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General Information

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?: Internet Search

Conflict of Interest

https://yoda.yale.edu/wp-content/uploads/2024/11/SV_57KskaKADT3U9Aq-R_7Gwd32m4I8X9HDb.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. NCT00253123 - RIS-USA-63/CR006022 - A Randomized, Double-Blind, Placebo-Controlled Study of Risperidone for Treatment of Behavioral Disturbances in Subjects With Dementia
2. - 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
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. - RIS-BEL-14 - Risperidone in the treatment of behavioural disturbances in patients with Alzheimer's dementia: a double-blind placebo-controlled trial
5. 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

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

Research Proposal

Project Title

Mediators of Mortality Risk in Older Adults with Dementia: Analysis of Multiple Pathways Using Risperidone Trial

Narrative Summary:

This study examines how risperidone contributes to mortality risk in older adults with dementia. By analyzing clinical trial data, we will investigate specific health events (pneumonia, fractures, stroke, heart failure, kidney injury, infections) that may mediate this risk and assess how timing of risperidone use affects outcomes. Using advanced mediation analysis, we aim to quantify each event's contribution to mortality risk and understand combined effects. Findings will help identify high-risk complications, guide monitoring, and inform safer prescribing and preventive strategies to mitigate risks associated with risperidone use in this vulnerable population.

Scientific Abstract:

Background:
Risperidone is commonly prescribed to manage behavioral symptoms in older adults with dementia, but its use is associated with increased mortality risk. While prior studies indicate higher mortality with antipsychotic use, the specific health complications driving this risk are not well understood, nor is the impact of timing in these risks.

Objective:
To investigate the mediating pathways through which risperidone contributes to mortality in older adults, quantifying the role of specific adverse events and assessing how timing of risperidone use influences mortality risk.

Study Design:
A secondary analysis of randomized controlled trial data to examine associations between risperidone use and mortality mediated by various adverse events.

Participants:
Older adults with dementia who participated in randomized trials comparing risperidone to placebo.

Primary and Secondary Outcome Measures:
The primary outcome is mortality within the follow-up period. Secondary outcomes include incidence of pneumonia, fractures, stroke, heart failure, acute kidney injury, venous thromboembolism, and bacterial infections.

Statistical Analysis:
Causal mediation analysis will be conducted to quantify the contribution of each adverse event to mortality risk, as well as joint and sequential mediation effects. Temporal analysis will assess event timing across current, recent, and past use periods. Sensitivity analyses will be performed to address potential misclassification of mediating events.

Brief Project Background and Statement of Project Significance:

Antipsychotic medications like risperidone are frequently prescribed to manage behavioral symptoms in older adults with dementia, despite known risks. Studies have shown increased mortality linked with antipsychotic use in this population, yet the specific health complications and pathways contributing to mortality has not been fully elucidated. This study aims to analyze how risperidone affects mortality risk by examining specific adverse events, including pneumonia, fractures, stroke, heart failure, and kidney injury. Understanding these pathways is crucial for improving clinical guidelines and helping healthcare providers minimize risk. Insights from this analysis could lead to safer prescribing practices and enhanced monitoring strategies to reduce adverse outcomes in vulnerable older adults.

Specific Aims of the Project:

1. Quantify the mediating effects of various health complications (such as infections, cardiovascular events, and fractures) on the overall mortality risk associated with risperidone.
2. Estimate the proportion of mortality risk explained by each specific pathway.
3. Assess the combined effects of multiple adverse events to understand how they interact in contributing to mortality risk.

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 safety

Confirm or validate previously conducted research on treatment safety

Preliminary research to be used as part of a grant proposal

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:
The study will use individual patient data (IPD) from clinical trials of risperidone for dementia-related behavioral symptoms, accessed through the YODA Project.

Inclusion Criteria:
Patients aged 65 years or older
Diagnosis of dementia or dementia-related behavioral symptoms
Initiated treatment with risperidone or received a placebo as part of the trial
Complete data on mortality outcomes and adverse events of interest (e.g., pneumonia, fractures, stroke, cardiovascular events)

Exclusion Criteria:
Patients with pre-existing conditions that contraindicate antipsychotic use (e.g., severe cardiac conditions)
Patients with insufficient follow-up data or missing key outcome measures
This selection aims to provide a well-defined sample of older adults with dementia, ensuring the relevance and reliability of results for assessing mortality risks associated with risperidone.

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

Primary Outcome:
All-cause mortality (Binary): Defined as death from any cause within the study follow-up period, used to assess overall mortality risk.

Secondary Outcomes:
Pneumonia (Binary): Diagnosis recorded during follow-up.

Fractures (Binary): Any reported fractures, with a focus on hip fractures.
Stroke (Binary): Ischemic or hemorrhagic stroke as verified in records.
Cardiovascular Events (Binary): Includes heart failure and venous thromboembolism.
Acute Kidney Injury (AKI) (Binary): Documented AKI instances.
Bacterial Infections (Binary): Other infections documented aside from pneumonia.

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

Independent Variable: Risperidone Use
Category: Binary
Definition: Indicates whether the patient received risperidone (1) or placebo (0) during the trial. This variable serves as the primary exposure.

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

Age (Continuous): Patient age in years at trial start, used to adjust for age-related risks.
Sex (Binary): Patient gender, coded as male (1) or female (0).
Race (Categorical): Self-identified race, categorized into groups such as White, Black, Asian, Hispanic, and Other, to control for racial differences in health outcomes.
Comorbidities (Binary for each condition): Presence of pre-existing conditions such as cardiovascular disease, diabetes, respiratory disorders, and kidney disease, coded as present (1) or absent (0).
Concomitant Medications (Binary for each medication type): Use of additional medications that could influence outcomes, including antihypertensives, anticoagulants, and antidiabetic drugs, coded as used (1) or not used (0).
Duration of Exposure to Risperidone (Continuous): Total days of risperidone exposure, allowing dose-response analysis.
Timing of Adverse Events (Categorical): Timing relative to risperidone initiation: current use (0–90 days), recent use (90–180 days), and past use (after 180 days), to assess timing effects on risk.

Statistical Analysis Plan:

Our analysis will proceed through several structured phases to address the study objectives systematically. We will begin with propensity score analysis to account for potential confounding in treatment assignment. Using logistic regression with all baseline covariates, we will calculate propensity scores and implement inverse probability of treatment weighting (IPTW). Treatment groups will be balanced when standardized differences are less than 0.1. To ensure robustness, we will conduct sensitivity analyses using alternative propensity score methods including matching weights and overlap weights.

For the first objective of quantifying mediating effects, we will implement a formal causal mediation analysis for each potential pathway. This involves fitting sequential models: a logistic regression model for the exposure-mediator relationship and a Cox proportional hazards model for the mediator-outcome relationship, both incorporating IPTW adjustment. We will calculate natural direct and indirect effects using the product method, and estimate controlled direct effects under hypothetical interventions. For each pathway, we will compute the proportion mediated on the risk difference scale with bootstrapped 95% confidence intervals.

To address the second objective regarding the proportion of risk explained by each pathway, we will employ sequential mediation analysis for ordered multiple mediators. This approach will use inverse odds ratio weighting to address mediator-outcome confounding. We will calculate path-specific effects through different combinations of mediators and apply structural equation modeling approaches for parallel multiple mediators.

For the third objective examining combined effects, we will estimate joint mediation effects using VanderWeele's approach and calculate interaction measures between mediators on both additive and multiplicative scales. We will apply g-computation for complex pathways involving multiple

mediators and use random forest models to identify important mediator combinations. Time-varying analyses will employ marginal structural models with time-varying IPTW and analyze mediator-outcome relationships using time-dependent Cox models. We will assess for time-varying effect modification and evaluate the temporal ordering of multiple adverse events.

All analyses will incorporate robust standard errors and bootstrap resampling (n=1000) for confidence intervals. Results will be presented as risk ratios, risk differences, and proportions mediated with 95% confidence intervals. To account for multiple testing, we will apply the Benjamini-Hochberg procedure for adjustment of p-values. Missing data exceeding 5% will be handled using multiple imputation with chained equations, creating 20 imputed datasets and combining results using Rubin's rules. This comprehensive analytical approach will provide robust estimates of both direct and indirect effects while accounting for potential sources of bias and confounding.

Software Used:

RStudio

Project Timeline:

Following data access approval, we anticipate completing this project within 12 months. The key milestone dates are:
Data Access and Initial Setup: January 2025. We will spend the first month organizing data and establishing analysis protocols.
Preliminary Analysis Completion: March 2025. Initial descriptive statistics and propensity score analyses will be completed.
Primary Analysis Completion: June 2025. Mediation analyses and sensitivity analyses will be finalized.
Manuscript Preparation: July-August 2025. First draft of the manuscript will be completed and internally reviewed.
Manuscript Submission: September 2025. Initial submission to target journal.
Results Reported to YODA Project: October 2025. Complete findings will be reported back to YODA.

Dissemination Plan:

Our primary manuscript will target JAMA Psychiatry or the American Journal of Psychiatry.

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