Learning from Failure—Investigating Reasons for Failure of Effective Treatments Identified in a Meta-analysis of Alzheimer's Disease Studies

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Clinical Trials: Results
P004

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Take home message: **Treatments have failed despite being safe and efficacious due in part to a failure to evaluate all evidence effectively, which is worse for patients, caregivers, clinicians, sponsors, and the field in general.**

INTRODUCTION

Alzheimer's disease (AD) clinical trials have a long history of failure, and recently, real-world barriers have made successes inaccessible to patients. Given the significant investments in moving treatments through the various phases of clinical research, these failures cannot be casually dismissed. Although memantine was approved in 2003, the next successful FDA approvals for AD treatments (aducanumab, lecanemab, and donanemab) didn't occur for nearly 20 years. During that 20-year gap, hundreds of treatments were investigated, yet none made it to market. Thus, the future of AD clinical trials hinges on understanding the factors that contributed to these failures and their absence on the market.

METHODS

A meta-analysis of over 200 placebo-controlled randomized clinical trials for patients with MCI due to AD or mild to moderate AD identified several treatments with evidence of comparable efficacy to approved treatments. Study results were included if at least two of the cognitive, function, and global domains were reported. A global statistical test (GST) combining cognitive, functional, and global domains assessed overall efficacy. Other metrics of efficacy were also examined (i.e. Cohen's d). Using the GST, all investigated treatments were compared to approved therapies. Finally, any treatments that demonstrated greater efficacy than the approved treatments were further investigated to establish a specific cause of failure.

Figure 1: Month 6 GST Forest Plot

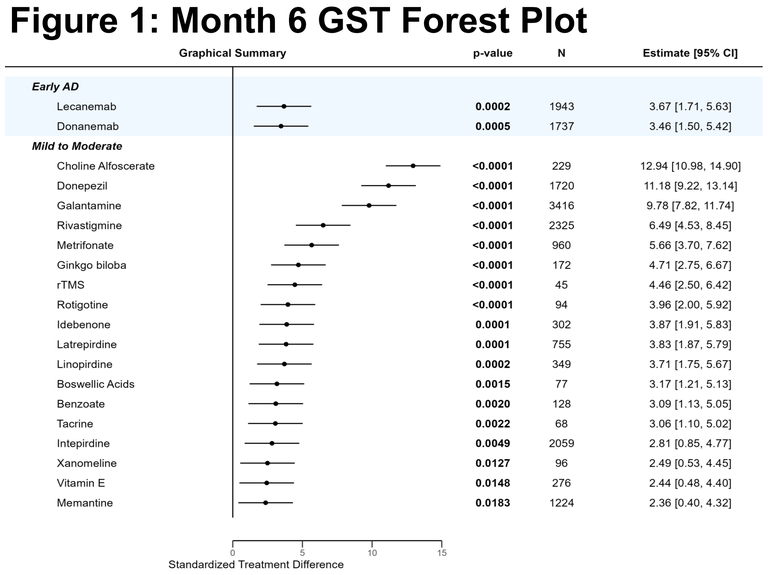

Figure 1: Forest plot of 6-month GST estimates and 95% Confidence Interval (CI) for studies with a greater effect size (Cohen's D) than Memantine at 6 months. Results are broken down by population, sorted by estimate. Results are standardized such that positive estimates favor treatment.

RESULTS

Figure 2: Month 6 Cohen's d Forest Plot

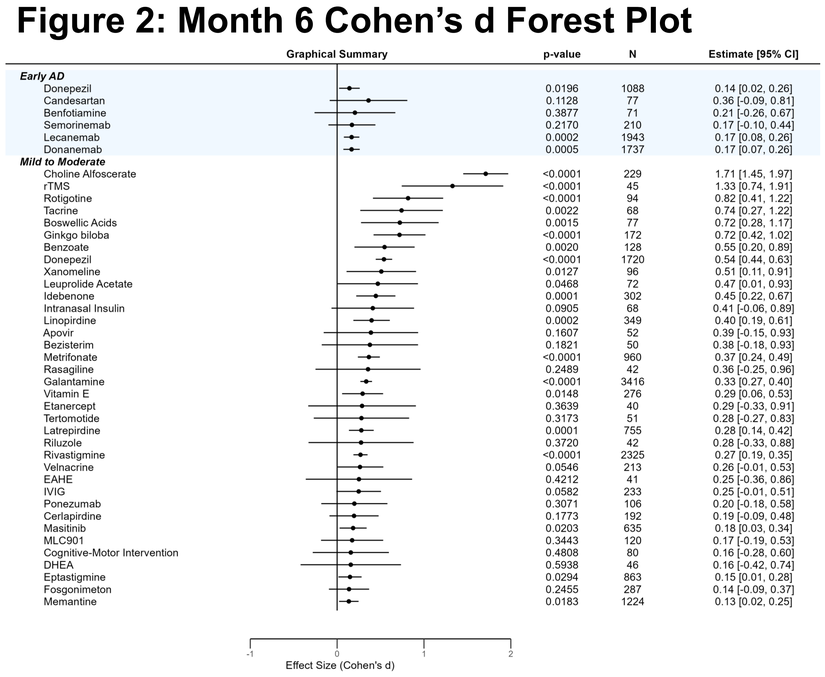

Figure 2: Forest plot of 6 month standardized treatment differences (Cohen's D) and 95% CI for studies with a greater effect size than Memantine at 6 months. Results are broken down by population, sorted by estimate. Results are standardized such that positive estimates favor treatment.

Figure 3: Month 18 GST Forest Plot

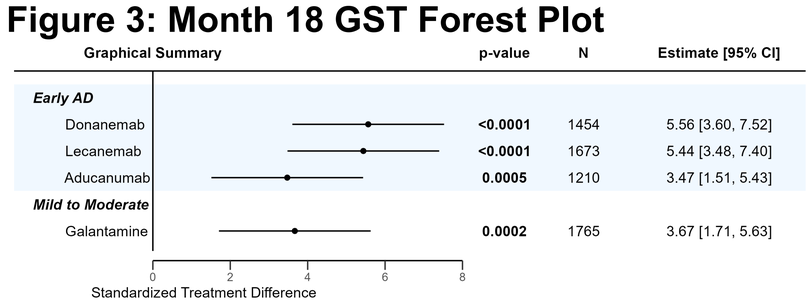

Figure 3: Forest plot of 18-month GST estimates and 95% CI for studies with a greater effect size than Memantine at 18 months. Results are broken down by population, sorted by estimate. Results are standardized such that positive estimates favor treatment.

Figure 4: Month 18 Cohen's d Forest Plot

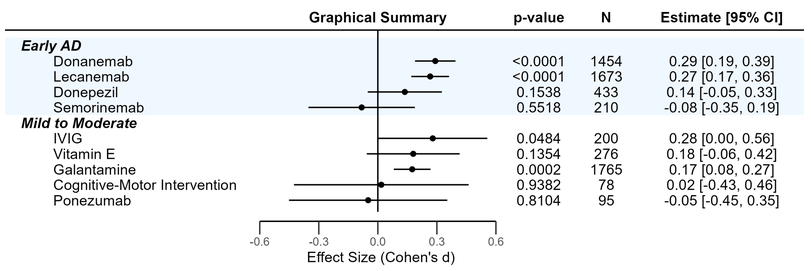

Figure 4: Month 18 Cohen's d Forest Plot

Forest plot of 18-month standardized treatment differences (Cohen's D) and 95% CI for studies with a greater effect size than Memantine at 6 months. Results are broken down by population, sorted by estimate. Results are standardized such that positive estimates favor treatment.

Figure 5: Comparison of GST vs. Primary Outcome

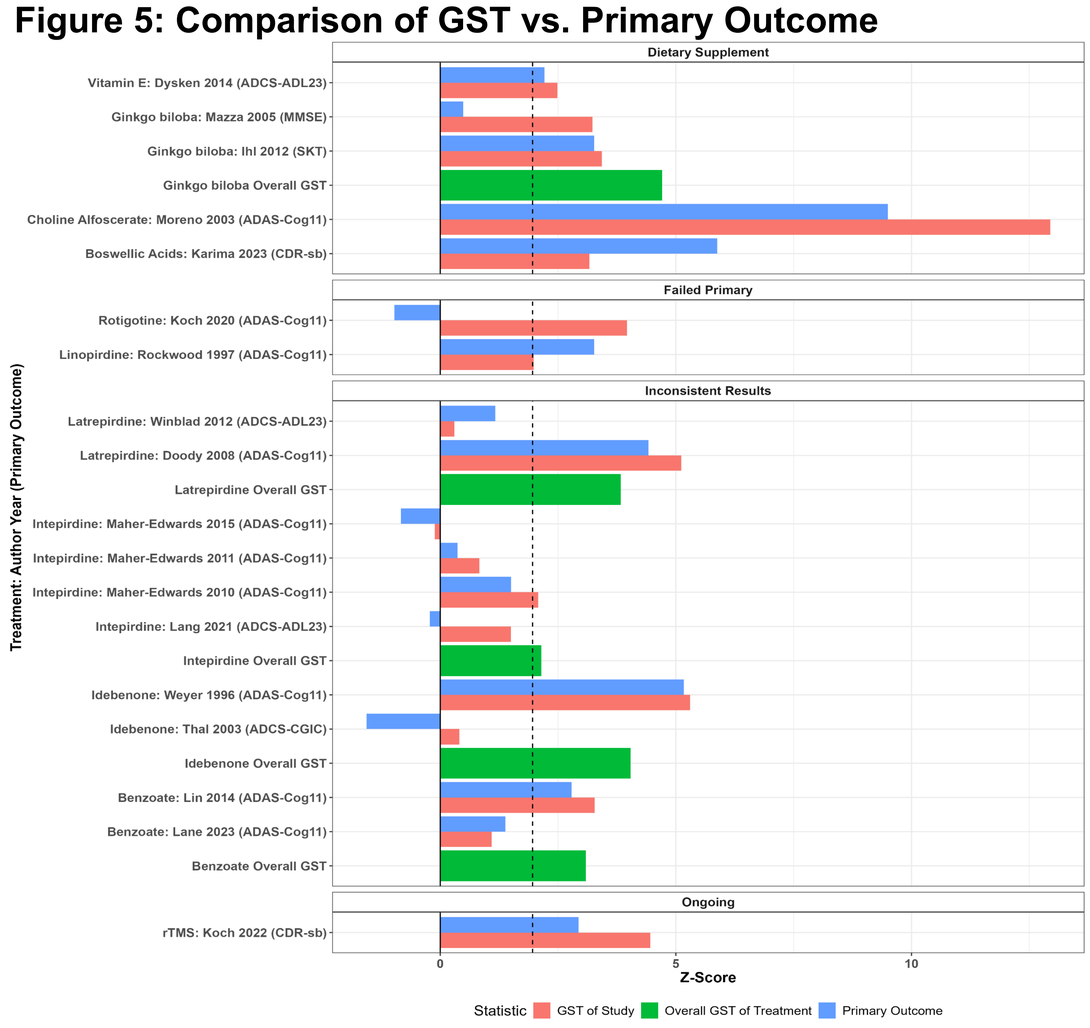

Figure 5: Comparison of GST vs. Primary Outcome

Bar plot comparing the GST and primary outcome of each study along with the GST for each drug across studies. The bar plot is further grouped by the reason why it is not on the market. The goal of this figure is to show that some of these studies have evidence of efficacy when using a metric that combines evidence but failed on a single outcome.

DISCUSSION

The inherent variability in a single outcome assessment causes random chance to play an outsized role in AD clinical trials. Thus, a greater emphasis needs to be placed on using metrics that combine evidence across different outcomes, such as a GST. This analysis demonstrates that when applying a combined evidence approach, over half of the studies that had evidence of efficacy still failed for unsatisfying reasons. Additionally, it is likely that many more studies would have shown similar levels of efficacy if they had been able to achieve larger sample sizes.

There are many costs associated with developing AD treatments, but some of the most difficult to pay are opportunity costs, especially those associated with promising treatments that have failed. Each failure that should have been a success moves the field away from what may be a critical component to the treatment of AD.

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