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General Information

Key Personnel (other than PI):
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Primary Affiliation: The University of Sydney
SCOPUS ID:
Requires Data Access? Yes

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: Dementia Australia Research Foundation
How did you learn about the YODA Project?: Internet Search

Conflict of Interest

https://yoda.yale.edu/wp-content/uploads/2024/04/Tan_COI.pdf
https://yoda.yale.edu/wp-content/uploads/2024/04/Le_COI.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. NCT00249158 - RIS-AUS-5/CR006010 - Risperidone in the Treatment of Behavioural and Psychological Signs and Symptoms in Dementia (BPSSD): a Multicentre, Double-blind, Placebo-controlled Parallel-group Trial
2. - RIS-BEL-14 - Risperidone in the treatment of behavioural disturbances in patients with Alzheimer's dementia: a double-blind placebo-controlled trial
3. 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
4. NCT00253123 - RIS-USA-63/CR006022 - A Randomized, Double-Blind, Placebo-Controlled Study of Risperidone for Treatment of Behavioral Disturbances in Subjects With Dementia
5. - RIS-USA-70 (EXTENSION OF RIS-USA-63) CR003361, RIS-USA-T216 - An open-label, long-term study of risperidone for the treatment of behavioral disturbances in patients with dementia

6. - RIS-INT-83 - Efficacy and safety of a flexible dose of risperidone versus placebo in the treatment of psychosis of Alzheimer’s disease. A double-blind, placebo-controlled, parallel-group study.
7. NCT00034762 - RIS-USA-232/CR002764 - Efficacy And Safety Of A Flexible Dose Of Risperidone Versus Placebo In The Treatment Of Psychosis 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

Predicting individual risks and benefits of antipsychotic treatment in people living with dementia

Narrative Summary:

There is limited guidance for prescribing antipsychotics in people with dementia. Current guidelines are too broad and general, meaning that patients who would benefit from pharmacotherapy may miss out. There is a need for ways to predict who is likely to benefit from treatment and who is at risk of serious adverse outcomes. This would ensure judicious and rational use of antipsychotics in specific individuals and reduction in patient harm.

Scientific Abstract:

Background: There is limited guidance for prescribing antipsychotics in people with dementia. There is a need for ways to predict who is likely to benefit from treatment and who is at risk of serious adverse outcomes. This would ensure judicious and rational use of antipsychotics in specific individuals and reduction in patient harm.
Objective: To develop and validate a clinical prediction model for antipsychotic use in people with dementia on treatment response, adverse events and mortality.
Study Design: Population-based cohort studies
Participants: Patients with dementia included in the trials listed above
Primary and Secondary Outcome Measures: Clinical response (change in psychosis, agitation, aggression); sedation; extrapyramidal side-effects; cardiovascular; cerebrovascular adverse effects; falls; mortality
Statistical Analysis: Multivariable Cox regression analysis to develop predictive models. The performance of the prognostic models will be evaluated by discrimination and calibration. Models will be internally and externally validated.

Brief Project Background and Statement of Project Significance:

Current guidelines for prescribing antipsychotics are too general and ‘blunt’ and do not take into consideration individual patient characteristics and preferences. Given limited guidance and the potential for serious adverse effects, clinicians may be hesitant to prescribe antipsychotics in people with dementia; thus, people who may benefit miss out on critical therapy. Clinical prediction models can be developed to allow personalised, patient-centered care, providing clinicians and patients with individualised information on response to therapy (Steyerberg 2019). To date, few models have been developed to directly predict individual response to specific treatments in dementia. Previous research has successfully developed and validated clinical prediction models in people with dementia taking xerogenic medications (Tan 2020, Tan 2022). We will build on this expertise to develop models for antipsychotic prescribing. These models can then be used to inform the development of prescribing aids, such as outcome prediction calculators, that can be used by clinicians in routine clinical practice.

Specific Aims of the Project:

To develop and validate a clinical prediction model for antipsychotic use in people with dementia on treatment response, adverse events and mortality

Study Design:

Meta-analysis (analysis of multiple trials together)

What is the purpose of the analysis being proposed? Please select all that apply.

Participant-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:

Data source: Trials listed above.
Inclusion criteria: as stated in trials, i.e. participants with a diagnosis of dementia using antipsychotics (i.e. risperidone)
Exclusion criteria: none

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

Primary outcome measure: time to treatment response (e.g. change in BEHAVE-AD [total score and subscales], CGI severity of symptom scores, etc.)
Secondary outcome measures: time to adverse events (e.g. sedation, extrapyramidal side-effects, arrythmia, postural hypotension, cerebrovascular effects, falls etc.) and mortality

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

The main predictors to be analysed will include patient demographic and clinical characteristics:
- age (continuous in years)
- sex (male/female, binary)
- race/ethnicity (categorical)
- living situation (e.g. home vs residential care, categorical)
- carer type (e.g. relative vs nurse, categorical)
- caregiver burden (score, continuous)
- comorbidities (type of conditions Y/N, binary; number of conditions, continuous)
- concomitant medications (type of medications Y/N, binary; number of medications, continuous)
- dementia type/subtype
- time since dementia onset (months/years, continuous)
- cognitive and other symptoms (e.g. MMSE score, continuous)
- dementia severity (e.g. Clinical Dementia Rating score, categories, mild/moderate/severe)
- functional capacity (e.g. activities of daily living, continuous score)
- vital signs
- risperidone dose (in mg, continuous; low/med/high categories where indicated)
- risperidone duration of use (in days/weeks, continuous)

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

N/A

Statistical Analysis Plan:

Descriptive statistics will be used to describe characteristics of the sample population. The prediction model development will start with univariable assessment of all possible predictors with the predefined outcomes. Multivariable Cox regression analysis will be performed, and the best predictive model will be developed. The performance of the prognostic models will be evaluated by discrimination and calibration. The discriminative performance (i.e. the extent to which the prognostic models enable discrimination between patients with and without outcome) will be described by the concordance (or c) statistic (or area under the receiver operating characteristic curve) and its 95% CI. Internal validation of the model will be determined by a bootstrapping procedure with 200 replications. In each replication, a random sample from the original dataset will be drawn with replacement. We will multiply the regression coefficients by the shrinkage factor derived from the bootstrapping procedures to quantify the amount of optimism and to correct for over-fitting if necessary. Calibration of the prediction models (i.e. the agreement between observed and predicted risks) will be assessed by the Gronnesby and Borgan test and graphically with a calibration plot. The developed prediction model will be externally validated in population-based dementia cohorts in Australia and overseas. Predictive ability of the model will be assessed for discrimination and calibration, and the model will be updated as necessary.

Software Used:

R

Project Timeline:

Start date: Jul 2024
End date: Jul 2025
Milestones:
Data extraction and preparation of database (2 months)
Develop clinical prediction models (4 months)
Model validation (3 months)
Manuscript preparation (3 months)

Dissemination Plan:

Journal publications and scientific presentations. Potentially suitable journals include Journal of Alzheimer’s Disease, Journal of the American Medical Directors Association etc.

Bibliography:

Steyerberg EW. Clinical prediction models: A practical approach to development, validation, and updating 2ed: Springer Cham; 2019
Tan ECK, Lexomboon D, Häbel H, Fastbom J, Eriksdotter M, Johnell K, et al. Xerogenic medications as a predictor for dental health intervention in people with dementia. J Alzheimers Dis. 2020;75:1263-71.
Tan ECK, Lexomboon D, Häbel H, Fastbom J, Eriksdotter M, Johnell K, et al. Validating a model for medication-related dental outcomes in older people. Oral Dis. 2022;28:1697-704.