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General Information

Key Personnel (other than PI):
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SCOPUS ID:
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

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

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

Research Proposal

Project Title

Gender differences in the efficacy 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 are more affected, comprising 60% of patients. Further, cognitive decline is twice as fast in women, and their brain atrophy rate is 1-1.5% higher.
AChE-inhibitors, which slow AD progression by increasing Acetylcholine levels in the brain, may work differently in men and women. This project aims to systematically review these potential sex differences in treatment efficacy, 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 nnot 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 of antidementia drugs may lead to more tailored and sex-specific treatment approaches for patients with AD.
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 measure(s); The primary outcome measure, that will be analyzed, is change from baseline in cognition, tested using the ADAS-Cog 11 or MMSE. No secondary endpoints will be evaluated.
Statistical analysis: We will first perform a systematic review following PRISMA guidelines. For a meta-analysis, we will follow the PRISMA guidelines and then perform a random effects meta-analysis with three levels.

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. The study 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. To achieve this, the project will utilize a combination of clinical data analysis and sex-stratified statistical modeling to evaluate and identify any significant differences in treatment outcomes.

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.
Exclusion criteria:
None

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 Endpoints:
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.

No secondary Endpoints.

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 stand to 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, hence, no statistical analysis will be done.

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. This will allow us to examine whether AChE-inhibitors are differently effective in men an women.
For a meta-analysis, we will follow the PRISMA guidelines and then perform a random effects meta-analysis with three levels. We will de-compose heterogeneity to account for within- and between-study heterogeneity. In addition, we will use Q-statistic to evaluate whether heterogeneity is evident or not and I-square statistic to quantify heterogeneity. If heterogeneity is present (i.e., τ2> 0, regardless of the results of the Q-test), we will provide prediction intervals for the true outcome. To control for publication bias, we will use Egger regression. To control for p-hacking, we will use p-curve analysis. We will examine heterogeneity of effect sizes (between and within studies) and will evaluate the 95% confidence interval. Missing data will be excluded.
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 - June 2025
Manuscript draft - August 2025
Submitted for publication - Ocotber 2025

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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