A Meta-Analysis to Demonstrate the Incidence of Placebo Effect in Alzheimer's Disease and Mild Cognitive Impairment Trials: Mitigating for Impacts on Trial Endpoints

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Abstract

Background: Placebo effect is a known confound across many Alzheimer's Disease (AD) and Mild Cognitive Impairment (MCI) trials. There is the potential for response bias in trials with patient and study partner reported outcomes, most often identified as the primary or secondary endpoints in AD and MCI studies. A study participant's expectations of treatment benefits, increased standard of care, or anticipated side effects of the experimental drug, can influence test performance, trial commitment, study partner relationships and bias towards endpoint reporting (Hrobjartsson, Kaptchuck & Miller, 2011). The quality of data collection and overall trial outcome may be impacted, warranting efforts towards the implementation of mitigation strategies.

Method: A multinational meta-analysis of 14 AD and MCI placebo-controlled efficacy studies (18 effects) evaluating cognition, behavior, and function was completed. The study population reviewed (*N*= 4667) included participants diagnosed with MCI, Early-Stage to Severe AD, as well as AD patients with clinically significant agitation. All studies required the participation of a study partner in support of primary and secondary outcome measures: Clinical Dementia Rating Scale Sum of Boxes, ADCS-Clinical Global Impression of Change, ADCS-Activities of Daily Living and Disability Assessment for Dementia. The studies were of mixed results and revealed a high incidence of adverse event reporting. Further exploration into the placebo and treatment assigned groups was conducted with consideration to the participant's experience of AEs and its potential influence on cognitive and functional endpoint reporting. A literature review of such impacts covered placebo control strategies.

Results: There were 3085 placebo and 3855 Donepezil participants reviewed across common adverse event categories: Gastrointestinal, Anorexia, Sleep Disturbance, and Behavioral. Moderate (d=0.68, 95% CI $0.81<\delta<0.58$) and homogeneous ($Q=25.23[17]$, $p=0.09$) effects were found in AD and MCI groups for Donepezil and placebo AEs. The data indicates no significant difference in AEs between Donepezil and placebo with a further analysis of specific common adverse event categories to be presented. Methods to control the placebo response were not noted across studies. This suggests an absence of mitigation strategies for patients and study partners in support of reliable data collection across endpoints.

Conclusion: The value in applying methods towards the control of placebo response in MCI and AD clinical trial design is well supported by this data. This analysis revealed a placebo effect across trials as evidenced through high incidence of AE reporting between groups. Trial participants assigned to placebo experienced common adverse effects with those assigned to treatment. Most studies reporting positive outcomes separated from placebo; however, a strong placebo response may have confounded results in the trials that did not produce symptomatic improvement or where clinical benefit was uncertain. Introducing placebo mitigation practices through participant and study partner education, site training, the practice of neutrality in the research environment and overall management of site and participant expectations, may prove to reduce the placebo response in future AD and MCI trials forward.

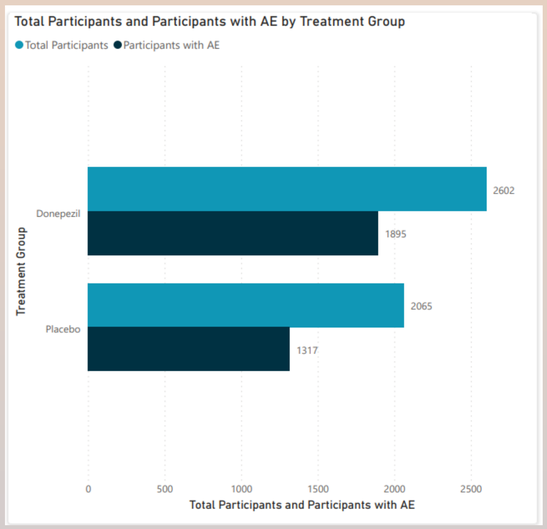

Figure 1. Incidence of AE reporting between Donepezil and Placebo treatment groups

Background

Placebo effect is a known confound across many Alzheimer's Disease (AD) and Mild Cognitive Impairment (MCI) trials. There is the potential for response bias in trials with patient and study partner reported outcomes, most often identified as the primary or secondary endpoints in AD and MCI studies. Several factors contribute to increased placebo or nocebo response. A study participant's expectations of treatment benefits, increased standard of care, or anticipated side effects of the experimental drug, can influence test performance, trial commitment, study partner relationships and bias towards endpoint reporting (Hrobjartsson, Kaptchuck & Miller, 2011).

The potential impacts to the quality of data collection and overall trial outcomes warrant efforts towards the implementation of placebo response mitigation strategies. Evans, et al., 2021 reviewed how placebo effects are especially problematic in studies that rely on subjective reporting, such as with study partner involvement (e.g. ADCS-ADL, CDR-SB, ADCS-CGIC, etc.), as well as effort-dependent clinical outcome assessments (e.g. MMSE, ADAS-Cog, etc.). Methods towards neutralizing the placebo response warrant further examination in an effort mitigate related risks and to allow for a better measure of drug's true efficacy.

Method

A selection of 22 multinational AD and MCI placebo-controlled efficacy studies evaluating cognition, behavior, and function was compiled to review the frequency of adverse event (AE) reporting between treatment and placebo groups. The study population in this review offered a notable sample size for the examination of placebo response frequency and impacts *(N= 6940),* however a further analysis of data resulted in a reduction. A detailed review of the data revealed that the AE's identified in eight of the original selected studies had been segmented into various symptom domains. The potential for a co-occurrence of multiple event reports within study participants was evident as the number of total participants who had reported AEs was not noted. Data review findings resulted in the exclusion of those eight studies and included participants from 14 of the original 22 selected for analysis *(N=4667; Figure 1*).

Method (cont.)

All studies included in this analysis required the participation of a study partner in support of primary and secondary outcome measures: Clinical Dementia Rating Scale (CDR), ADCS-Clinical Global Impression of Change (ADCS-CGIC), ADCS-Activities of Daily Living (ADCS-ADL) and Disability Assessment for Dementia (DAD). The studies were of mixed results and overall revealed a high incidence of adverse event reporting across both treatment and placebo assigned groups.

Further exploration into the placebo and treatment assigned groups was conducted with consideration to the participant's experience of AEs and the potential influence on cognitive and functional endpoint reporting. A literature review of such impacts covered placebo control strategies along with the involvement of study partners in the collection of data.

All studies were reviewed to identify intervention strategies that might have been included to mitigate for a placebo effect. The recruitment of participants and study partners was assessed along with the inclusion and exclusion criteria and requirements towards participant and care partner eligibility. The review also sought to identify training methods of the research staff to ensure a standardized administration of clinical outcome assessments requiring participant response. Training and education towards the facilitation of the care partner and subjective assessments were additional variables under review.

Results

The final data set resulted with 2065 placebo and 2062 Donepezil participants reviewed across common adverse event categories, including but not limited to:

- Gastrointestinal
- Anorexia
- Sleep Disturbance
- Behavioral

Moderate (d=0.68, 95% CI $0.81<\delta<0.58$) and homogeneous ($Q=25.23[17]$, $p=0.09$) effects were found in AD and MCI groups for Donepezil and placebo AEs. The data indicates no significant difference in the incidence of AEs between Donepezil and placebo (*Figure 2*).

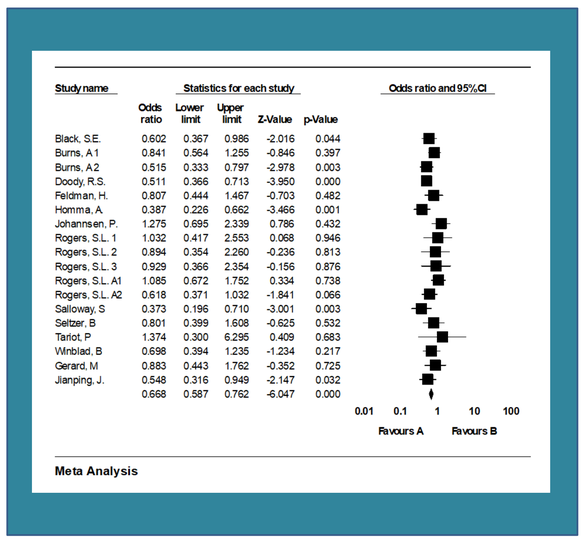

Figure 2. Analysis of total adverse events showed that effect size for AEs did not differ between placebo (left) or Donepezil (right) groups.

Results (cont.)

Common adverse event categories were further examined to reveal significant similarities between treatment groups *(Figure 3.)* There were, however, limitations to the analysis with risk of an over representation of reported AEs within participants as review was limited to the data included in the publications. Collecting individual AEs into common event categories such as nausea and vomiting in GI or agitation and sleep disruption under behavioral could have potentially inflated the findings due to a dual capture of co-occurring symptoms. Methods to control the placebo response were not noted across studies. This suggests a potential absence of mitigation strategies for participants and study partners in support of reliable data collection across endpoints. As noted, the studies included in the analysis were of mixed results. It is reasonable to speculate that the significant presence of a placebo response had the potential to impact signal detection.

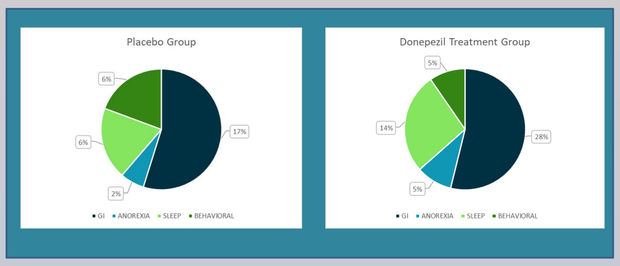

Figure 3. Common adverse event categories between groups

Conclusion

The value in applying methods towards placebo response mitigation in MCI and AD clinical trial designs is well supported by this data. This analysis revealed a placebo effect across trials as evidenced through high incidence of AE reporting between groups. Trial participants assigned to placebo did not significantly differ from the treatment group in the reporting of AEs. Most studies reporting positive outcomes separated from placebo; however, an argument can be made that the presence of placebo response may have confounded results in the trials that did not produce symptomatic improvement or where clinical benefit was uncertain. Introducing placebo mitigation practices may prove to reduce the placebo response in future AD and MCI trials forward:

- Participant and study partner education: purpose of the trial; placebo and nocebo
- Staff training: minimize expectations
- Clinical assessment training: standardized administration and scoring
- Neutrality in the research environment
- Research vs. Therapeutic Rapport
- Management of the study visit: limit time spent with participants and study partners; minimize potential for therapeutic benefit
- Consider and minimize participant and study partner burden

Implementing such practices in future trials may serve to minimize vulnerability and improve trial success ultimately leading to greater confidence in study outcomes data and a higher availability of treatments.