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## General Information

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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?:** Data Holder (Company)

## Conflict of Interest

https://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_2019_jb.pdf
https://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_2019_sr.pdf
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## 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. 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
2. NCT00253123 - RIS-USA-63/CR006022 - A Randomized, Double-Blind, Placebo-Controlled Study of Risperidone for Treatment of Behavioral Disturbances in Subjects With Dementia

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

## Research Proposal

## Project Title

A predictive model to guide safer risperidone prescribing in people with Alzheimer's disease

**Narrative Summary:**

Antipsychotic drug use is controversial in people with dementia due to concerns regarding side effects and an increased risk of death. Guidelines advocate 'use the lowest possible dose' but offer no information on optimal dosing for individual drugs. This analysis aims to identify factors that may predict differing risperidone side effect profiles in older people with dementia, using data from two clinical trials in which risperidone was evaluated as a treatment for delusions and/ or agitation. This information will be used to predict the required dose adjustments for risperidone to minimise emergent side effects in people with dementia, to guide safer prescribing in this frail population

**Scientific Abstract:**

Background: Antipsychotic drug treatment of psychosis in Alzheimer's disease is restricted by safety concerns. Guidelines advocate use of the 'lowest possible dose' but offer no information on optimal dosing for individual drugs.
Objective: To investigate sources of variability in the pharmacokinetic profiles of risperidone and 9-hydroxy (OH)-risperidone, and how this relates to clinical outcome (treatment response, extrapyramidal side effects) to guide safer prescribing
Study Design: Pharmacokinetic and clinical outcome data will be extracted from NCT00253123 (626 participants) and NCT00249145 (349 participants).
Participants: Diagnosed Alzheimer's disease, vascular dementia or a combination of the two, clinically significant delusions, hallucinations, or agitation.
Main Outcome Measure(s): Extrapyramidal side effects (EPS), indexed by Extrapyramidal Symptom Rating Scale (ESRS); BEHAVE-AD (Paranoid and Delusions Ideation, Hallucinations, Aggressiveness and Global scores); QTc interval; AE data.

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Statistical Analysis. A mixed effects-based approach will be used to describe the concentration-time profiles of risperidone and 9-OH-risperidone. Model based outputs will be used to estimate peak, trough and average concentrations of risperidone, 9-OH-risperidone and 'active moiety' (combined concentrations). The associations of pharmacokinetic biomarkers with emergent EPS and responder status (delusions, hallucinations) will be investigated using logistic regression. Model based simulation will be used to optimise dose predictions, based on covariates of interest.

**Brief Project Background and Statement of Project Significance:**

Antipsychotic drug use is controversial in people with Alzheimer's disease (AD) due to concerns regarding side effects (sedation, falls, extrapyramidal side effects, stroke) and increased mortality (1, 2). Guidelines emphasise the need to treat with the 'lowest possible dose' but offer no formal guidance on the optimal dose range for individual drugs. Meta-analyses of placebo-controlled trials of risperidone (3) suggest that 1mg/day may optimally balance the risks and benefits specifically in the treatment of psychosis in AD (2). However this 'average' does not account for factors that predict differing sensitivities to response and side effects.
Risperidone is metabolized by cytochrome P450 2D6 (CYP2D6) to the active metabolite 9-hydroxy (OH)-risperidone, which is renally excreted (4). There is wide variability in the relationship between risperidone dose and active moiety concentrations (combined concentrations of parent and metabolite) due to genetic variation in CYP2D6 genotype, use of CYP2D6 inhibitors or inducers, and the effects of age on phase 1 metabolism and renal clearance (5). Consensus guidelines, based on therapeutic drug monitoring (4), pharmacokinetic modelling, (6) and striatal dopamine D2/3 receptor occupancy data (7) in risperidone treated patients with schizophrenia, recommend active moiety concentrations of 20–40 ng/mL (3-6mg/day) (6) as higher concentrations increase the risk of extrapyramidal side-effects (EPS). Recent guidance on personalised risperidone prescribing advocates dose reductions for those with slower active moiety clearance, indexed by concentration-to-dose ratios over 14 ng/mL per mg/day (8).
We have previously used a mixed effects based approach to investigate sources of variability in the pharmacokinetic profiles of risperidone and 9-hydroxy-(OH)-risperidone, and their association with clinical outcome, using data from 108 participants in the Clinical Trials of Intervention Effectiveness in Alzheimer's disease (CATIE-AD) study (9). We found an age-related reduction in risperidone clearance and estimated that 24 (22%) patients cleared the active moiety more slowly (concentration-to-dose ratio 20.2±7.2 versus 7.6±4.9 ng/mL per mg/day). Trough 9-OH-risperidone concentrations, and lower MMSE (greater dementia severity) were associated with EPS. Model based predictions suggested that the optimum dose would range from 1mg/day (75 years, MMSE 15) to 0.25mg/day (85 years, MMSE 5), with alternate day dosing required for those with slower drug clearance (manuscript under review by JNNP).
The aim of the proposed project is to refine dose predictions for risperidone use in older people with Alzheimer's disease, using existing data from two placebo-controlled trials. The larger dataset (NCT00253123, 626 participants) will be used to develop a predictive model for risperidone use, based on factors that contribute to pharmacokinetic variability and/or are associated with clinical outcome. The model will then be tested in a second dataset NCT00249145 (349 participants). Combined, this information will be used to guide safer risperidone prescribing, based on personal and clinical characteristics.

**Specific Aims of the Project:**

To investigate sources of pharmacokinetic variability for risperidone and its active metabolite, 9-hydroxy (OH)-risperidone, and how this relates to clinical outcome, in order to guide personalised prescribing.
Objective 1:
The concentration-time profiles of risperidone and 9-OH-risperidone will be evaluated using data from risperidone treated participants in NCT00253123 and will test the hypothesis that age will have a significant effect on clearance of both risperidone and active metabolite 9-OH-risperidone. Model based outputs will be used to predict pharmacokinetic biomarkers peak, trough and average concentrations of risperidone, 9-OH risperidone and active moiety.
Objective 2:
Logistic regression will be used to establish the associations of each pharmacokinetic biomarker with EPS and responder status, in NCT00253123 participants, and will test the hypothesis that trough concentrations of 9-OH-risperidone and lower MMSE scores will be associated with emergent EPS.
Objective 3:
Model based outputs from NCT00253123 participants will be used to simulate and predict optimum dose adjustments to avoid emergent extrapyramidal symptoms. The accuracy of predictions will be evaluated using data from NCT00249145 (349 participants).

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**What is the purpose of the analysis being proposed? Please select all that apply.**
Confirm or validate previously conducted research on treatment safety
Participant-level data meta-analysis
Participant-level data meta-analysis using only data from YODA Project
Research on clinical prediction or risk prediction

## Research Methods

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

Data Source:
NCT00253123 (626 participants) and NCT00249145 (349 participants).

Inclusion criteria:
• Patients with dementia of the Alzheimer's type, mixed dementia, or vascular dementia, (as classified by the Diagnostic and Statistical Manual of Mental Diseases, 4th edition [DSM-IV]) and have behavioral disturbances
• a score >=4 on the Functional Assessment staging rating scale (FAST)
• a score <=23 on the MMSE
• a Behavior Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD) total score >=8, and a BEHAVE-AD global rating >=1
• must be institutionalized.

Exclusion Criteria:
• Patients with untreated, reversible causes of dementia
• with general medical or neurological conditions in which cognition is diminished (for example, untreated vitamin deficiency, severe liver or kidney malfunctions, brain tumor, etc.)
• with dementia related to HIV infection (human immunodeficiency virus)
• with a substance-induced persisting dementia
• with psychiatric disorders that could account for the behavior disturbances, such as schizophrenia.

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

• Extrapyramidal side effects (EPS), indexed by scores on the Parkinsonism and akathisia component of the Extrapyramidal Symptom Rating Scale (ESRS)
• BEHAVE-AD (Paranoid and Delusions Ideation, Hallucinations, Aggressiveness and Global scores)
• QTc prolongation (>460 ms for men or >470 ms for women)
• AE data (parkinsonism, sedation, oedema, arrythmia, postural hypotension, falls).

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

Pharmacokinetic biomarkers: Peak, trough and average steady state concentrations of risperidone, 9-OH-risperidone, and active moiety (their summed concentrations).

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

Mini Mental State score at baseline, age at baseline, gender, presence/absence of concomitant medications that may interact in terms of pharmacokinetics (eg cholinesterase inhibitors donepezil and rivastigmine)

**Statistical Analysis Plan:**

The R package rstan for Bayesian pharmacokinetic-pharmacodynamic modelling will be used to implement non-linear mixed effects based modelling of pharmacokinetic data from the specified trials NCT00253123 (626 participants) and NCT00249145 (349 participants), including dose, frequency of administered dose, and plasma concentrations of risperidone and 9-OH-risperidone.
The larger dataset (NCT00253123) will be used to develop a predictive model, and will involve the following stages:
1) Pharmacokinetic model.

Plasma concentration-time profiles of risperidone and 9-OH-risperidone will be described, and will include the following parameters: i) Risperidone clearance (CLRISP), ii) Risperidone volume of distribution (VRISP), iii) Absorption rate constant (ka), iv) 9-OH risperidone volume of distribution (V9-OH-RISP), and v) 9-OH-risperidone clearance (CL9-OH-RISP). Plasma concentration will be converted from ng/mL to mcg/L for use in model building. The model will allow estimation of the probability of there being more than one subpopulation in relation to risperidone clearance, by including a latent covariate. Covariates (height, age, gender, smoking, weight) will be introduced in a stepwise manner. Model based estimates will be used to calculate peak, trough, and average concentrations of risperidone, 9-OH-risperidone and active moiety (their combined concentrations) for each individual. Each pharmacokinetic biomarker will be incorporated into an excel spreadsheet for analysis in R sofware.
2) Pharmacokinetic-Pharmacodynamic model
Each pharmacokinetic biomarker will be individually considered as an independent variable (regressor) in binary logistic regression models that describe the probability of a specified clinical outcome. Our primary outcomes of interest are extrapyramidal side effects and treatment response (delusions, hallucinations and agitation). The models will account for random effects, and adjusted for potential confounders (age, sex, MMSE, height, weight, specific concomitant medications). Best fit models will be used to simulate and predict plasma concentrations and probability of the specified clinical outcome (in R).

The predictive model will then be applied to the smaller dataset (NCT00249145), with the aim of establishing the accuracy of the model to predict emergent EPS.
The second dataset will also be analysed independently, using the methods described above (pharmacokinetic-pharmacodynamic variability).
Combined this information will be used to refine and optimise the predictive model, to guide personalised prescribing.
Software Used:
RStudio

**Project Timeline:**

Anticipated start date:
August 2020: Data accessed, including pharmacokinetic data. This will facilitate a Fellowship application, which will seek the involvement of a full time researcher.
September – November 2020: Application submitted and, pending review and response from the funding body, the researcher will have one day per week to begin the analysis. The initial stage will focus on data relevant to the analysis of pharmacokinetic data
December 2020-March 2021: Extraction and analysis of clinical outcome data in relation to clinical outcome and side effects
April -May 2021: Model based simulations and predictions
June- August 2021: Testing and refining model based predictions in dataset 2

**Dissemination Plan:**

Dissemination Plan
Dissemination of the findings will involve:
• Publication in peer-reviewed, high impact international open-access journals. The research team will work closely with Alzheimer's Society and Alzheimer's Research UK to develop a dissemination plan and maximise publicity associated with journal publications through University and Charity media releases, Twitter feeds and University websites.
• National and international academic conferences, including specialist Alzheimer's disease and dementia meetings and geriatric medicine conferences.
• Talks, training and seminars delivered via existing platforms including 1) Royal College of Psychiatrists: Old Age Faculty, 2) British Association Psychopharmacology: Old Age Module, 3) Regional educational forums
Provide a description of anticipated products and target audience(s), including expectation for study manuscript(s) and potentially suitable journals for submission of the completed research project.

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