

Principal Investigator

First Name: Iris
Last Name: Sommer
Degree: MD. PhD.
Primary Affiliation: University Medical Center Groningen
E-mail: e.d.angremont@rug.nl
Phone number:
Address:

City: Groningen
State or Province: Groningen
Zip or Postal Code: 9713GZ
Country: Netherlands
SCOPUS ID: 56140431800

General Information

Key Personnel (in addition to PI):

First Name: Iris
Last name: Sommer
Degree: MD, PhD
Primary Affiliation: UMCG
SCOPUS ID: 56140431800

First Name: Teus
Last name: Van Laar
Degree: MD, PhD
Primary Affiliation: UMCG
SCOPUS ID: 7003630275

First Name: Emile
Last name: d'Angremont
Degree: MSc
Primary Affiliation: UMCG
SCOPUS ID:

Are external grants or funds being used to support this research?: External grants or funds are being used to support this research.

Project Funding Source: ZonMw project number 636310010

How did you learn about the YODA Project?: Data Holder (Company)

Conflict of Interest

https://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_2019_eda_updated.pdf
https://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_2019_ies_updated.pdf
https://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_2019_tvI_updated.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. [NCT00253214 - GAL-INT-10 - Placebo-Controlled Evaluation of Galantamine in the Treatment of Alzheimer's Disease: Safety and Efficacy of a Controlled-Release Formulation](#)
3. [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

Meta-analysis of efficacy of cholinesterase inhibitors on individual neuropsychiatric symptoms in AD, PD and DLB

Narrative Summary:

Cognitive deficits, such as problems with memory, planning and reasoning, and neuropsychiatric disturbances, such as depression and anxiety, are both important features of these diseases. Cholinesterase inhibitors (ChEIs), such as donepezil and rivastigmine, form a type of drug that has a well established effect on the cognitive deficits. However, the beneficial effect on neuropsychiatric disturbances is much less clear [2,3]. A possible explanation for the inconsistent results of ChEIs on neuropsychiatric disturbances is that the definition of 'neuropsychiatric' is too broad, as it includes symptoms such as hallucinations and delusions, but also depression, anxiety and irritability.

Scientific Abstract:

Background: Recent meta-analyses have confirmed the efficacy of cholinesterase inhibitors (ChEIs) on cognitive function in Alzheimer's disease (AD) and Lewy body disorders (LBD) [1,2]. The results of these meta-analyses also suggest a beneficial effect on behavioral disturbances, but this effect is much less pronounced. A possible explanation for the inconsistent results of ChEIs on behavioral disturbances is the multidimensionality of the behavioral domain, which includes hallucinations, depression and aberrant motor behavior, among others. It remains unclear which subdomains respond well to ChEI treatment and which do not.

Objective: To assess which behavioral subdomains are positively affected by ChEI treatment in Alzheimer's disease, Parkinson's disease and dementia with Lewy bodies.

Study design: Systematic review and meta-analysis.

Participants: Randomized, placebo-controlled trials assessing efficacy of rivastigmine, donepezil or galantamine in Alzheimer's disease, Parkinson's disease or dementia with Lewy bodies with a neuropsychiatric or behavioral outcome measure.

Main Outcome Measure: Individual items of outcome measures assessing behavioral or neuropsychiatric symptoms.

Statistical Analysis: We will use Hedges's g to quantify effect sizes (ES) for the mean difference between change scores (end of treatment minus baseline) of the active treatment group vs. placebo group. We will apply a random effects model to calculate a mean weighted ES for each individual neuropsychiatric subdomain. Also, meta-regression will be performed with several covariates.

Brief Project Background and Statement of Project Significance:

Recent meta-analyses have confirmed the efficacy of cholinesterase inhibitors (ChEIs) on cognitive function in Alzheimer's disease and Lewy body disorders [2,3]. The results of these meta-analyses also suggest a beneficial effect on neuropsychiatric disturbances, but this effect is much less pronounced. A possible explanation for the inconsistent results of ChEIs on neuropsychiatric disturbances is the multidimensionality of this domain, which

includes hallucinations, depression and aberrant motor behavior, among others. Several case series or open-label trials have reported marked improvement of specific neuropsychiatric subdomains, such as delusions and hallucinations [4-8]. Very few RCTs perform a secondary analysis on the individual neuropsychiatric inventory (NPI) items and they are usually not powered for this analysis. Thus, it remains unclear which subdomains respond well to ChEI treatment and which do not.

We include randomized, placebo-controlled trials assessing efficacy of rivastigmine, donepezil or galantamine in AD, PD or DLB with a neuropsychiatric outcome measure. We will include all patients in the ChEI and placebo treatment arm to calculate the between group differences of mean changes after treatment, based on an intention-to-treat analysis. We will impute missing values using last observation carried forward (LOCF).

It can be expected that there are some differences in response between the different diseases. However, especially for PD and DLB, a limited number of RCTs have been performed. In our analysis, we will look both at the response in each disease separately and with the diseases pooled together. If the Q-value or I²-statistic shows a large heterogeneity, we will perform a sensitivity analysis with treatment duration as one of the confounding factors. We will divide the studies into two groups based on the median treatment duration of all studies, similar to the meta-analysis of Matsunaga et al. [3].

A meta-analysis of the requested data, together with data obtained elsewhere, enables us to draw conclusions on the subdomains of neuropsychiatric outcome measures, including hallucinations and delusions.

Specific Aims of the Project:

We want to conduct a meta-analysis on the efficacy of ChEIs on all individual items of neuropsychiatric/behavioral outcome measures. We hypothesize that ChEIs are effective for a specific subset of the behavioral domain, specifically hallucinations and delusions, and less to others, such as sleep and appetite.

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

Participant-level data meta-analysis pooling data from YODA Project with other additional data sources

Research Methods

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

Randomized, placebo-controlled trials assessing efficacy of rivastigmine, donepezil or galantamine in Alzheimer's disease, Parkinson's disease or dementia with Lewy bodies with a neuropsychiatric or behavioral outcome measure.

Other data sources:

- Vivli (M10-984 (AbbVie) and NCT00630851 (Pfizer))

- ClinicalStudyDataRequest (GSK-AVA105640, NOVARTIS-CENA713D1301, NOVARTIS-CENA713B2311, EISAI-E2020-J081-231, EISAI-E2020-A001-315 and EISAI-E2020-A001-311)

- Individual authors (NCT00211588 and NCT01519271)

Main Outcome Measure and how it will be categorized/defined for your study:

The main outcomes measures are the differences between mean changes (+SD) for all subdomains of behavioral outcome measures. For the most commonly used measure, the neuropsychiatric inventory (NPI), these are: delusions, hallucinations, agitation, depression, anxiety, elation, apathy, disinhibition, irritability, aberrant motor behavior, sleep and apatite. Assuming that these outcomes are not included in the CRF's, we require the full datasets.

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

Treatment with donepezil, galantamine or rivastigmine, in any form, versus treatment with placebo

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

We will also look at/correct for:

- baseline behavioral scores (mean NPI + SD)
- baseline cognition scores (mean MMSE (Mini-mental state examination) + SD)
- age (mean + SD)
- sex (% male)
- diagnosis (Alzheimer's disease, Parkinson's disease, dementia with Lewy bodies)
- type of ChEI (rivastigmine, donepezil, galantamine)
- treatment duration
- time since diagnosis

If any of these variables are not presented in the data, the study will be excluded from the specific subanalysis

Statistical Analysis Plan:

The criteria used for selecting a study were: randomized, double-blind, placebo-controlled trials assessing efficacy of rivastigmine, donepezil or galantamine in AD, PD or DLB with a neuropsychiatric outcome measure.

Effect sizes are computed using Comprehensive Meta-Analysis Version (CMA) 2.0, Biostat (Borenstein, M., Hedges, L. V., Higgins, J. P. T. & Rothstein, H. R. Introduction to Meta-Analysis. Wiley, Chichester, 2009), or R if it is not achieved to run CMA on the research environment. For every individual study, Hedges' g will be calculated for each neuropsychiatric subdomain. To obtain this effect size, the mean difference between change scores (end of treatment minus baseline and SD) of the active treatment group vs. placebo group is used for each individual neuropsychiatric subdomain, or pre- and post-means (+ SDs) per treatment arm. To avoid overestimation of the true effect sizes caused by the pre-post treatment correlation, change scores are preferred. When these values are not reported, we use exact F-, t-, or p-values. All effect sizes are calculated twice independently from the original articles to check for errors. Studies will be combined to calculate a mean weighted ES (Hedges' g) for the effect on individual neuropsychiatric subdomains, using a random effects model. Studies with multiple treatment groups (e.g. different treatment doses) and one placebo group were entered as individual study samples. ES of $p < 0.05$ (two-tailed) will be considered statistically significant, 0.2 reflecting a small, 0.5 a medium, and ≥ 0.8 a large effect (Cohen, J. (1988). Statistical Power Analysis for the Behavioural Science (2nd Edition). USA: Statistical Power Analysis for the Behavioral Sciences).

To investigate whether studies can be combined to share a common population effect size, the Q-value and I²-statistic will be evaluated for each analysis. The Q-statistic tests the existence of heterogeneity and displays a chi-square distribution with $k - 1$ degrees of freedom ($k =$ number of study samples). Q-values higher than the degrees of freedom (df) indicate significant between-studies variability. I² indicates the proportion of the observed variance in true effect sizes rather than sampling error, ranging from 0 to 100%. I²-values of 25, 50, and 75% will be considered as low, moderate, and high heterogeneity, respectively (Higgins, J. P., Thompson, S. G., Deeks, J. J., & Altman, D. G. (2003). Measuring inconsistency in meta-analyses testing for heterogeneity. *BMJ (Clinical Research Ed.)*, 327(7414), 557–560. <https://doi.org/10.1136/bmj.327.7414.557>). For significant results, potential publication bias will be investigated by means of a visual inspection of the funnel plot and Egger's test ($p < 0.1$, two-tailed).

Further investigating potential heterogeneity between studies, moderator analyses will be performed to evaluate whether study characteristics covary with intervention effectiveness; including baseline NPI and baseline MMSE, time since diagnosis (years), treatment duration (weeks) and age (years) and gender distribution (% male) of the included study samples. Additionally, subgroup analysis will be performed to evaluate whether the effect on favorable outcome differs between the different types of ChEIs (rivastigmine, donepezil and galantamine) or the different diagnoses (Alzheimer's disease, Parkinson's disease, dementia with Lewy bodies). P-values < 0.05 will be considered significant.

Software Used:

I am not analyzing participant-level data / I will not be using these software for analyses in the secure platform

Project Timeline:

September 1, 2020: Data collection completed.

November 1, 2020: Statistical analysis completed.

December 1, 2020: Manuscript draft completed.

December 31, 2020: First submission and results reported back to the YODA Project.

Dissemination Plan:

The anticipated product is a publication of the results in a Q1 peer-reviewed journal, for example Journal of neurology, neurosurgery, and psychiatry or The international journal of neuropsychopharmacology.

Bibliography:

- [1] Li, D. D., Zhang, Y. H., Zhang, W., & Zhao, P. (2019). Meta-analysis of randomized controlled trials on the efficacy and safety of donepezil, galantamine, rivastigmine, and memantine for the treatment of Alzheimer's disease. *Frontiers in Neuroscience*, 13(MAY). <https://doi.org/10.3389/fnins.2019.00472>
- [2] Matsunaga, S., Kishi, T., Yasue, I., & Iwata, N. (2016). Cholinesterase inhibitors for Lewy body disorders: A meta-analysis. *International Journal of Neuropsychopharmacology*, 19(2), 1–15. <https://doi.org/10.1093/ijnp/pyv086>
- [3] Goldman, J. G., & Holden, S. (2014). Treatment of psychosis and dementia in parkinson's disease topical collection on movement disorders. *Current Treatment Options in Neurology*, 16(3). <https://doi.org/10.1007/s11940-013-0281-2>
- [4] Thomas, A. J., Burn, D. J., Rowan, E. N., Littlewood, E., Newby, J., Cousins, D., ... McKeith, I. G. (2005). A comparison of the efficacy of donepezil in parkinson's disease with dementia and dementia with lewy bodies. *International Journal of Geriatric Psychiatry*, 20(10), 938–944. <https://doi.org/10.1002/gps.1381>

Supplementary Material:

https://yoda.yale.edu/sites/default/files/supplemental_narrative_summary_21-01-08.pdf