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

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_edu_0.pdf
https://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_2019_ies_0.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:

Cholinesterase inhibitors (ChEIs) have a well established effect on cognitive function in Alzheimer’s disease and Lewy body disorders (Parkinson’s disease and dementia with Lewy bodies). There also seems to be a beneficial effect on behavioral disturbances, although 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. We want to conduct a meta-analysis on the efficacy of ChEIs on all individual items of behavioral outcome measures, to assess which subdomains benefit from treatment.

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 [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. Several case series or open-label trials have reported marked improvement of specific behavioral subdomains, such as delusions and hallucinations [3,4]. Very few RCTs perform a secondary analysis on the individual neuropsychiatric inventory (NPI) items and none are not powered for this analysis. Thus, it remains unclear which subdomains respond well to ChEI treatment and which do not.

**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))
- Individual authors (NCT00211588 and NCT01519271)

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

The main outcome 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 apetite. 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

**Statistical Analysis Plan:**

Per study, 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 for each individual neuropsychiatric subdomain. Hereafter, 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 the other variables mentioned above as covariates.

Software Used:

R

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: