

**A Longitudinal Analysis of the Effectiveness of Existing Treatments for Alzheimer's
Disease**

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Abstract:

Alzheimer's Disease is a neurocognitive disorder that affects approximately 35 million people worldwide. It impacts aspects of daily life ranging from relationships to quality of life, and full recovery is not yet possible. Alzheimer's disease disproportionately affects the elderly, meaning that an increase in human lifespan also increases individuals at risk of developing Alzheimer's disease. This paper details the relative longitudinal efficacy of three different types of Alzheimer's treatments: anti-amyloid, symptomatic, and cognitive therapy. It builds upon a previous research project which established that there is not a significant difference in cognitive improvement between anti-amyloid and symptomatic treatments when compared at a certain endpoint. It compares cognitive improvement trends in the Alzheimer's Disease Assessment Scale - Cognitive Subscale (ADAS-Cog) and Mini Mental State Examination (MMSE) scores for the aforementioned treatments. Data analysis was completed via the creation of scatterplots with a 95% confidence interval to view change in ADAS-Cog/MMSE score over time, and was done via Rstudio.

Key Words: Alzheimer's Disease, Cognitive Decline, Anti-Amyloid, Symptomatic, Cognitive Therapy

Introduction

Background

Alzheimer's disease is a progressive neurodegenerative disease that causes irreversible neuron damage which eventually results in death. It primarily occurs in elderly individuals, disproportionately impacting 10% of seniors above 65 years of age and 33% of seniors above 85 years of age.^[1] As the expected lifespan increases due to better global health standards, more people are at risk for developing Alzheimer's disease. As of 2026, the most widely accepted cause of Alzheimer's disease is an excessive buildup of amyloid plaques and tau tangles around the neurons. Amyloid plaque accumulation occurs when the Amyloid Precursor Protein (APP), which is believed to normally play a role in neuron growth, is sliced incorrectly by beta-secretase then gamma-secretase.^[2] This causes the production of Amyloid-beta peptides, which are very prone to accumulation and form clumps around neurons, leading to neuron dysfunction and inefficient signal transmission. Eventually, inflammatory immune responses cause neuron degeneration and, over time, brain volume shrinkage. It is important to note, however, that many non-demented seniors do have amyloid plaques in the brain yet are cognitively normal, which can be due to genetic factors. Tau tangles, which also build up around neurons, are composed of hyperphosphorylated tau proteins, produced by the reduced activity of the PP2A enzyme that regulates the dephosphorylation of tau. Tau is normally essential for the stabilization of microtubules, which organize transportation within the cell and maintain its structure, however, when hyperphosphorylated, it accumulates around the neuron and is toxic to other, normally functioning tau.^[3] Both amyloid plaques and tau tangles cause progressive neuron damage that cannot be reversed, starting from the hippocampus. The hippocampus, responsible for the conversion of short-term

memories to long-term memories, is damaged in the initial stages of Alzheimer's disease, and as the disease progresses, the temporal, parietal, and frontal lobes of the brain undergo shrinkage. Symptoms such as memory loss, cognitive decline, lack of coordination, and lack of emotional regulation characterize Alzheimer's disease and are caused by neuron death in these regions of the brain.^[3]

Treatments

This paper will compare three different types of Alzheimer's disease treatments, namely anti-amyloid treatments, symptomatic treatments, and cognitive therapy. Anti-amyloid treatments target amyloid plaques by binding to them and signaling the microglial cells to clear the plaques from the brain.^[4]

Lecanumab (sold under the brand name Leqembi), Adacantumab (Aduhelm) and Donanemab (Kisunla) were used to represent anti-amyloid treatments in this study. Some side effects include flu-like symptoms, nausea, and brain bleeding and swelling.^[5] The latter is a severe side effect that discourages doctors from advising anti-amyloid treatments, as well as patients from taking them.

Symptomatic treatments operate through a variety of mechanisms other than targeting the root cause itself in order to address the symptoms of Alzheimer's disease. Donepezil (Aricept), Galantamine (Razadyne), and Rivastigmine (Exelon) were the cholinesterase inhibitors used in this study.

Cholinesterase inhibitors prevent the breakdown of an excitatory neurotransmitter, acetylcholine, thus increasing its concentration in the synaptic cleft. This causes neuron stimulation and improves nerve signal efficiency, counteracting the effects of amyloid plaques on signal transmission.^[4] Another type of symptomatic treatment is NMDA Receptor Antagonists, which was represented by Memantine (Namenda) in this study. These substances bind to NMDA receptors on the post-synaptic neuron,

blocking the effect of the excitatory neurotransmitter glutamate. In Alzheimer's disease, neurons are overstimulated by high amounts of glutamate in the extracellular space, which binds to NMDA receptors on the axon. Blocking these receptors inhibits the excitatory effects of glutamate, which relieves stress on the neurons. Symptomatic treatments have side effects such as diarrhea, nausea, gastrointestinal distress, and insomnia.^[4] Cognitive therapy is another type of treatment that has minimal side effects and is often administered alongside other drug treatments. Cognitive Stimulation Therapy (CST) and Repetitive Transcranial Magnetic Stimulation (rTMS) represented cognitive therapy in our study. This type of therapy aims to improve neuroplasticity and reduce cognitive impairment through consistent cognitive stimulation for a given period of time. CST usually consists of 14 group activity sessions, with two sessions each week, that engage the audience and encourage cognitive stimulation. Participating in stimulating activities strengthens and forms connections between neurons due to usage, improving overall cognition.^[6] Maintenance Cognitive Stimulation Therapy (MCST) is a type of CST that extends for a longer period of time compared to the usual 7 weeks. Repetitive Transcranial Magnetic Stimulation (rTMS) is another treatment that involves cognitive stimulation. Unlike CST, however, it uses a device containing electromagnetic coils that sends magnetic pulses into the brain in order to induce stimulation.^[7] Apart from headaches and dizziness, rTMS has no major side effects. Data regarding the longitudinal cognitive effects of the aforementioned treatments was quantified and compared in this study using the ADAS-Cog and MMSE scales.

Methodology:

Primary Outcomes

The primary outcome is the change in Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) score over time compared to a placebo. The ADAS-Cog test is a 70 point test first developed in 1983, with lower scores corresponding to better cognitive function. It tests for short term word recall, spatial orientation, comprehension of language, proprioception, and constructional praxis (the ability to execute complex motor tasks).^[8] Scores between 0pts and 9pts indicate normal cognitive function, 10pts to 15pts indicate mild cognitive impairment, and >15pts mid-level to moderate dementia.^[9] The key limitation is-it is less effective at measuring small changes in mild cognitive decline. Comparing the treatment score to the placebo score removes random noise from the data, revealing if a treatment is genuinely effective.

The secondary outcome of the analysis is the changes in the Mini-Mental State Examination (MMSE). The MMSE is a 30 point quiz, with its most common version being developed in 1997. The higher the score, the less cognitive decline is present, with scores of above 25 being considered normal and scores between 18 and 26 indicating mild dementia. Individuals are tested on registration of stimuli, attention, motor skills, retention, and language. The MMSE has been praised for its accuracy for diagnosing cognitive decline over time, and for diagnosing Alzheimer's disease.^[10] However, the test has been criticized due to individuals without complete fluency in English scoring worse.^[11]

Data Search

Data was sourced from Pubmed Clinical Trials, the United States National Institute of Health, and Google Scholar. In order to ensure a fair statistical comparison, inclusion criteria was established to decide what studies to analyse. The criteria for the clinical trials consisted of: must be a randomized control trial, must use only one of the treatments (either a Cognitive method, a symptomatic method, or an anti amyloid method), must have over 28 participants, population must have probable to mild Alzheimer's disease, must provide data on the MMSE or ADAS-Cog tests over a given period of time, and must consist of participants aged 60 or above.

Data Filtering:

All trials were sourced from Pubmed Clinical Trials and the United States National Institute of Health. The initial collection of data was taken by searching the drug name and “Alzheimers” and filtering for randomized control trials only. Afterwards the trial titles were screened to determine relevance to the study, and then the abstracts were screened for the same reasons. The methods were screened to ensure that they aligned with the inclusion criteria (ie. only one treatment used, participant number). Lastly, the trials were screened to ensure that data on the primary outcomes (ADAS-Cog and MMSE) were provided.

Data Extraction

After filtering all trials to fit the inclusion criteria, data was collected on different aspects of each trial. Specifically, data was taken on: trial population number, study number, treatment type, specific drug, time (weeks), year of publication, average patient age, dosage (mg/day), mean improvement from

placebo, and standard error. The upper and lower bounds were then calculated via the formula $CI = \bar{x} \pm 1.96 * \frac{s}{\sqrt{n}}$. Studies that contained both MMSE and ADAS-Cog data were given different study numbers.

Data Analysis:

Due to the nature of the data collected, the data was plotted as a facet wrapped scatter plot with error bars showing the 95% confidence interval and a linear regression line, as well as a “jittered” facet wrap in order to make error bars of individual data points easier to see. The Y axis was plotted as the amount of improvement on either the ADAS-Cog or MMSE test, and the X axis was plotted as the time in weeks. Rstudio was used to analyze and visualize the data, using packages such as ggplot2, dplyr, and ggthemes to create the jittered scatterplot and confidence interval. The color of each point would show the treatment type (cognitive, anti-amyloid, or symptomatic). Initially different drugs within a treatment type (symptomatic, anti-amyloid, or cognitive therapy), would be compared to view similarity in performance on reducing cognitive decline, with drugs within a treatment type that are not similar being removed from the study **to accurately represent each treatment type to ensure a fair comparison for the treatment types**. The drugs that had similar efficacy were then plotted with the other treatment types in order to compare all three treatment types over time. This plot allowed for trends to be determined, as well as an estimate to the statistical significance of the impact of the drug on a specific score.

Results

Data filtering

The initial search on PubMed yielded 392 total trials after filtering randomized controlled trials. After screening the papers' titles based on their relevance to this study's objective, 94 papers remained. Afterwards, the abstracts of the papers were evaluated according to the specified inclusion criteria, resulting in 68 trials. Subsequently, after examining the methods used to conduct each study, trials that did not involve cohorts detailed by the inclusion criteria were removed, leaving 54 papers. Lastly, data provision screening was performed to ensure that the trials contained interpretable, relevant data, which led to 28 trials in the end. The total number of participants at the baseline across all of the filtered trials was 11,909 people, and the average age across all of the participants was 74 years. Overall, 175 time points were analyzed across all of the trials.

Figure 1. *Flow Chart of Data Filtration Process.*

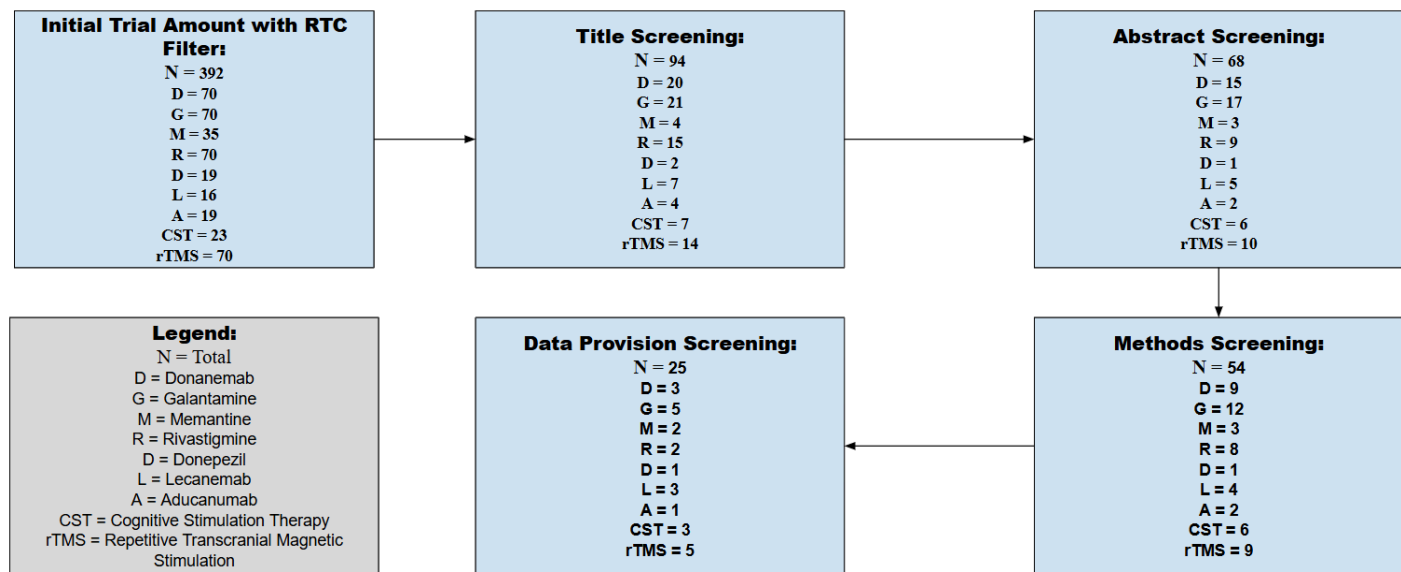


Figure 1. *A flow chart depicting the number of trials at each filter (n = total) after each filter.*

Figure 2. *Facet Wrapped Scatter Plot Showing Impact of Symptomatic Treatments on MMSE Scores*

Over Time Compared to a Placebo: n=17

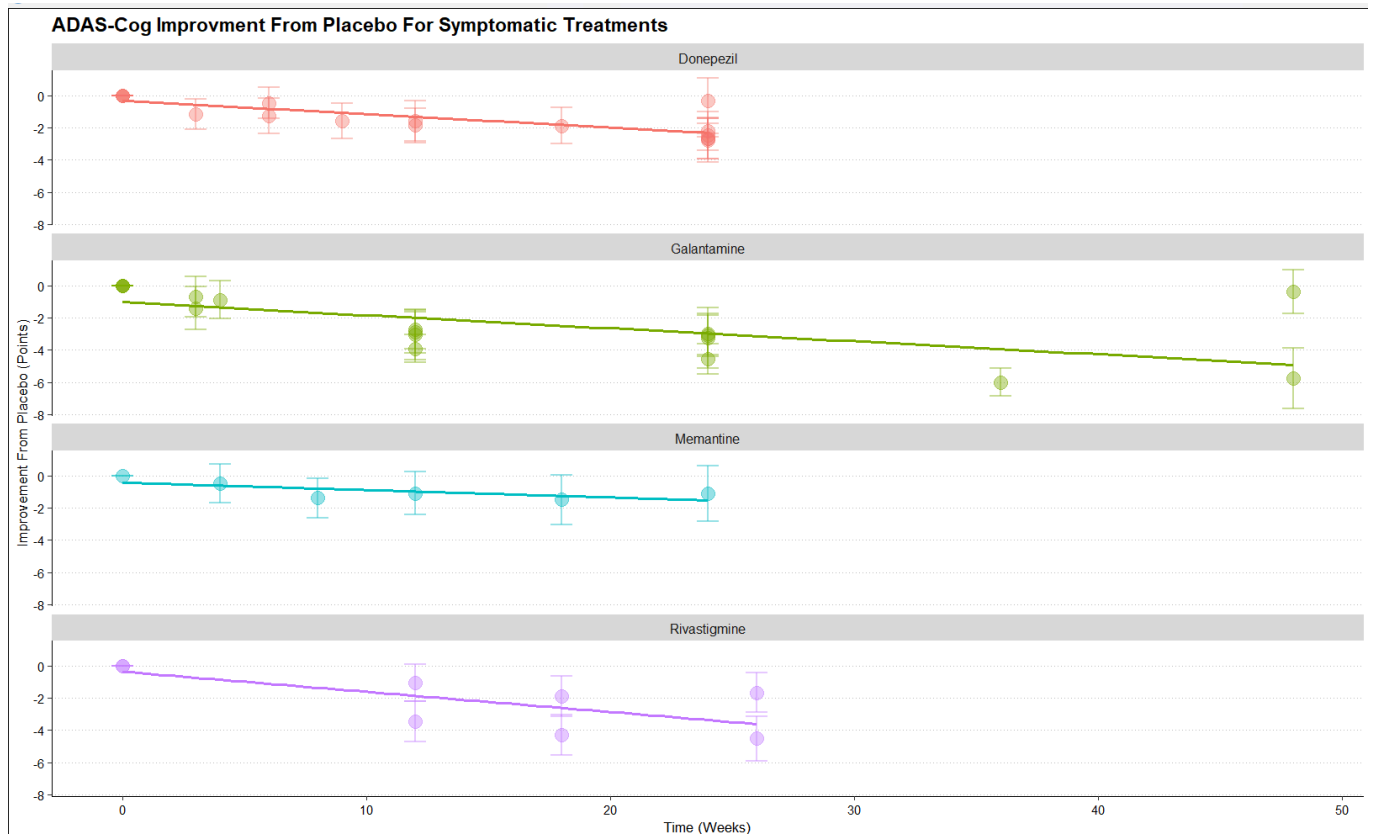
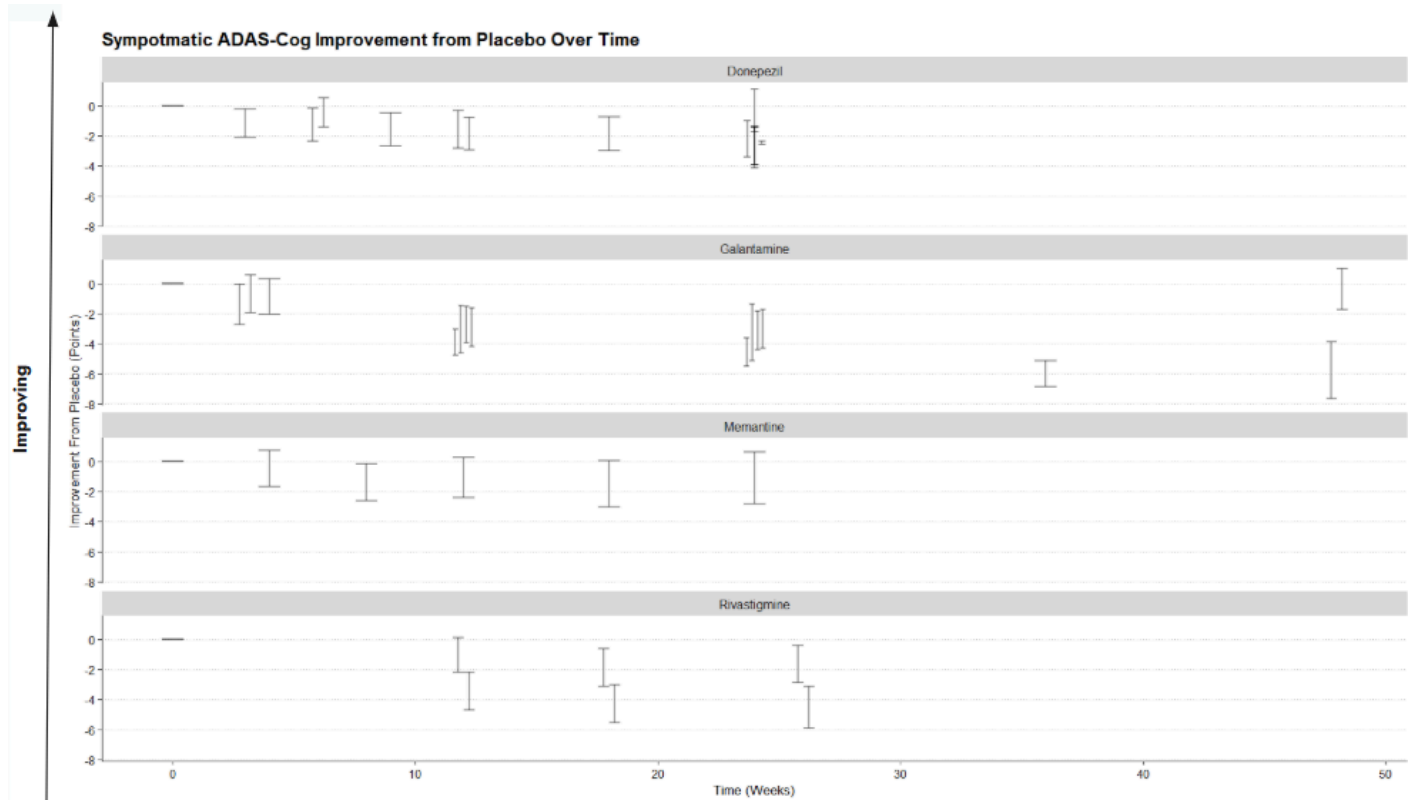


Figure 2.1. *Jittered Facet Wrapped Scatter Plot Showing Impact of Symptomatic Treatments on MMSE*

Scores Over Time Compared to a Placebo: n=17



Figures 2.1 and 2.2 are facet wrapped scatter plots depicting the mean difference between treatment and placebo groups in MMSE improvement with a 95% confidence interval with the points jittered in order to better show error bars of individual data points, with higher scores indicating more improvement. The mean improvement at each time is the midpoint of the error bars. The drugs shown in the graph are: Donepezil, Galantamine, Memantine and Rivastigmine. Overall, each drug improved scores on the ADAS-Cog Test compared to the placebo, with Galantamine improving ADAS-Cog scores the most over time with relatively low variation. The error bars of each individual data point at a given time heavily overlapped, showing how there is little variation in how a given drug performs at a specific time interval, aside from rivastigmine which had comparatively more variation. The error bars and

means of all the drugs overlap with each other, meaning that they are suitable to be grouped and compared against other treatment types.

Figure 3. *ADAS-Cog Improvement from Placebo Over Time for Anti Amyloid Treatments. N = 5*

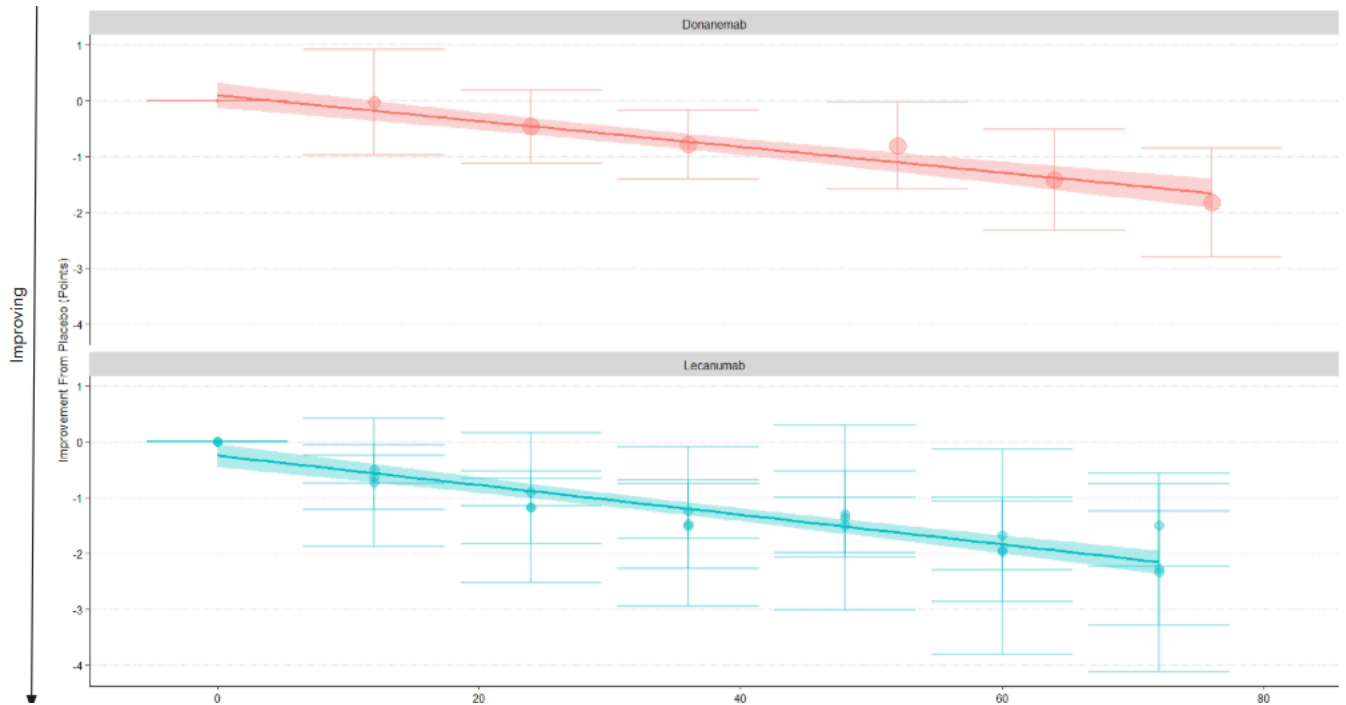


Figure 3.1. *Jittered Facet Wrapped Scatter Plot Showing Impact of Anti Amyloid Treatments on ADAS-Cog Scores Over Time Compared to a Placebo. N = 5*

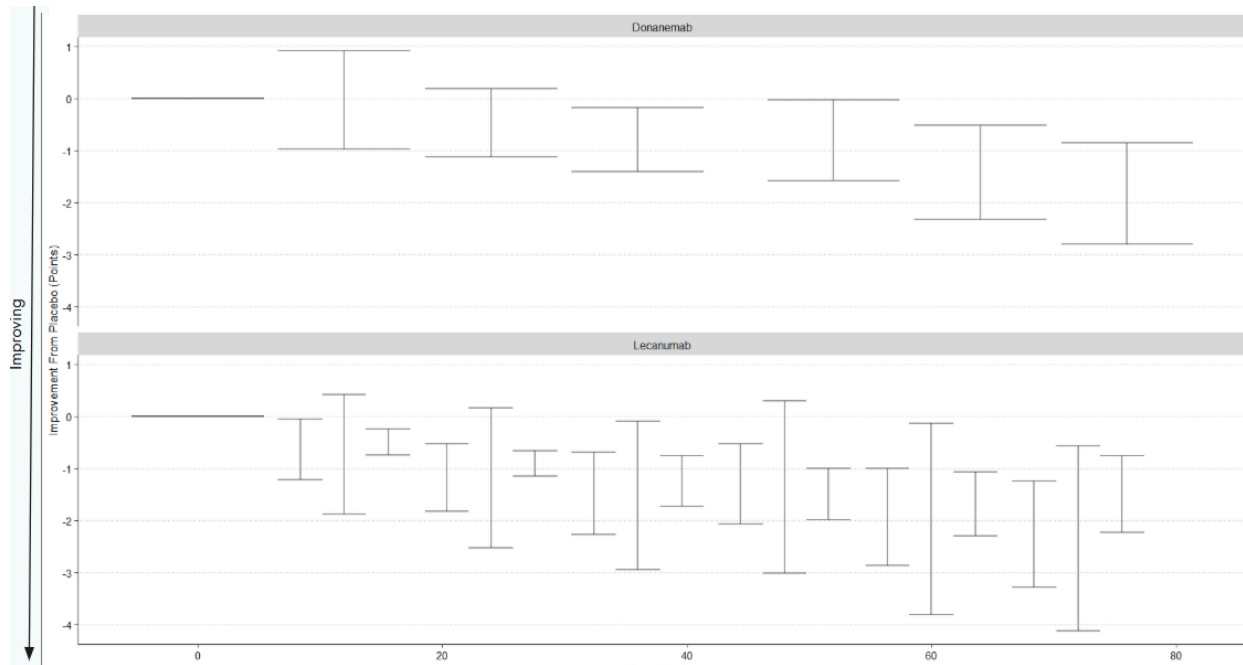


Figure 3 is a facet wrapped forest plot showing the improvement on the ADAS-Cog score compared to a placebo over time with a 95% confidence interval. The drugs depicted in the graph are Donanemab and Lecanumab. Both drugs are improving more than the placebo over time, and Lecanumab is consistent in its performance, shown by the heavy overlap of the error bars at the same time point. Both drugs perform very similar to each other at every point in time, meaning that they are similar enough to be joined in a comparison with drugs that use other mechanisms of action.

Figure 4. Scatterplot depicting Improvement in MMSE Score for Cognitive Treatments Compared to Placebo Treatment. $n = 7$.

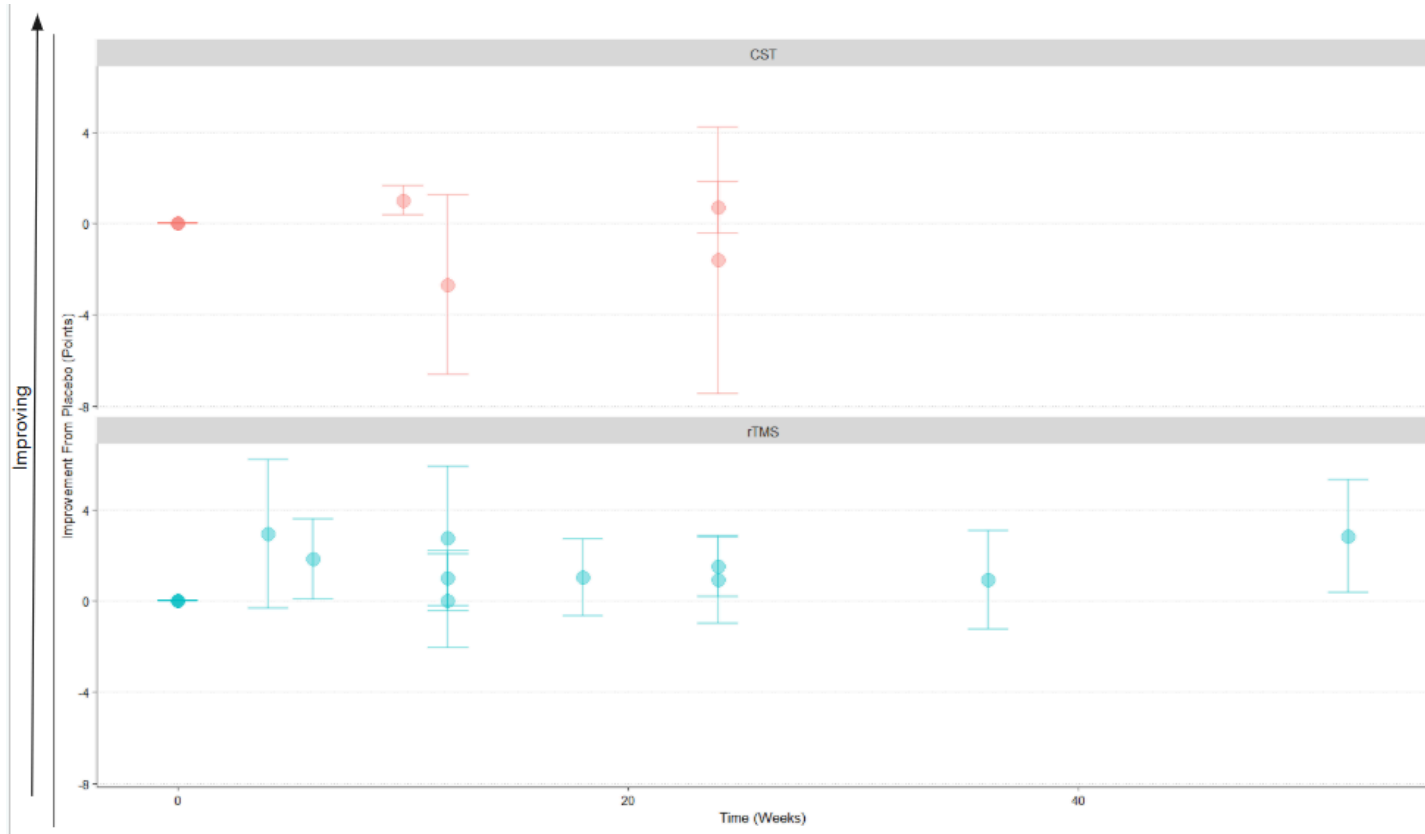


Figure 4.1. *Jittered Scatterplot depicting Improvement in MMSE Score for Cognitive Treatments*

Compared to Placebo Treatment. $n = 7$.

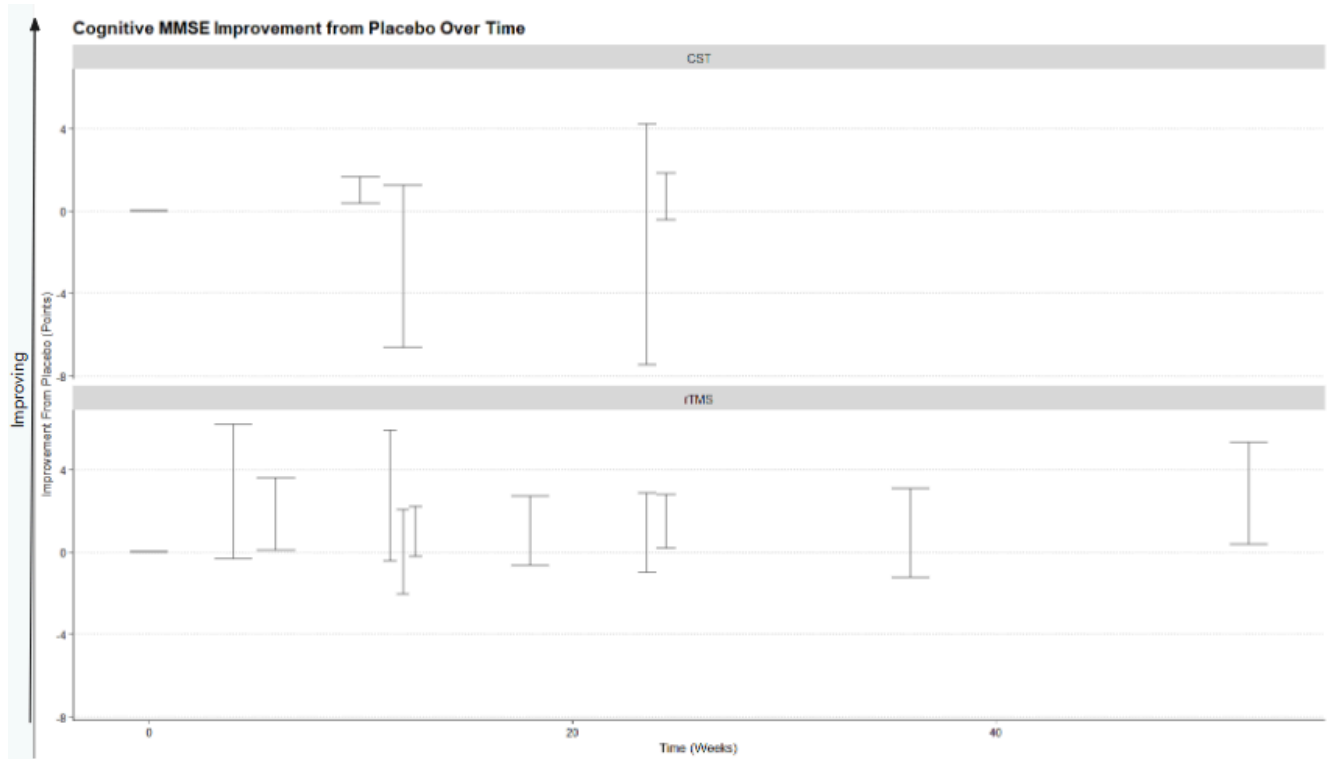


Figure 4 is a facet wrapped scatterplot showing the effect of Cognitive treatments on the MMSE score over time compared to a placebo. The plot gives a 95% confidence interval with the points jittered to clarify error bars at a given time period. Both treatments have more variation, shown by the large error bars, compared to anti amyloid and symptomatic treatments, with CST varying more than rTMS. The treatments have similar effects on the MMSE score at given time intervals, allowing them to be grouped together for an analysis with other drugs with different mechanisms of action.

Figure 5. *Facet wrapped scatterplot of three different treatment types effect on MMSE score over time. n*

= 14

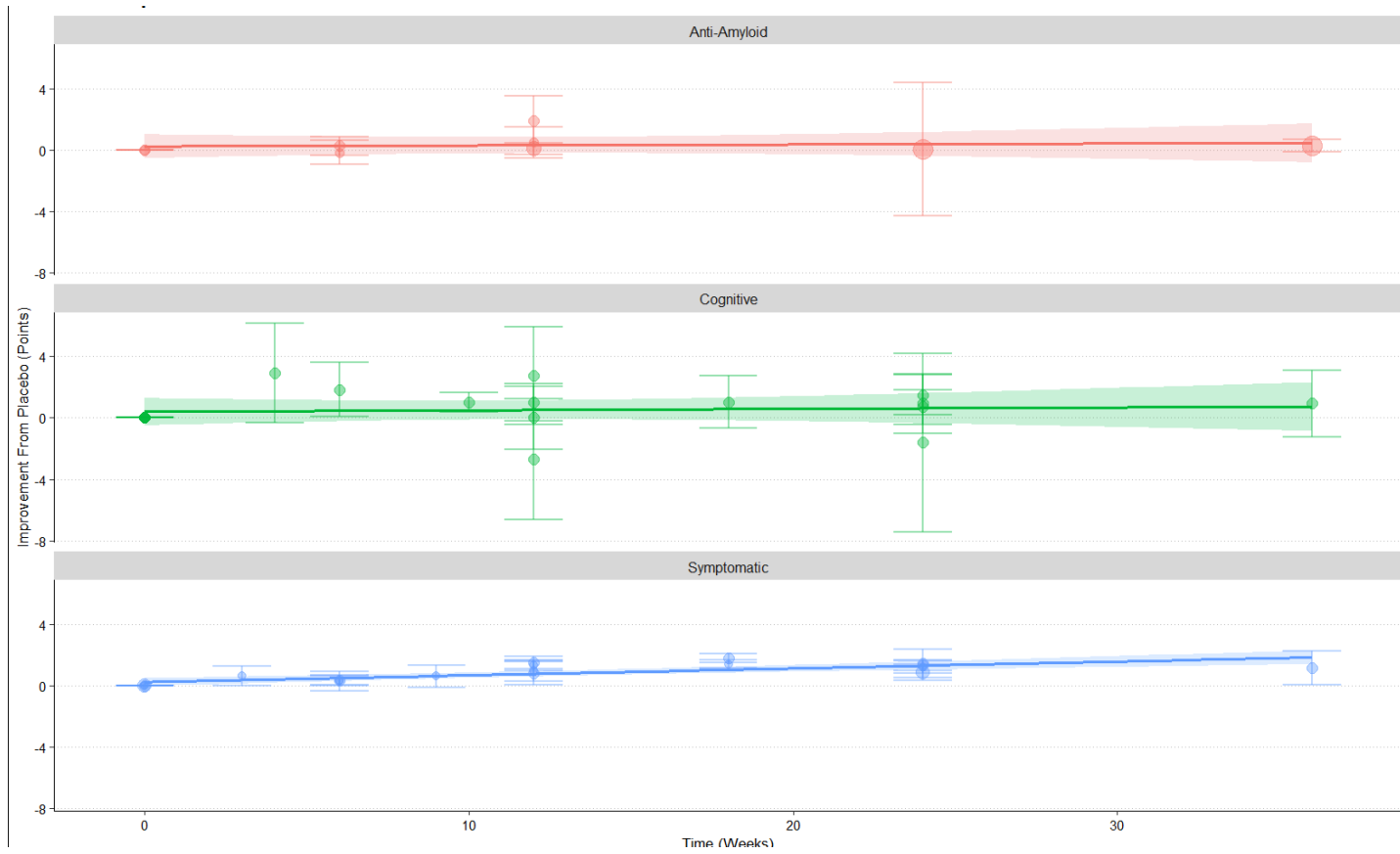


Figure 5.1 *Jittered facet wrapped scatterplot of three different treatment types effect on ADAS-Cog*

improvement from placebo over time. n = 14

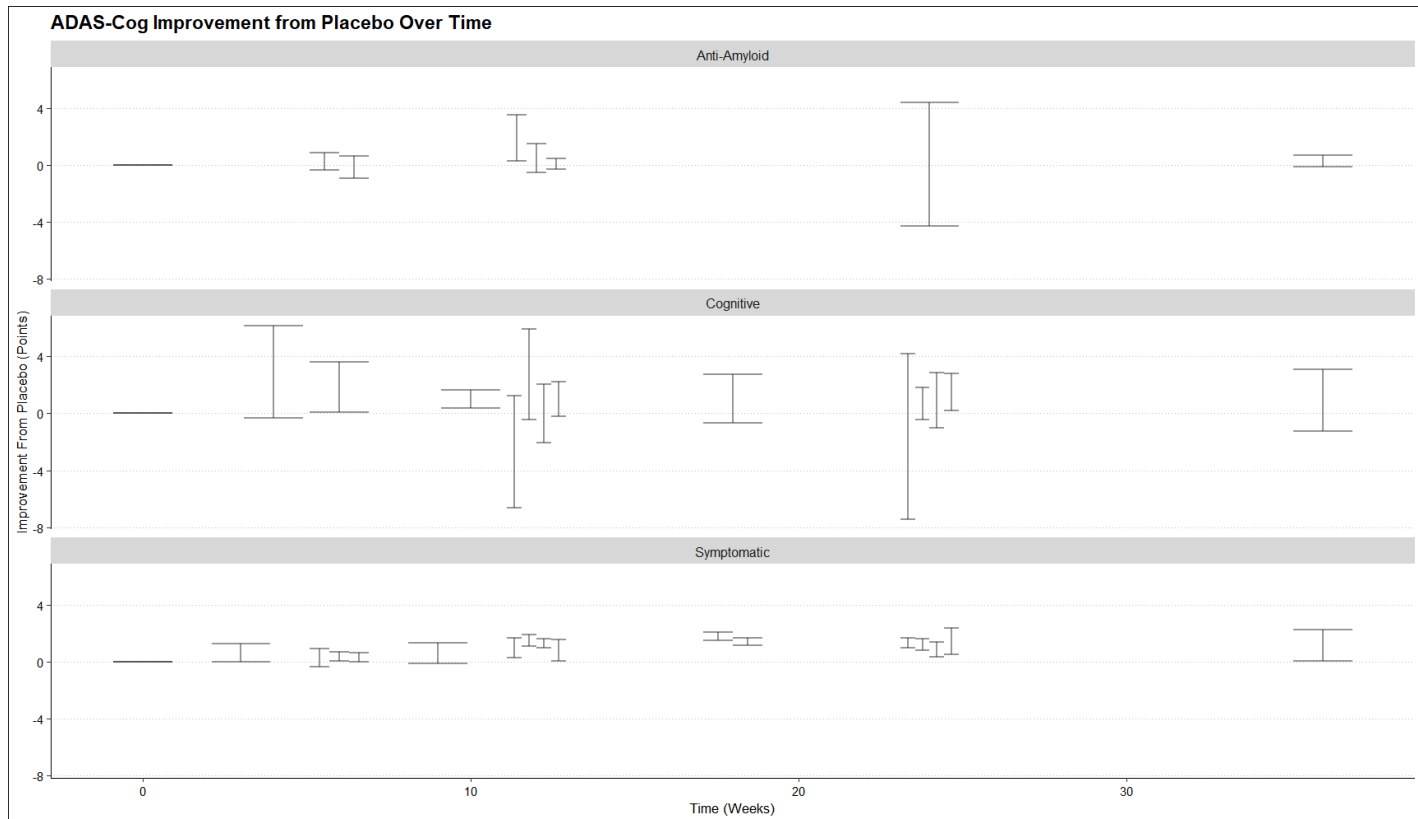


Figure 5.1 is a facet wrapped scatterplot of the impact of three treatment types (anti-amyloid, symptomatic, and cognitive therapy) on the MMSE score over time. All treatments improved by some amount over time compared to the placebo. Symptomatic treatments have a larger regression slope, indicating larger improvement over the same timeframe. Cognitive treatments have a lot of variation between datapoints, evidenced by the large error bars. Symptomatic treatments perform consistently, and anti amyloid treatments perform less consistently over time compared to symptomatic treatments. All treatments performed similarly <25 weeks.

Figure 6. Facet wrapped scatterplot of three different treatment types effect on ADAS-Cog score over time.

$n = 23$

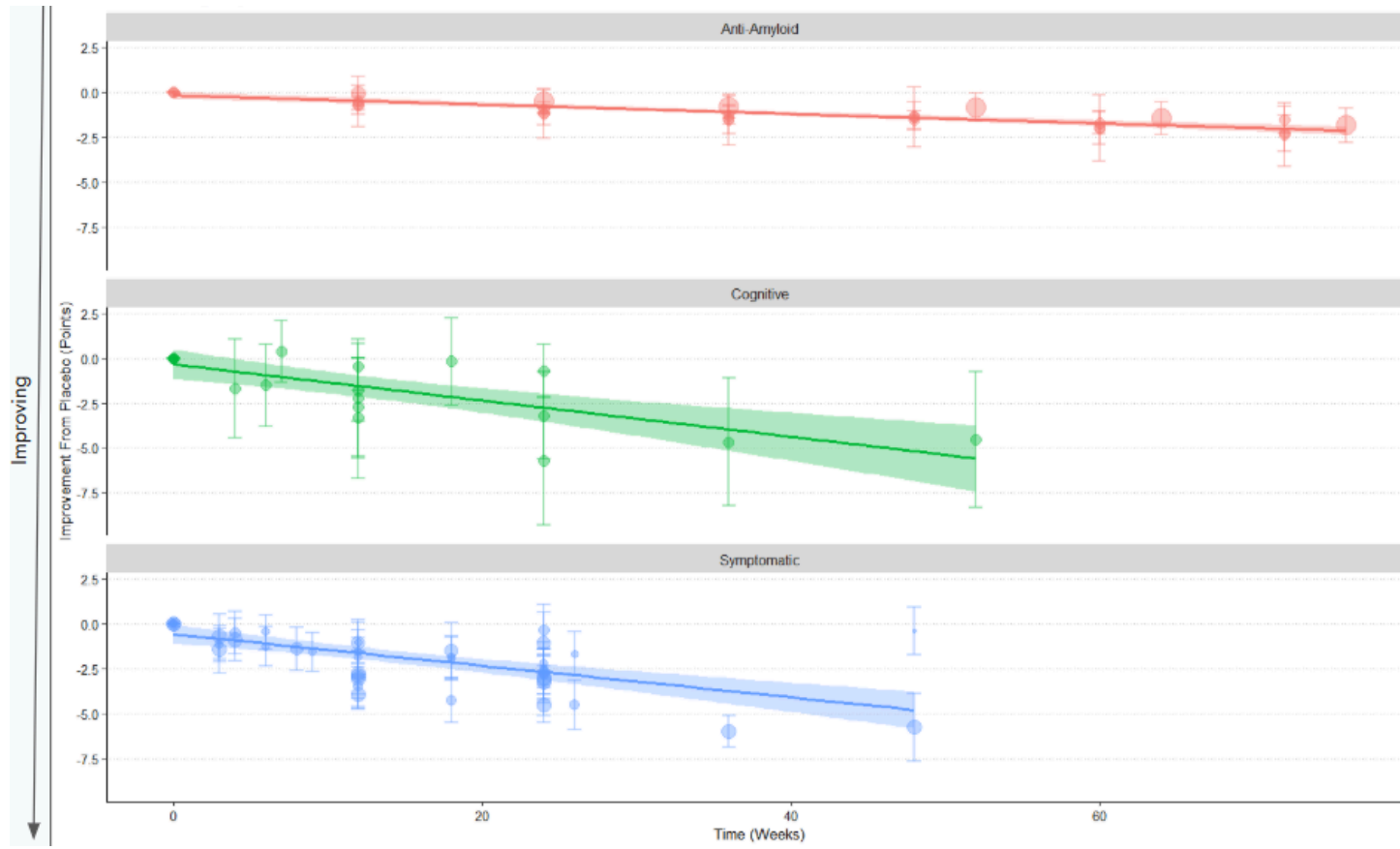


Figure 6.1. *Jittered facet wrapped scatterplot of three different treatment types effect on ADAS-Cog improvement from placebo over time. $n = 23$.*

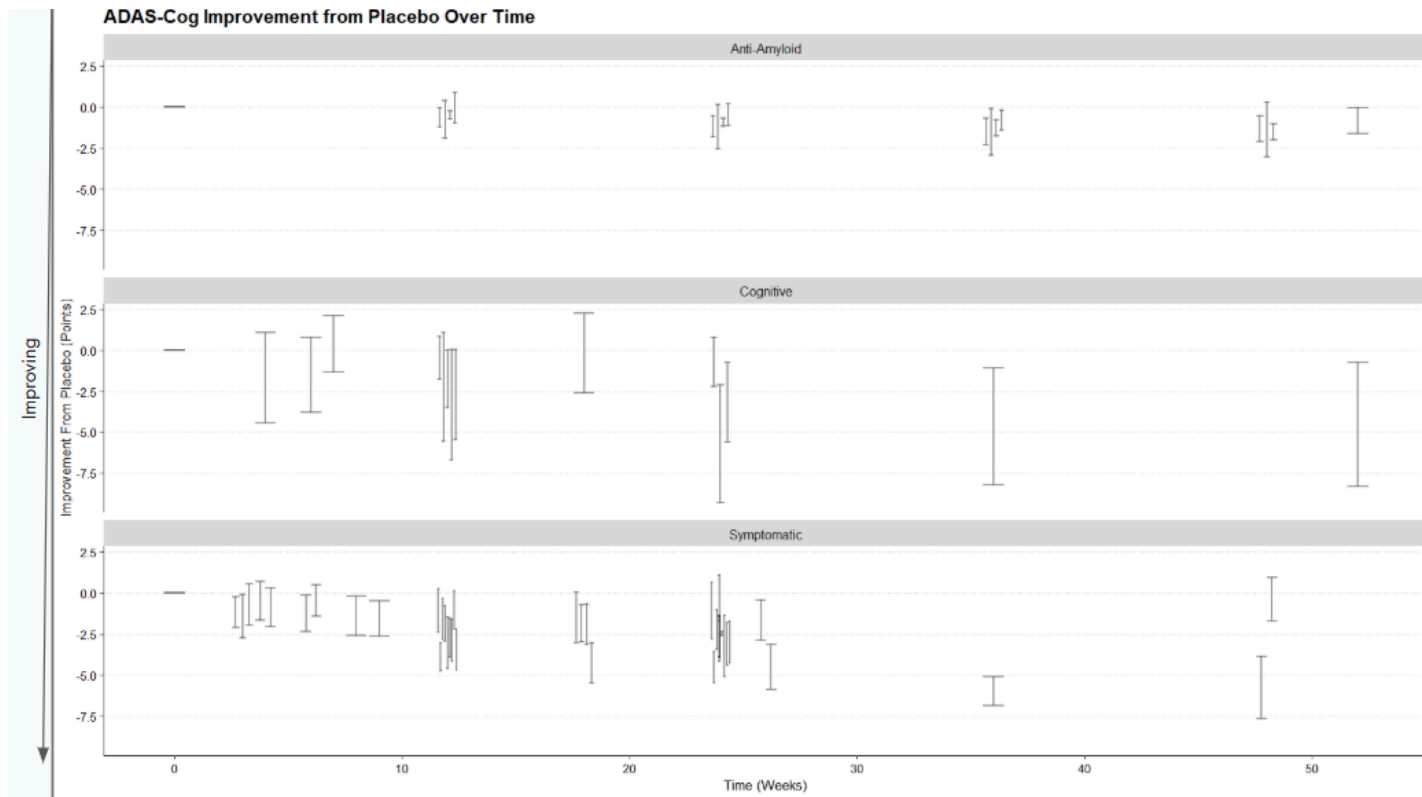


Figure 6.1 is a facet wrapped scatterplot of the impact of three treatment types (anti-amyloid, symptomatic, and cognitive therapy) on the ADAS-Cog score over time. All treatments improved by some amount over time compared to the placebo. Symptomatic treatments have a larger regression slope, indicating larger improvement over the same timeframe and more variation compared to anti-amyloid treatments. Anti-amyloid treatments have very consistent improvement with little variation compared to the other treatment types. Cognitive treatments have a lot of variation between datapoints, shown by the large error bars.

Discussion

To the best of the reviewer's knowledge, this is the first meta analysis that compares multiple cognitive, symptomatic and anti amyloid treatments. The data in figures 5 and 6 show that symptomatic treatments are better at reducing cognitive decline in a shorter period of time compared to anti amyloid and cognitive treatments. Anti amyloid treatments are very consistent in their ability to reduce cognitive decline, shown by their comparatively small error bars and consistent decreasing in score. Cognitive therapies have a lot of variation at each data point, shown by their comparatively larger error bars, which supports previous research on the topic. All three treatments had more variation for each data point on the MMSE test compared to the ADAS-Cog test. This can be explained by the scale difference, as the MMSE is on a 30pt scale and ADAS-Cog is on a 70pt scale. This means that a fluctuation by one point on the MMSE scale is a 3.33% change, which is larger than a one point fluctuation on the ADAS-Cog (1.42% change). This leads to larger variation being viewed graphs using the MMSE rather than the ADAS-Cog. Patients concerned with safety can also prioritise taking symptomatic treatments over anti amyloid treatments as symptomatic treatments are comparatively safer with less dangerous side effects due to the risk of brain bleeding and swelling associated with anti-amyloid treatments.

The results also assist in speculation regarding the Amyloid Hypothesis. The data suggests that treating just the symptoms of Alzheimer's Disease is more effective at reducing cognitive decline compared to attacking the plaques, which is suggested to be the root cause. This implies that amyloid plaques are at the very least less correlated with the cognitive decline in Alzheimer's disease than previously believed. It is then possible that amyloid plaques are a symptom of the cognitive decline, or correlated with

rather than causative. The anti amyloid hypothesis has also been criticised due to the ineffectiveness of anti-amyloid treatments for cognitive decline, meaning that even though plaque concentration decreased, the symptoms were still present. This furthers this claim by comparing the effectiveness of anti amyloid treatment with symptomatic treatments, showing that reduced cognitive decline can be treated better without attacking the plaques.^[11,12] This paper also saves medical professionals and researchers a large amount of time, as they do not have the time to search through literature, and combine and analyze the data provided. This review summarizes these findings, allowing for time to be spent with patients rather than reading paper.

The major limitation of this study was the lack of total data that was collected. This is due to the recency of Anti-Amyloid treatments in particular, with the first treatment (Adacantumab) being released on June 7th, 2021.^[13] Symptomatic treatments in comparison were first released for Alzheimer's disease in 1996.^[14] Furthermore, studies tended to give longitudinal data on a few specific dates, being 12, 24, and 52 weeks after T_0 , meaning that there was less data in between those points. This would mean that longitudinal trends for the effect of each drug on cognitive decline could be better established if the time points were spread out more uniformly. Trials studying the effects of solely cognitive treatments were also rare, as CST is usually used in tandem with symptomatic treatments. Finding more trials using CST or losing the inclusion criteria would give more data points to draw stronger conclusions. Furthermore, the review could be strengthened by having more outcomes to compare with to ensure that the results on the two outcomes were not an anomaly. Most papers gave data on the ADAS-Cog due to its reliability and reputation, or the MMSE due to its quick

and cheap nature, or both tests. Including other reputable tests such as the Integrated Alzheimer's Disease Rating Scale (iARDS), Montreal Cognitive Assessment (MoCA), and others, would aid judgements on the quality of each drug in relation to cognitive decline more rigorous.

Conclusion

The purpose of this systematic review was to determine the relative effectiveness of three different treatments for Alzheimer's disease, those being treatments that attack the amyloid plaques, treatments that confront the symptoms, and non pharmaceutical cognitive stimulation treatments. 392 studies were screened, with 25 total individual studies being included in the analysis. It was concluded that symptomatic treatments cause a greater improvement in MMSE and ADAS-Cog scores in a shorter amount of time compared to anti-amyloid and cognitive treatments. Anti amyloid treatments were the most consistent and had the least variation, and cognitive treatment had the most variation. Future research and analysis can be done with more data pertaining to anti amyloid treatments, as they are the newest form of treatment available.

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