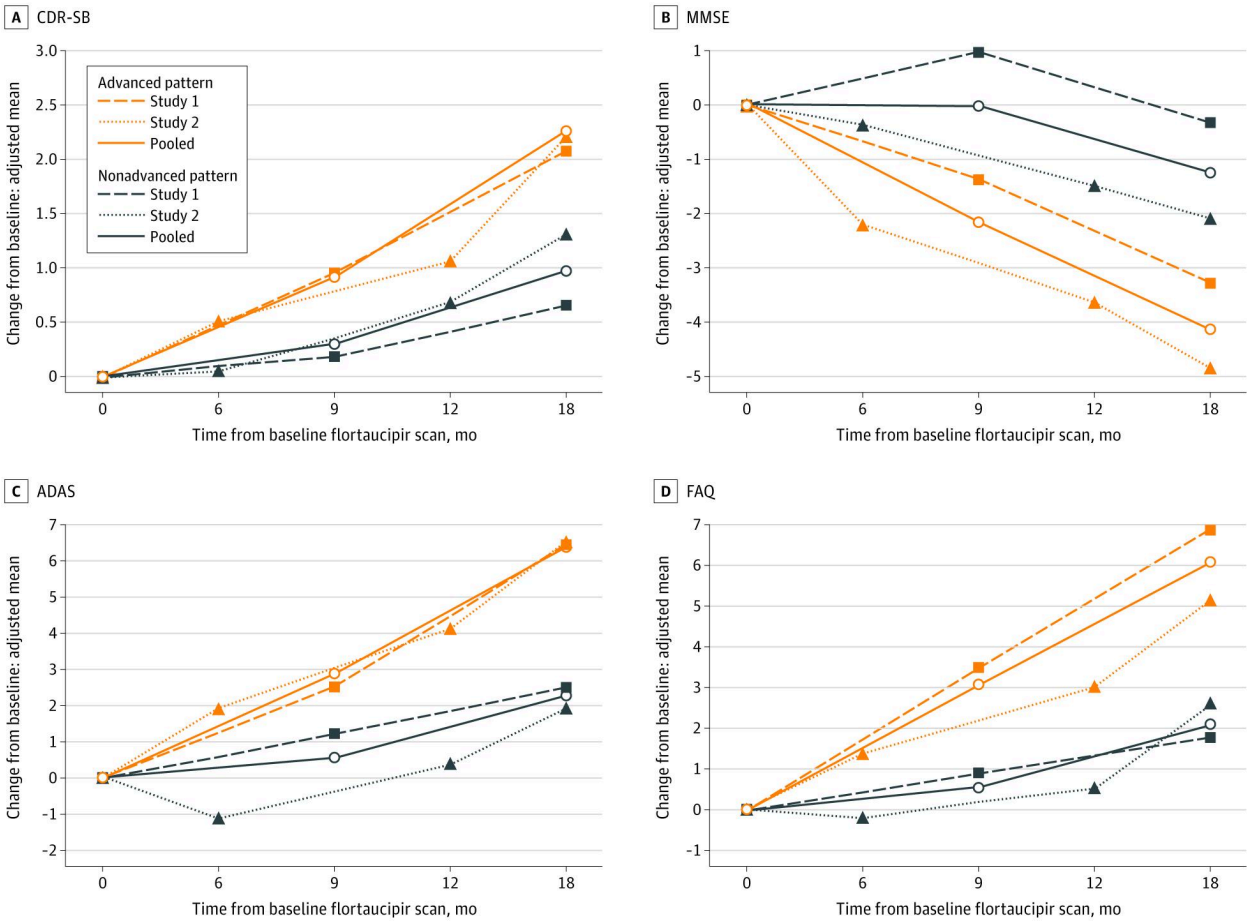
Changes in Tau Pathology

The tau pathology graph compared the control, hypothetical anti-tau, and combination scenarios. The final tau burden was 0.0783 in the control condition, 0.0482 in the anti-tau condition, and 0.0309 in the combination condition.

The anti-tau scenario produced a lower final tau burden than the control condition. The combination scenario produced the lowest value of the three. This result was consistent with the model's structure, in which the hypothetical anti-tau intervention increased the modeled tau clearance rate, while the combination scenario included multiple interventions that influenced connected disease-related processes.

These results suggest that the model's tau trajectory was sensitive to the treatment assumptions and to interactions between the modeled variables. However, the simulation did not directly measure tau protein in biological samples, and its outputs should be interpreted as normalized model values rather than actual tau concentrations.

Figure 3. Modeled Tau Pathology

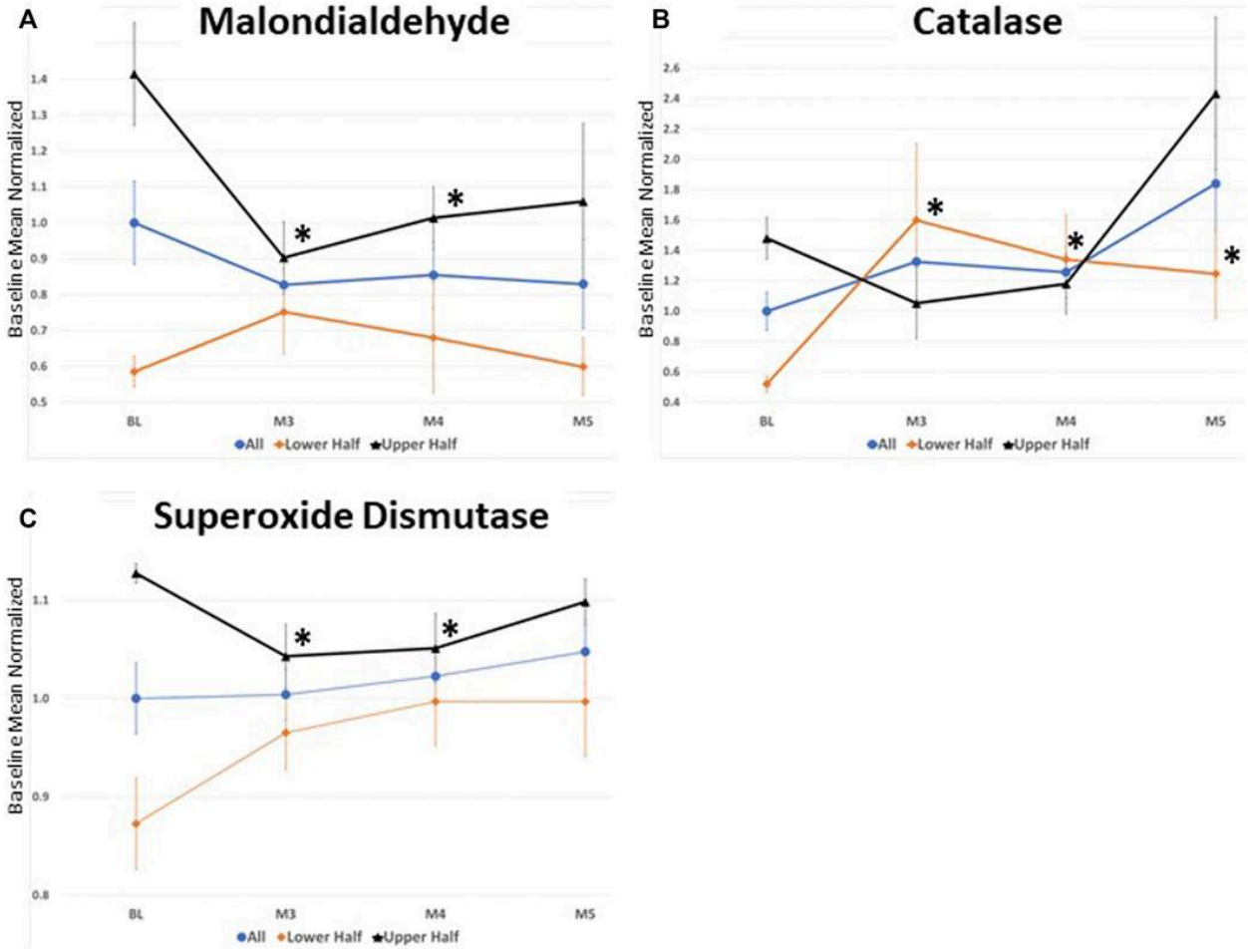


Inflammation, Oxidative Stress, and Cholinergic Function

The simulation also tracked inflammation, oxidative stress, and cholinergic function. At month 420, the control condition had an inflammation value of 0.0496 and an oxidative stress value of

0.0265. The combination condition had lower values of 0.0166 for inflammation and 0.0143 for oxidative stress.

Figure 4. Inflammation and Oxidative Stress



The final cholinergic function value was 0.8804 in the control condition and 0.9115 in the combination condition. The donepezil scenario had an underlying cholinergic function value of 0.8804, the same as the control condition. However, its effective cholinergic function was higher because the model represented donepezil as a boost to the cholinergic signal used in the cognition calculation rather than as a reversal of the underlying modeled loss of function.

These results illustrate how the simulation connected several disease-related variables. Changes in one modeled process could influence other variables through the equations. Nevertheless, these relationships were simplified representations and did not capture the full biological complexity of Alzheimer's disease.

Sensitivity Analysis

A one-at-a-time sensitivity analysis was conducted by changing each model parameter to 75% and 125% of its original value. The final cognition difference between the combination and control conditions was then recalculated. Under the original parameter values, this difference was 0.0649.

The largest changes in the modeled treatment difference occurred when amyloid-related parameters were varied. Reducing amyloid production by 25% decreased the combination-minus-control difference to 0.0538, a change of approximately -0.0110 from the baseline difference. Increasing amyloid production by 25% increased the difference to 0.0743, approximately 0.0095 above baseline. Reducing amyloid clearance by 25% increased the difference to 0.0758, while increasing amyloid clearance by 25% reduced it to 0.0564.

Changes to tau-related parameters also influenced the modeled treatment difference. Increasing tau production by 25% increased the difference to 0.0687, while decreasing tau production by 25% reduced it to 0.0608. The other parameters generally produced smaller changes in the combination-minus-control difference under the tested perturbations.

Overall, the sensitivity analysis showed that the modeled comparison between combination treatment and control depended on the selected parameter values. Amyloid production and clearance had particularly noticeable effects in this analysis. Because the parameters were varied individually, the analysis did not evaluate every possible interaction between parameter changes.

Table 2. Sensitivity Analysis

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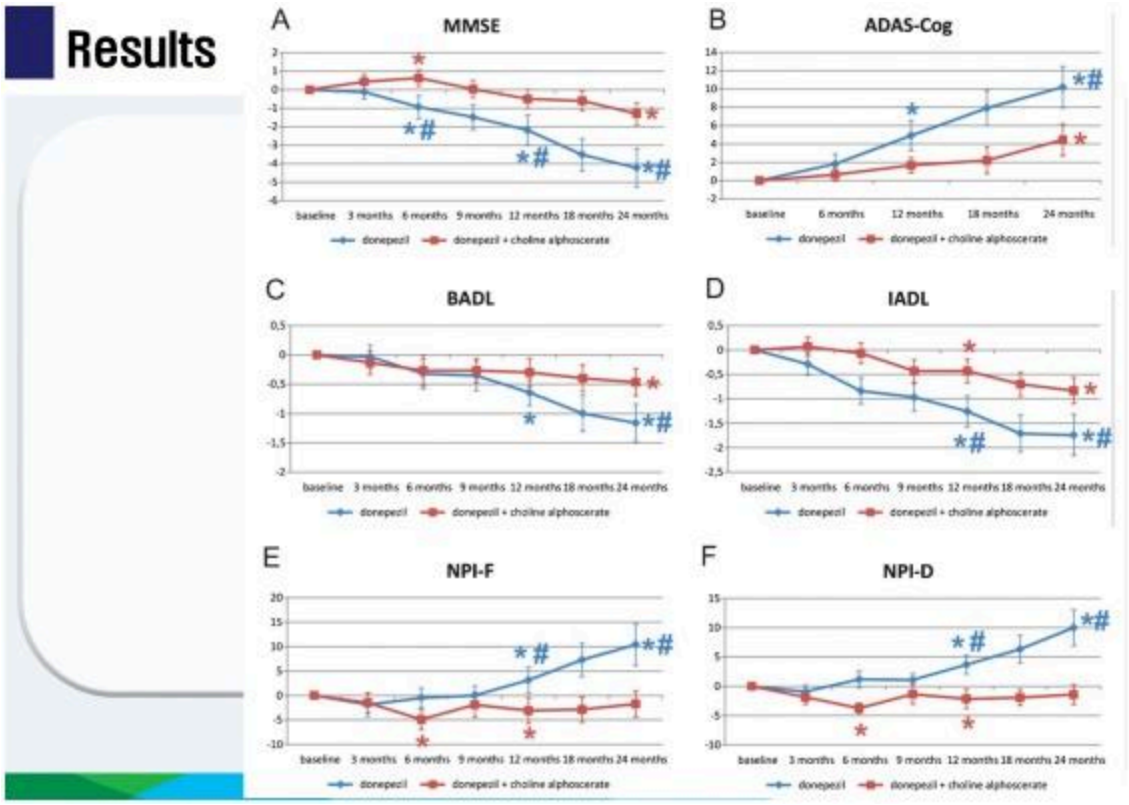
Parameter change	Combination minus control	Change from baseline difference
Baseline parameters	0.06490	0.00000
Amyloid production decreased 25%	0.05381	-0.01100
Amyloid production increased 25%	0.07427	0.00946
Amyloid clearance decreased 25%	0.07584	0.01103
Amyloid clearance increased 25%	0.05644	-0.00837
Tau production decreased 25%	0.06078	-0.00402
Tau production increased 25%	0.06868	0.00387

Note. Each parameter was varied individually by 25%; results are model-dependent.

Figure 5. Effective Cholinergic Function



Summary of Findings

Across the six simulated treatment conditions, the combination scenario produced the highest final cognition score and the lowest final tau, inflammation, and oxidative stress values. Lecanemab alone produced a lower final amyloid burden than the control condition, while the hypothetical anti-tau treatment produced a lower final tau burden than the control condition. The sensitivity analysis showed that changing amyloid-related parameters altered the modeled difference between combination treatment and control.

These findings describe the behavior of the computational model under its specified assumptions. They do not establish that one treatment or combination is clinically superior to another. Further parameter calibration, comparison with published experimental or clinical data,

and validation of the model's behavior would be necessary before using the simulation to make claims about actual Alzheimer's disease progression or treatment outcomes.

Discussion

The simulation suggests that Alzheimer’s disease may be better understood as a combination of interacting biological processes rather than a condition driven by one factor. The combination treatment produced the highest final cognitive function score of 0.9537, compared with 0.8888 in the control condition. It also reduced amyloid, tau, inflammation, and oxidative stress. Within the model, these results suggest that targeting multiple disease-related processes may produce greater improvements in cognitive function than targeting only one.

Lecanemab produced the largest improvement among the individual treatments, reducing final amyloid burden from 0.2036 to 0.1237. Donepezil also improved the cognitive function score, but it did not change the underlying disease-related variables because its effect was modeled through cholinergic signaling. The hypothetical anti-tau and anti-inflammatory treatments reduced their targeted variables but produced smaller changes in cognitive function when used individually.

The sensitivity analysis showed that changes in amyloid production and clearance had a greater effect on the difference between combination treatment and control than most other parameter changes tested. This suggests that the model’s predictions depend partly on its assumptions about amyloid dynamics.

However, these results must be interpreted cautiously. The model uses simplified biological relationships and illustrative parameter values that have not been validated against clinical data.

Its cognitive function score is a simulated index, not a clinical measurement. Therefore, the results do not prove that combination treatment would be more effective in patients.

Future research could improve the simulation by using published clinical data to estimate parameters and test whether its predictions match observed disease progression. Additional variables, including APOE ε4 status and treatment timing, could also help explore differences in disease progression and treatment response.

Conclusion

This study used a computational simulation to examine how amyloid, tau, inflammation, oxidative stress, and cholinergic function may interact in Alzheimer's disease. The combination treatment produced the highest simulated cognitive function score, suggesting that targeting multiple disease processes may have advantages over individual treatments within the model. However, the results depend on simplified assumptions and have not been validated using clinical data. Further research using real patient data could help determine whether these patterns reflect Alzheimer's disease progression and treatment responses.

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