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Are external grants or funds being used to support this research?: No external grants or funds are being used to support this research.

How did you learn about the YODA Project?: Colleague

Conflict of Interest

https://yoda.yale.edu/system/files/coi_form_aj.pdf
https://yoda.yale.edu/system/files/coi_form_gb.pdf
https://yoda.yale.edu/system/files/coi_form_ka.pdf
https://yoda.yale.edu/system/files/coi_form_kk_0.pdf
https://yoda.yale.edu/system/files/coi_form_ks.pdf
https://yoda.yale.edu/system/files/coi_form_tb.pdf

Certification

Certification: All information is complete; I (PI) am responsible for the research; data will not be used to support litigious/commercial aims.

Data Use Agreement Training: As the Principal Investigator of this study, I certify that I have completed the YODA Project Data Use Agreement Training

1. [NCT00253227 - GAL-INT-2 - Galantamine in the Treatment of Alzheimer's Disease: Flexible Dose Range Trial](#)
2. [NCT00249158 - RIS-AUS-5/CR006010 - Risperidone in the Treatment of Behavioural and Psychological Signs and Symptoms in Dementia \(BPSSD\): a Multicentre, Double-blind, Placebo-controlled Parallel-group Trial](#)
3. [RIS-BEL-14 - Risperidone in the treatment of behavioural disturbances in patients with Alzheimer's dementia: a double-blind placebo-controlled trial](#)
4. [NCT00249145 - RIS-INT-24/CR006046 - Risperidone in the Treatment of Behavioral Disturbances in Demented Patients: an International, Multicenter, Placebo-controlled, Double-blind, Parallel-group Trial Using Haloperidol as Internal Reference](#)
5. [RIS-INT-83 - Efficacy and safety of a flexible dose of risperidone versus placebo in the treatment of psychosis of Alzheimer's disease. A double-blind, placebo-controlled, parallel-group study.](#)
6. [NCT00034762 - RIS-USA-232/CR002764 - Efficacy And Safety Of A Flexible Dose Of Risperidone Versus Placebo In The Treatment Of Psychosis Of Alzheimer's Disease](#)
7. [NCT00253123 - RIS-USA-63/CR006022 - A Randomized, Double-Blind, Placebo-Controlled Study of Risperidone for Treatment of Behavioral Disturbances in Subjects With Dementia](#)
8. [NCT00261573 - GAL-INT-6 - The Safety and Efficacy of Galantamine in the Treatment of Vascular and Mixed Dementia](#)
9. [NCT00253214 - GAL-INT-10 - Placebo-Controlled Evaluation of Galantamine in the Treatment of Alzheimer's Disease: Safety and Efficacy of a Controlled-Release Formulation](#)
10. [GAL-MVD-302 - Galantamine treatment of vascular dementia: a randomized trial](#)
11. [NCT00216593 - GAL-ALZ-302 \(PMID # 19042161-CR003940\) - Treatment of Severe Alzheimer's Disease in a Residential Home, Nursing Home, or Geriatric Residential Setting: Evaluation of Efficacy and Safety of Galantamine Hydrobromide in a Randomised, Doubleblind, Placebo-Controlled Study](#)
12. [NCT00645190 - GAL-CHN-T100 - A Randomized, Double Blind, Active Control, Flexible Dose, Multicenter Study to Evaluate Galantamine HBr in the Treatment of Alzheimer's Disease: Safety and Effectiveness of an Immediate-release Table Formulation.](#)
13. [GAL-USA-10 - Placebo-controlled evaluation of galantamine in the treatment of Alzheimer's disease: Evaluation of safety and efficacy under a slow titration regimen](#)

What type of data are you looking for?: Individual Participant-Level Data, which includes Full CSR and all supporting documentation

Research Proposal

Project Title

Individual-level and study-level predictors of neuropsychiatric symptom placebo response in Alzheimer's Disease

clinical trials

Narrative Summary:

Behavioral and psychiatric symptoms of dementia (BPSD) are common features of Alzheimer's Disease (AD). Development of new therapeutics for BPSD is complicated by high levels of placebo response observed across multiple independent clinical trials of patients with dementia. Understanding factors associated with placebo response is therefore critical for optimally designing clinical trials to meet the outstanding need of AD patients suffering from BPSD.

Scientific Abstract:

Background: Behavioral and psychiatric symptoms of dementia (BPSD) are common features of Alzheimer's Disease (AD) and include symptoms of psychosis, depression, irritability, and aggression [1]. Although BPSD are a primary cause of caregiver burden and patient distress, few pharmacological treatments exist for safe and long-term amelioration of their negative effects [2]. Development of new therapeutics for BPSD is complicated by high levels of placebo response observed across multiple independent clinical trials of patients with dementia [3], which could arise from a number of factors, including regression toward the mean, expectancy bias, psychosocial effects of trial enrollment, and baseline clinical and demographic patient characteristics [4]. This placebo response has even motivated the use of alternative trial frameworks to mitigate placebo, such as sequential parallel comparison design. Understanding factors associated with placebo response is therefore critical for optimally designing clinical trials to meet the outstanding need of AD patients suffering from BPSD.

Objective: We will quantify the magnitude, onset, and duration of BPSD placebo response across multiple randomized clinical trials of AD and non-AD dementia. We will further identify replicable study- and individual-level predictors of BPSD placebo response.

Study Design: We will perform both individual-level analyses and study-level meta-analyses to identify predictors of BPSD severity change in the placebo arm of clinical trials studying AD and non-AD dementia. The relationship between available individual-level features and BPSD placebo response will be tested using standard regression frameworks, multivariate predictive models, as well as causal inference approaches.

Participants: Participants will be drawn from clinical trials of AD and non-AD dementia that contain an assessment of BPSD symptoms (e.g. NPI, CMAI, BEHAVE-AD).

Primary and Secondary Outcome Measure(s): The primary outcome will be placebo response on the Neuropsychiatric Inventory (NPI), NPI subscales, CMAI, and BEHAVE-AD. Secondary outcome measures will include placebo response on the Clinical Global Improvement (CGI) scale.

Statistical Analysis: We will use mixed-effect meta-regression to test the relationship between study-level features and placebo response [5]. Study-level features may include sample size, number of sites, year, mean symptom severity, and mean caregiver burden. For individual-level analyses, we will use multivariate regression, multivariate predictive models (e.g. regularized linear regression, ensemble methods like XGBoost and Random Forests, Hierarchical Bayesian Regression), as well as causal inference approaches (e.g. Double Machine Learning, Doubly Robust Learning, meta-learners, Bayesian causal inference) to assess the relationship between individual-level features and BPSD placebo response. Bayesian hierarchical modeling will be used to jointly model study-level effects and individual-level feature's effect on BPSD placebo response. Finally, we will investigate the longitudinal timing, onset, and duration of the placebo response using linear mixed models and generalized models for location, scale, and shape (GAMLSS), a robust statistical framework for modeling longitudinal trajectories [6].

Brief Project Background and Statement of Project Significance:

AD is a common and devastating neurodegenerative disorder that primarily affects cognition and memory with accompanying neuropsychiatric symptoms that include psychosis, depression, irritability, and aggression [7]. Referred to as behavioral and psychiatric symptoms of dementia (BPSD), such symptoms are associated with worse patient outcomes, including rapid disease progression, earlier admission to permanent care facilities, and increased caregiver burden [8,9]. Current treatment approaches for psychiatric symptoms in AD include

antipsychotics, antidepressants, benzodiazepines, and anticonvulsants [10]. However, these medications have both limited efficacy and significant adverse effects, including sedation, extrapyramidal symptoms, cardiovascular risks, and increased mortality [10].

Given the limitations of current treatment options for psychiatric symptoms in AD, there is an urgent need to characterize patient responses to pharmacological and non-pharmacological interventions. The development of novel pharmacological treatments has been particularly hindered by a limited understanding of patient characteristics linked with placebo response, which can complicate the interpretation of clinical trial results. Multiple studies have reported significant BPSD symptom improvement in the placebo arms of randomized clinical trials [4], motivating the adoption of trial designs that mitigate placebo response. This research project aims to advance our understanding of BPSD placebo response in AD clinical trials.

Specific Aims of the Project:

This project aims to quantify the duration, onset, and course of BPSD placebo response in existing randomized clinical trials of AD and non-AD dementia. We will further identify individual-level causal factors underlying exaggerated placebo response.

What is your Study Design?:

Other

What is the purpose of the analysis being proposed? Please select all that apply.

New research question to examine treatment effectiveness on secondary endpoints and/or within subgroup populations

Participant-level data meta-analysis

Summary-level data meta-analysis using only data from YODA Project

Develop or refine statistical methods

Research on clinical trial methods

Research on comparison group

Research Methods

Data Source and Inclusion/Exclusion Criteria to be used to define the patient sample for your study:

We will analyze clinical trials of AD and non-AD dementia that include a placebo arm and measure of BPSD. Requested trials must include RIS-INT-83, RIS-USA-232, GAL-USA-10, GAL-MVD-302, GAL-INT-10, GAL-INT-2, GAL-INT-6, GAL-CHN-T100, GAL-ALZ-302, RIS-INT-24, RIS-USA-63, RIS-AUS-5, RIS-BEL-14.

Primary and Secondary Outcome Measure(s) and how they will be categorized/defined for your study:

Primary outcome measures will be placebo response on the NPI, CMAI, and/or BEHAVE-AD scales (and their item-level subscales). Secondary outcomes include placebo response on the CGI.

Main Predictor/Independent Variable and how it will be categorized/defined for your study:

The main predictors to be analyzed will include patient demographic and clinical characteristics.

Demographics will include:

- Age
- Sex
- Race/ethnicity
- Country
- Study site.

Clinical characteristics include:

- At-home vs care facility
- Caregiver type (e.g. relative vs nurse)
- Baseline BPSD severity (e.g. NPI, CMAI, and/or BEHAVE-AD)
- Time since dementia/BPSD onset
- Dementia type (e.g. amnestic vs non-amnestic)
- Cognitive impairment (e.g. MMSE)
- Dementia severity and domain (e.g. ADAS)
- Psychiatric history
- Patient capacity (e.g. ADL)
- Baseline CGI
- Vital signs
- Neurological history (e.g. stroke)

Meta-analytic analyses will include study level characteristics such as:

- Study year
- Trial length
- Number of study sites
- Size of placebo arm
- Trial design (two vs multi-arm)
- Percent male/female
- Percent patients in care facility
- Mean age
- Enrollment criteria
- Mean BPSD severity
- Mean caregiver burden

The independent variables examined may change slightly after closer inspection of raw measurement data available in the requested YODA clinical trials.

Statistical Analysis Plan:

We will use mixed-effect meta-regression to test the relationship between study-level features and placebo response⁵. Study-level features may include sample size, number of sites, year, mean symptom severity, and mean caregiver burden. For individual-level analyses, we will use multivariate regression, multivariate predictive models (e.g. regularized linear regression, ensemble methods like XGBoost and Random Forests, Hierarchical Bayesian Regression), as well as causal inference approaches (e.g. Double Machine Learning, Doubly Robust Learning, meta-learners, Bayesian causal inference) to assess the relationship between individual-level features and BPSD placebo response. Bayesian hierarchical modeling will be used to jointly model study-level effects and individual-level feature's effect on BPSD placebo response. Finally, we will investigate the longitudinal timing, onset, and duration of the placebo response using linear mixed models and generalized models for location, scale, and shape (GAMLSS), a robust statistical framework for modeling longitudinal trajectories⁶.

We will employ both meta-analytic and individual trial analyses in this project. We will focus analyses on patients with clinically significant BPSD symptoms. Meta-analytic techniques will identify study-level characteristics (e.g. mean age, site size, enrollment criteria) associated with increased placebo response. For example, prior studies noted an increase in BPSD placebo response over time, so we will control for study year in our analyses [3]. Individual trial analyses will identify patient-level baseline characteristics (e.g. overall severity, caretaker burden) associated with increased BPSD improvement in the placebo arm. Parallel regression analyses will employ proper corrections for multiple comparisons when determining statistical significance and we will assess study-level characteristics that may bias results, such as patient drop out. Multivariate predictive models will be trained in a cross-validation framework and care will be taken to avoid data leakage between training and test data. When possible, a leave-one-study-out framework will be used to provide the strongest test of model generalization.

Across analyses, we will focus on clinical and demographic features that are present across multiple clinical trials to allow for replication of results.

Software Used:

Python

Project Timeline:

Anticipated Project Start Date: Sept 1 2023

Meta Analyses Completion Date: December 2023

Individual Analyses Completion Date: June 2024

Manuscript Drafted: July 2024

Manuscript Submitted and Results Reported back to YODA: August 2024

Dissemination Plan:

This work will be submitted for publication in a peer-reviewed academic journal if our analyses yield results that merit publication.

Bibliography:

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