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General Information

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Requires Data Access? Yes

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Requires Data Access? Yes

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?: Data Holder (Company)

Conflict of Interest

https://yoda.yale.edu/wp-content/uploads/2024/09/SV_57KskaKADT3U9Aq-R_8C7372ql0ku3jF0.pdf
https://yoda.yale.edu/wp-content/uploads/2024/09/COI_Wassner.pdf
https://yoda.yale.edu/wp-content/uploads/2024/09/YODA_COI_SG.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. - 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
2. 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.
3. 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
4. NCT00679627 - GALALZ3005 - A Randomized, Double-Blind, Placebo-controlled Trial of Long-term (2-year) Treatment of Galantamine in Mild to Moderately-Severe Alzheimer's Disease
5. NCT00253214 - GAL-INT-10 - Placebo-Controlled Evaluation of Galantamine in the Treatment of Alzheimer's Disease: Safety and Efficacy of a Controlled-Release Formulation
6. - GAL-93-01 - A group comparative, placebo-controlled, double-blind trial of the efficacy and safety of galantamine hydrobromide, 7.5 mg (6 mg galantamine base) TID, 10 mg (8 mg galantamine base) TID and 15 mg (12 mg galantamine base) TID taken orally for 12 weeks in patients with a diagnosis of senile dementia of the Alzheimer's type
7. NCT00253227 - GAL-INT-2 - Galantamine in the Treatment of Alzheimer's Disease: Flexible Dose Range Trial
8. NCT00253188 - GAL-INT-1 - Efficacy, Tolerability and Safety of Galantamine in the Treatment of Alzheimer's Disease
9. NCT00253201 - GAL-USA-1 - Efficacy, Tolerability and Safety of Galantamine in the Treatment of Alzheimer's Disease
10. NCT00304629 - GAL-USA-3 - Long Term Safety and Efficacy of Galantamine in Alzheimer's Disease (Extension INT-8)
11. - GAL-INT-3 - Long Term Safety and Efficacy of Galantamine in the treatment of Alzheimer's Disease
12. - GAL-INT-7 - Long Term Safety and Efficacy of Galantamine in the treatment of Alzheimer's Disease

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

Research Proposal

Project Title

Sex differences in the efficacy and adverse events of anti-dementia medication in Alzheimer's disease: a systematic review

Narrative Summary:

Dementia affects 55 million people worldwide, with most cases caused by Alzheimer's disease (AD). In AD, proteins accumulate in the brain, leading to memory loss, cognitive decline, and ultimately death. Women compromise two thirds of AD patients. Cognitive decline seems to be faster in women, and their brain atrophy rate is 1-1.5% higher.
Cholinesterase inhibitors, which slow AD progression by increasing Acetylcholine levels in the brain, may work differently in men and women. Potential sex differences in efficacy and differing rates of adverse events have not previously been examined systematically for cholinesterase inihibitors. This project aims to systematically review potential sex differences in treatment efficacy and adverse events, potentially leadindg to a more tailored, sex-specific treatment for AD patients.

Scientific Abstract:

Background: Dementia due to Alzheimer's disease (AD) affects women more than men not only epidemiologically but also in terms of disease progression (Ferretti et al., 2018). Some evidence suggest that AChE-inhibitors, which can be used to slow down cognitive decline, may affect women and men differently (Farlow et al., 1998; Giacobini & Pepeu, 2018).
Objective: The consolidation of available data on whether there are notable variations between sexes in the effectiveness or adverse events of antidementia drugs may lead to more tailored and

sex-specific treatment for AD patients.
Study design: We will perform a systematic literature review of high-quality studies (such as clinical trials) investigating the effectiveness of AChE-inhibitors. We will focus on studies that report treatment outcome based on sex. Should there be enough studies to perform a meta-analysis (i.e., minimum of 3 studies according to Cochrane), we will do a meta-analysis.
Participants: Patients diagnosed with AD according to the National Institute of Neurological and Communicative Disorders and Stroke −Alzheimer's Disease and Related Disorders Association criteria or to the DSM-IV criteria.
Primary outcome measures: The primary outcome measure, that will be analyzed, is change from baseline in cognition, tested using the ADAS-Cog or MMSE. Secondary outcome measure includes rates of adverse events.
Statistical analysis: For a meta-analysis, we will follow the PRISMA guidelines and perform a random effects meta-analysis of sex differences in cognitive outcome measures and in rates of adverse events.

Brief Project Background and Statement of Project Significance:

Dementia is a global public health challenge, with millions of individuals affected worldwide. Despite the widespread use of anti-dementia medications, there is growing evidence suggesting that their efficacy may differ between sexes (Nebel et al, 2018). Understanding these differences is crucial, as it could lead to more personalized and effective treatment strategies for both men and women. Previous research has indicated that biological, hormonal, and pharmacokinetic factors may contribute to these disparities, yet comprehensive studies examining these differences in the context of anti-dementia drugs remain limited.

The significance of this project lies in its potential to uncover critical sex-specific variations in the response to anti-dementia medications, which could materially enhance our understanding of how these treatments work in different populations. By identifying whether and how the efficacy of these medications varies between sexes, this research could lead to improved, sex-specific treatment guidelines and inform future drug development. The findings from this study will contribute to the broader scientific and medical knowledge base, with the potential to influence public health strategies aimed at more effectively managing dementia.

This project builds on prior work that has explored sex differences in disease progression and treatment response (Canevelli et al, 2017), but it uniquely focuses on the context of dementia. By advancing our understanding of these differences, the research could have a significant impact on clinical practice and public health policy.

Specific Aims of the Project:

The primary objective of this project is to investigate sex differences in the efficacy of anti-dementia medications, with the aim of determining whether these medications exhibit varying levels of effectiveness between male and female patients. Additionally, we will explore potential sex differences in incidence and severity of adverse events due to cholinesterase inihibtor treatment. We will explore the hypothesis that anti-dementia medications may be more effective in one sex compared to the other, potentially due to biological, hormonal, or pharmacokinetic differences. We consider the direction of difference in treatment effect as exploratory.
Regarding the adverse event analysis, we hypothesize that (severe) adverse events may appear more frequently in one sex than the other.

We will utilize a combination of clinical data analysis and sex-stratified statistical modeling to evaluate and identify any significant differences in treatment outcomes and adverse events.

Study Design:

Meta-analysis (analysis of multiple trials together)

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

Summary-level data meta-analysis

Meta-analysis using only data from the YODA Project

Research Methods

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

Inclusion criteria:
- Patients with dementia due to Alzheimer's disease diagnosed according to the National Institute of Neurological and Communicative Disorders and Stroke −Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria [19] or to the Diagnostic and Statistical Manual of mental disorders − fourth edition (DSM-IV) criteria.
-Randomized placebo-controlled trials of cholinesterase inhibitors (Donepezil, Rivastigmine, Galantamine) or Memantine
- Studies reporting cognitive outcome data (for example MMSE, ADAS-Cog, ADCS-ADL-MCI, SIB or other cognitive outcome measures)

Exclusion criteria:
- Studies published before 2017, as these trials were already systematically screened in the prior review by Canevelli et al. (2017)7.
- Non-placebo-controlled trials (e.g., active comparators) and trials evaluating combination therapies (e.g., ChEIs with any other intervention).
For the Meta-Analysis no other studies will be included in the statistical analysis.

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

Primary Outcome measures:
Change from baseline in
- Alzheimer's Disease Assessment Score - Cognitive Subscale 11 Item (ADAS-Cog 11)
- MMSE
These primary Endpoints will be analyzed by the baseline subgroups female/male.

Secondary outcome measures:
- Incidence of adverse drug reactions possibly, probably or likely associated to the intake of cholinesterase inhibitors
- Incidence of severe adverse drug reactions possibly, probably or likely associated to the intake of cholinesterase inhibitors
- Severity of adverse drug reactions

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

Independent variable: treatment with galantamine.

Other Variables of Interest that will be used in your analysis and how they will be categorized/defined for your study:

sex (female, male)

Statistical Analysis Plan:

We will perform a systematic search of the literature and identify high-quality studies (such as clinical trials) in which patients with Alzheimer's disease receive antidementia medication. We will focus on studies that report treatment outcome based on sex. We aim to provide a clearer understanding of which individuals gain the most from pharmacological treatment.
We chose studies that reported efficacy of AChE-inhibitors in Alzheimer's disease patients after June 2017 (because there has been a systematic review that analysed studies up to this point).
We will first perform a systematic review following PRISMA guidelines.

Should there be enough studies to perform a meta-analysis (i.e., minimum of 3 studies according to Cochrane), we will do a meta-analysis. To examine sex differences in efficacy we will perform a two-stage random effects meta-analysis according to the PRISMA guidelines. The outcome variable will be the standardized change from baseline score of the primary cognitive outcome, calculated separately within each study by dividing the change score by the pooled baseline standard deviation. This approach allows us to account for differences in outcome scales across studies.
We will estimate the treatment x sex interaction using a two-stage approach. First we will fit a mixed model of repeated measures (MMRM) to each study individually including treatment, sex, time, and their interactions, adjusting for age and baseline cognitive score. For each study, we will extract the fixed effect estimate of the treatment x sex interaction on the standardized change-from-baseline outcome, along with the respective standard error. Then, we will synthesize these study specific effects into a random-effects meta-analysis using the REML estimator, treating each study's interaction coefficient as one observation and weighting by the inverse of its within-study variance. We will assess between-study heterogeneity using tau2 and I2 statistic. We will perform a sensitivity analysis by handling missing data of the outcome at endpoint through multiple imputations using chained equations (mice package in R). We will perform Egger's regression to control for publication bias.

To examine sex differences in adverse events, we will perform descriptive statistics for the incidence of adverse events and severe adverse events by sex. We will use the Chi-Square test to assess whether there are significant differences in the overall incidence of adverse events and the incidence of severe adverse events between female and male patients. If sex differences are evident in the descriptive analyses, we will use logistic regression to assess the association between sex and the occurrence of adverse events, while adjusting for potential confounders such as age, baseline cognition, and dosage of galantamine.

For all analyses we will consider p-values < 0.05 as significant.

We will use R with Rstudio (version 4.2.1) (R Core Team, 2022) and the packages metafor and meta.

Software Used:

RStudio

Project Timeline:

Start date - January 2024
Analysis completion date - March 2026
Manuscript draft - June 2026
Submitted for publication - August 2026

Dissemination Plan:

A manuscript of this project will be submitted to peer-reviewed journals such Alzheimer's and Dementia, Alzheimer's Research and Therapy and International Journal of Alzheimer's Disease
We plan to present the findings of this project at national conferences such as the Nationale Demenz Konferenz.

Bibliography:

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