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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: NextGeneration EU European Union
How did you learn about the YODA Project?: Colleague

Conflict of Interest

https://yoda.yale.edu/wp-content/uploads/2025/02/yoda_conflict_of_interest.pdf
https://yoda.yale.edu/wp-content/uploads/2025/03/coi_helene_Speyer.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. NCT01662310 - R076477-SCH-3041 - Paliperidone Extended Release Tablets for the Prevention of Relapse in Subjects With Schizophrenia: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study
2. NCT01529515 - R092670PSY3012 - A Randomized, Multicenter, Double-Blind, Relapse Prevention Study of Paliperidone Palmitate 3 Month Formulation for the Treatment of Subjects With Schizophrenia
3. NCT00086320 - R076477-SCH-301 - A Randomized, Double-blind, Placebo-controlled, Parallel-group Study With an Open-label Extension Evaluating Paliperidone Extended Release Tablets in the Prevention of Recurrence in Subjects With Schizophrenia
4. NCT00111189 - R092670PSY3001 - A Randomized Double-blind Placebo-controlled Parallel Group Study Evaluating Paliperidone Palmitate in the Prevention of Recurrence in Patients With Schizophrenia, Placebo Consists of 20% Intralipid (200 mg/mL) Injectable Emulsion

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

Research Proposal

Project Title

Identifying predictors of symptom stability in absence of antipsychotic treatment

Narrative Summary:

Not all individuals with schizophrenia benefit from antipsychotic drugs. The majority experience immediate and long-term adverse effects raising risk/benefit dilemmas for patients and for prescribers. An alternative treatment scheme proposes a targeted or intermittent treatment approach, by which antipsychotic drugs are administered upon psychosis exacerbation and discontinued upon remission or stabilization, and renewed treatment in case of symptoms recurrence. However, there are currently no reliable biological or phenomenological markers able to predict which patients will maintain symptom stability in absence of antipsychotic treatment.

Scientific Abstract:

Background: Not all individuals with schizophrenia benefit from the antipsychotic drugs. The majority experience immediate and long-term adverse effects raising risk/benefit dilemmas for the patients and for the prescribers. An alternative treatment scheme proposes a targeted or intermittent treatment approach, by which antipsychotic drugs are administered upon psychosis exacerbation and discontinued upon remission or stabilization, and renewed treatment in case of symptoms recurrence. However, there are currently no reliable biological or phenomenological markers able to predict which patients will maintain symptoms stability in absence of antipsychotic treatment.
Objective: Identify markers that can help predict which patients maintain symptom stability in absence of antipsychotic treatment.
Study Design: Data from the requested studies will be merged into an integrated database to facilitate meta-analysis of individual participant data.
Participants: Six placebo-controlled antipsychotic trials with a double-blind phase of at least 8 months.
Primary and Secondary Outcome Measure(s); Time to: (1) relapse as measured on the PANSS, (2) discontinuation or (3) hospitalization. Secondary outcome measures time to relapse as measured on the CGI-S.
Statistical Analysis: Time to drop-out, relapse or hospitalization will be analyzed using Cox-regression. Predictor variables to be tested included routinely collected symptom, demographic and clinical variables in antipsychotic trials.

Brief Project Background and Statement of Project Significance:

Current pharmacological treatment of schizophrenia employs drugs that interfere with dopamine neurotransmission, aiming to suppress acute exacerbation of psychosis and maintenance treatment to reduce the risk of psychosis recurrence. However, not all individuals who meet DSM criteria for schizophrenia benefit from the antipsychotic drugs and the majority experience immediate and long-term adverse effects raising risk/benefit dilemmas for the patients and for the prescribers. An alternative treatment scheme proposes a targeted or intermittent treatment approach, by which antipsychotic drugs are administered upon psychosis exacerbation and discontinued upon remission or stabilization, and renewed treatment in case of symptoms recurrence. However, there are currently no reliable biological or phenomenological markers able to predict which patients will maintain symptoms stability in absence of antipsychotic treatment and which patients are likely to experience symptoms worsening shortly after treatment discontinuation. A recent study has

suggested that patients who experience high level of negative symptoms and low levels of symptoms related to agitation may be able to maintain symptoms stability and avoid hospitalization in absence of drugs which directly interfere with dopamine neurotransmission for at least 12 months (Rabinowitz et al, 2023).

Specific Aims of the Project:

The aim of this project is to identify markers that can help predict which patients maintain symptoms stability in absence of antipsychotic treatment. Based on previous work, I hypothesize that trial participants with predominantly negative symptoms and low agitation at baseline will sustain without relapse longer than patients without this symptom profile. Attempts will be made to develop and test other symptom typologies that predict stability in the absence of antipsychotic treatment.

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 data from the YODA Project and other data sources

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:

1. None.
2. Other studies from VIVILI
>Olanzapine Relapse Prevention Versus Placebo
https://benmeg.com/archives/rxarchives.org/uploads/2/4/4/6/24466638/1960_online.pdf
IDs: F1D-MC-HGGI

>Intramuscular Depot Formulation of Aripiprazole as Maintenance Treatment in Patients With Schizophrenia (ASPIRE)
https://clinicaltrials.gov/study/NCT00705783

3. We plan to pool the studies in VIVILI unless it can be done in YODA.

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

Primary outcome measures: Change on the PANSS total score, time to discontinuation and time to hospitalization. Secondary measures to be includes with be CGI-S, CGI-C and PSP.

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

The main independent variables will be symptomatology at baseline as measured on the PANSS items, subscales and total score, CGI-S, PSP and medical history (e.g., age of first illness, number of hospitalizations and medication history), smoking, tardive dyskinesia, akathisia, demographic variables (age, sex, race, ethnicity, region).

Other Variables of Interest that will be used in your analysis and how they will be

categorized/defined for your study:

These variables will be used interchangeably as independent variables and as other variables used to adjust in multivariate models: and medical history (e.g., age of first illness, number of hospitalizations and medication history), smoking, tardive dyskinesia, akathisia, demographic variables (age, sex, race, ethnicity, region).

Statistical Analysis Plan:

We will conduct a one-stage individual patient data (IPD) meta-analysis as the primary analytic framework (Campbell H, Maciel D, Chan K, et al, 2025). This approach will allow us to model all patient-level data simultaneously across the included trials, accounting for study-level heterogeneity through random effects. For the time-to-event outcome, we will implement a Cox proportional hazards model within the one-stage framework. Hazard ratios (HRs) with 95% confidence intervals (Cis) will be reported. Prognostic models will be used to identify baseline characteristics associated with outcomes regardless of treatment. We will fit a Cox proportional hazards models including baseline covariates as main effects and stratify by study to account for between-trial differences. Hazard ratios (HRs) with 95% confidence intervals (CIs) will be reported to quantify the association between each baseline factor and the risk of the event. Predictive models will be used to examine whether baseline characteristics modify the effect of treatment. These models will include interaction terms between treatment and the baseline covariates (treatment x covariate), in addition to the main effects. Stratification by study will account for differences in trial design. Significant interaction terms indicate that the effect of treatment varies according to the baseline characteristic. Subgroup-specific HRs will be reported for interpretation. Cox model development will follow a structured approach. Initially, univariable associations between each candidate predictor and the outcome will be examined. Predictors showing evidence of association (p < 0.1) will be considered for inclusion in multivariable models. A global multivariable Cox model will then be built, incorporating all selected variables, with stepwise evaluation to retain variables that contribute meaningfully to model fit. In the final analysis, we will use a network approach to connect patients and their characteristics across all included studies. This allows us to examine how different factors--such as symptom profiles, demographics, and prior treatment--interact to influence outcomes. By considering both direct and indirect relationships, the network analysis can help to identify patterns of symptom stability without medication more accurately than looking at each study or factor separately."

Predictor variables to be tested include symptomatology at baseline as measured on the PANSS items, subscales and total score, CGI-S, PSP and medical history (e.g., age of first illness, number of hospitalizations and medication history), smoking, tardive dyskinesia, akathisia, demographic variables (age, sex, race, ethnicity, region). To test the hypothesis that patients who manifest primarily negative symptoms are less likely to relapse on placebo dichotomous variables of meeting criteria for negative symptoms will be created using known negative symptom population groupings (Rabinowitz et al 2013; Rabinowitz et al, 2023) and compared to the effect of this grouping variable for patients on active treatment. This will be done by testing interaction of placebo vs. active treatment and yes/no negative symptom patient and separate models for placebo and active treatment will also be run and effects of the negative symptom grouping variable will be compared. To account for study differences study name will be included in the analysis as a control variable and we will also examine the interaction of study name and outcomes. We will also carefully compare the inclusion criteria and patient characteristics before pooling studies. Missing data due to dropout will be handled by censoring the patient from time of discontinuation. Thus, all patients will be included and no data will be imputed.

Software Used:

RStudio

Project Timeline:

Anticipated start date: April 15, 2025

Analysis completion date: Sept 15, 2025
Date manuscript drafted and first submitted for publication: Nov. 15, 2025
Date results reported back to the YODA Project: Nov. 15, 2025

Dissemination Plan:

Conference poster at schizophrenia conference on early findings and journal article in specialty journal upon project completion.

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