

## Principal Investigator

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## General Information

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**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:** This project is being supported by resources from Northwell Health Department of Psychiatry

**How did you learn about the YODA Project?:** Colleague

## Conflict of Interest

[http://yoda.yale.edu/system/files/yoda\\_project\\_coi\\_form\\_for\\_data\\_requestors\\_john\\_kane.docx](http://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_john_kane.docx)  
[http://yoda.yale.edu/system/files/yoda\\_project\\_coi\\_form\\_for\\_data\\_requestors\\_jose\\_rubio.pdf](http://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_jose_rubio.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

**Associated Trial(s):**

1. [NCT00589914 - A Randomized, Double-Blind, Parallel-Group, Comparative Study of Flexible Doses of Paliperidone Palmitate and Flexible Doses of Risperidone Long-Acting Intramuscular Injection in Subjects With Schizophrenia](#)
2. [NCT00604279 - A Randomized, Open-Label, Parallel Group Comparative Study of Paliperidone Palmitate \(50, 100, 150 mg eq\) and Risperidone LAI \(25, 37.5, or 50 mg\) in Subjects with Schizophrenia](#)
3. [NCT00590577 - A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Dose Response Study to Evaluate the Efficacy and Safety of 3 Fixed Doses \(25 mg eq., 100 mg eq., and 150 mg eq.\) of Paliperidone Palmitate in Subjects With Schizophrenia](#)
4. [NCT00111189 - 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](#)
5. [NCT00210717 - A Randomized, Double-Blind, Parallel Group, Comparative Study of Flexibly Dosed Paliperidone Palmitate \(25, 50, 75, or 100 mg eq.\) Administered Every 4 Weeks and Flexibly Dosed RISPERDAL CONSTA \(25, 37.5, or 50 mg\) Administered Every 2 Wee](#)
6. [NCT00119756 - A Randomized, Crossover Study to Evaluate the Overall Safety and Tolerability of Paliperidone Palmitate Injected in the Deltoid or Gluteus Muscle in Patients With Schizophrenia](#)
7. [NCT00210548 - A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Dose-Response Study to Evaluate the Efficacy and Safety of 3 Fixed Doses \(50 mg eq., 100 mg eq., and 150 mg eq.\) of Paliperidone Palmitate in Subjects With Schizophrenia](#)
8. [NCT00101634 - A Randomized, Double-blind, Placebo-controlled, Parallel-group, Dose-response Study to Evaluate the Efficacy and Safety of 3 Fixed Doses \(25 mg eq, 50 mg eq, and 100 mg eq\) of Paliperidone Palmitate in Patients With Schizophrenia](#)
9. [NCT00216476 - CONSTATRE: Risperdal® Consta® Trial of Relapse Prevention and Effectiveness](#)
10. [NCT00216580 - An Open-label Trial of Risperidone Long-acting Injectable in the Treatment of Subjects With Recent Onset Psychosis](#)
11. [NCT00074477 - A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of 50 and 100 Mg-eq of Paliperidone Palmitate in Patients With Schizophrenia](#)
12. [NCT01529515 - A Randomized, Multicenter, Double-Blind, Relapse Prevention Study of Paliperidone Palmitate 3 Month Formulation for the Treatment of Subjects With Schizophrenia](#)
13. [NCT01193153 - A Randomized, Double-Blind, Placebo-Controlled, Parellel-Group Study of Paliperidone Palmitate Evaluating Time to Relapse in Subjects With Schizoaffective Disorder](#)

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

## Research Proposal

### Project Title

Psychosis break through antipsychotic maintenance medication: An individual participant data meta-analysis

### Narrative Summary:

Antipsychotics are effective in reducing relapses in schizophrenia, yet adherence to these drugs is suboptimal and difficult to assess. This uncertainty limits the study of the role of antipsychotics in preventing relapses. Here, we propose to study the factors involved in breaking through antipsychotic maintenance medication (BAMM) in individuals adherent with long acting injectable antipsychotics, as a paradigm not confounded by suboptimal adherence. Though relapse in suboptimal medication adherence is potentially addressable, BAMM remains a barrier in relapse prevention in psychosis. Characterizing BAMM can help developing more efficacious interventions for relapse prevention.

**Scientific Abstract:**

Background: Long term antipsychotic use is associated with decreased risk of psychosis relapse, yet adherence with these medications tends to be suboptimal and difficult to assess. The study of the role of antipsychotics in preventing psychosis relapse is often confounded by suboptimal antipsychotic adherence. Objective: To study the incidence and moderators of breaking through antipsychotic maintenance medication (BAMM) in individuals adherent with long acting injectables (LAI). Study Design: Two-Stage individual participant data meta-analysis (IPD MA) of randomized controlled trials (RCTs) with at least one arm of LAI treatment. Participants: Individuals with schizophrenia-spectrum disorders treated for at least 3 months with a LAI as recommended by the package insert. Main Outcome Measure(s): Time to study-defined relapse. Secondary outcome measures will be relapse (categorical), hospitalization, number of psychiatric emergency services/month. Statistical Analysis: We will conduct a 2-Stage IPD MA of RCTs. After calculating the median time to relapse and its 95% confidence interval (95% CI) by the Kaplan-Meier method for each individual trial, we will pool the results following a traditional random-effects model in a 2-stage IPD MA. We will assess the role of independent predictors in the median time to relapse by conducting a maximum likelihood Cox regression model. We will also conduct subgroup analyses to explain potential heterogeneity. A multivariable analysis will be conducted to identify independent predictors of the secondary outcomes.

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

While most individuals with acute psychosis respond to antipsychotics,<sup>1</sup> the course of illness is characterized by a relapse-remitting pattern.<sup>2</sup> Therefore, relapse prevention is crucial for the long term management of schizophrenia. Though some studies have been able to study factors involved in relapse,<sup>2</sup> the role that antipsychotic drugs play in preventing this event is inadequately understood.

Failure to be adherent with antipsychotic drugs is consistently and by far the greatest predictor of relapse.<sup>2</sup> Importantly, adherence with antipsychotics is often suboptimal and difficult to assess in individuals with schizophrenia.<sup>3</sup> As a result, it is difficult to discriminate between psychosis relapse in individuals with suboptimal exposure to antipsychotics, from psychosis relapse breaking through antipsychotic maintenance medication (BAMM).

In this proposal we aim to study the role of antipsychotics in relapse prevention in a paradigm that is not confounded by non-adherence. We will study BAMM in individuals for whom antipsychotic exposure can be confirmed by the dates of administration of long acting injectable (LAI) antipsychotics. In particular, we will measure the cumulative incidence of BAMM, and its independent clinical predictors. Surprisingly, the literature on BAMM is very limited. To our knowledge, only post-hoc secondary analyses of one trial have examined the role of some sociodemographic and clinical variables involved in this phenomenon.<sup>5</sup> In this recent study, Alphas and colleagues found that only duration of illness was an independent predictor of relapse in a sample of individuals treated with LAI risperidone. However, the role of other factors remains to be understood.

A better understanding of BAMM is key to develop more effective interventions for relapse prevention in schizophrenia. While relapse due to insufficient antipsychotic adherence is potentially avoidable, BAMM remains as a barrier for the successful maintenance treatment in schizophrenia. We believe that the proposed study can help to advance the field in several ways. In the first place, by estimating the likelihood of BAMM over time we will determine the magnitude of this problem compared with relapse studies in other populations. Second, these results could help to identify individuals at risk of BAMM, where relapse prevention may be more challenging than in individuals insufficiently exposed to antipsychotics, so early interventions can be developed. Third, the clinical differences between BAMM and continued response can be informative about the antipsychotic effects and the pathophysiology of psychosis, by identifying what factors are associated with sustained antipsychotic efficacy. Fourth, the identification of clinical variables associated with BAMM can inform the design of studies that examine the biological correlates of this phenomenon. Fifth, the convergence of all this data can be used to develop personalized antipsychotic treatment in the future.

**Specific Aims of the Project:**

Aim 1: To measure the risk of BAMM over time in individuals with schizophrenia adherent with LAI in an IPD MA of multiple RCTs.

Aim 2: To identify independent predictors of time to BAMM among a comprehensive set of covariates.

Aim 3: To examine the consistency of the independent predictors of BMM by comparing the predictors for the primary outcome with those of other measures of treatment failure which will be utilized as secondary outcomes.

Aim 4: To explain potential heterogeneity in the analysis of the pooled sample by conducting subgroup analyses.

Hypothesis 1: A significant proportion of individuals treated with LAI will experience relapse of their psychotic symptoms despite adherence.

Hypothesis 2: Baseline predictors of poor response to antipsychotics will be independent predictors of BMM (greater baseline severity, shorter period of stability before randomization, greater number of previous hospitalizations, older age, longer DUP, history of medical illness, greater number of previous antipsychotic trials, worsening symptom trajectory).

Hypothesis 3: Predictors of primary outcome will overlap with the predictors of the secondary outcomes.

Hypothesis 4: Heterogeneity will be non-significant when restricting the analyses to subgroup populations

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

Research that confirms or validates previously conducted research on treatment effectiveness  
Participant-level data  
meta-analysis  
Participant-level data meta-analysis will pool 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:**

Inclusion criteria:

- Individuals diagnosed with DSM schizophrenia, schizoaffective, schizophreniform, and psychosis NOS
- Ages 18 to 65
- Participants had to be clinically stable upon randomization however defined by the study
- Randomized controlled clinical trials with at least 1 arm of long acting injectable (LAIs)
- Treatment with a LAI for at least 3 months, with no more than 21 days of cumulative delay in the administration from what is established in the package insert within the first trimester of treatment
- Data is available for our primary or secondary outcome measures
- Data is available for dates of administration of the LAI
- Trial duration of at least 6 months

The source of data will be IPD provided by the YODA project for RCT on long acting risperidone and paliperidone. We plan to combine these with IPD of industry sponsored RCTs on long acting aripiprazole and olanzapine meeting the same inclusion criteria, which will be provided directly to us by the companies. Analyses will be conducted in an intent to treat approach comparing individuals that meet criteria for BMM (relapse after treatment as defined above) with those with sustained response.

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

The main outcome measure will be relapse, however defined by each study. This outcome will be operationalized as time to event for each participant, counting between date 3 months after randomization to the reported date of relapse.

Secondary outcome measures will be relapse, however defined by each study, categorically defined. Also, psychiatric hospitalization will be used as a categorical variable, whereas psychiatric emergency room visits/month will be used as a continuous variable.

- Study defined relapse (dichotomous)
- Number of ED visits/month during treatment trial (continuous)
- Psychiatric hospitalization during trial (dichotomous)
- Psychiatric Hospitalization during trial (date)

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

For a full list and description of covariates see supplementary materials:

- LAI dose
- Dose trajectory
- Sex
- Race
- Age
- DSM diagnosis

- Duration of untreated psychosis
- Total illness duration
- Time since last hospitalization
- Number of previous hospitalizations lifetime
- Number of hospitalizations in 2 years prior to randomization
- Medical Hospitalization during trial
- Medical comorbidities at baseline
- Number of prior antipsychotic trials different to the antipsychotic being randomized to
- Co-treatment with oral antipsychotic
- Duration of use of standing concomitant oral antipsychotic
- Use of concomitant psychotropic medications other than antipsychotics
- Use of concomitant chronic non-psychotropic medication
- Psychiatric comorbidities
- Regular cannabis use
- Regular nicotine smoking
- Baseline and trajectory of BPRS/PANSS
- Baseline and trajectory of CGI score
- Baseline and trajectory of depressive symptoms
- Baseline and trajectory of functioning and quality of life
- History of psychological trauma
- Baseline BMI
- Psychosocial stressors during trial
- Side effect
- Site

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

In addition to the covariates above, we will need the following variables in order to build the model:

- Dates of administration of LAIs
- Dates of study defined relapse
- Dose of LAIs at each administration
- BPRS/PANSS score at each assessment
- CGI score at each assessment
- Depressive symptoms score at each assessment
- Functioning scale score at each assessment
- Quality of life scale score at each assessment

**Statistical Analysis Plan:**

Analysis of main outcome:

The general analytic approach will be to conduct a IPD MA comparing individuals with BMM as defined above with sustained response through trial course, following the recommendations stated in the PRISMA-IPD Statement.<sup>5</sup> We believe that this method will have advantages over study-based meta-analyses to test the aforementioned hypotheses, given the heterogeneity found in treatment response in schizophrenia.<sup>7</sup> In this proposal, we aim to conduct a MA combining IPD from the industry sponsored RCTs on risperidone long acting injectable and paliperidone palmitate provided by the YODA project, along with IPD of the industry sponsored RCTs for the other LAIs in the market (i.e., aripiprazole monohydrate, aripiprazole lauroxil, olanzapine palmoate), which will be provided to us directly by the companies. All the IPD data from sources other than YODA will be uploaded to the secure platform, where the analyses will be conducted using SAS. We will choose a 2-stage method for the IPD MA, which is often preferred for using standard meta-analytic procedures in the second stage and producing virtually the same results than a single stage method.<sup>8</sup> In the first stage we will proceed to calculate for each RCT the median time to relapse and its respective 95% confidence intervals using the Kaplan-Meier method, after excluding patients that do not complete the first 3 months of adherence and stability. We will next calculate again for each independent RCT the effects of the covariates using a maximum likelihood estimation to fit a Cox regression model. Based on the recommendation by Hernández et al.,<sup>9</sup> we will adjust for known predictors of relapse, including age of illness onset, duration of illness, baseline functioning score, baseline PANSS/BPRS score, cannabis use, and number of previous hospitalizations, as predictive covariates. Once we have calculated the within group differences for each trial, we will combine the effects in each trial using the standard meta-analytic

method of random-effects, both to calculate the pooled median time to relapse, and the pooled effects of the covariates.<sup>10</sup> We will measure heterogeneity using the I<sup>2</sup>.

Subgroup analysis:

One of the advantages of IPD MA is that it allows for subgroup analysis that may not be possible in individual trials due to small sample size. Since we will be conducting a Cox regression to identify independent predictors, we will restrict the use of subgroup analysis to identify sources of heterogeneity, if I<sup>2</sup> >50%. In the event of significant heterogeneity, we will conduct subgroup analyses for the variables that were significant in the Cox regression. We will then compare the I<sup>2</sup> for both the total group excluding the subgroup of interest and the subgroup itself, to find the removal of which subgroups reduces heterogeneity, therefore explaining it.

Analysis of secondary outcomes:

We will conduct the analyses of the secondary outcomes following the same structure of a 2-stage IPD MA as we described above for the primary outcome. In the first step, we will calculate for each RCT its risk ratio (RR) for categorical variables (study defined relapse, psychiatric hospitalization during trial) and standard mean deviation (SMD) for continuous variables, using logistic regression analyses, and adjusting for the same covariates as in the main outcome analyses. In the second stage, we will combine the effect estimates and variance for each trial (within trial estimates) and combine them in a usual random-effects meta-analysis, for the estimation of both the RR/SMD for each outcome, as well as the effects of the covariates in each model. We will examine the same subgroup analyses as described above for the main outcome.

### **Project Timeline:**

The proposed dates for completion of the key milestones of the project would be:

- Initiation: By November 2017
- Data cleaning and harmonization: By January 2017
- Completion of analyses: By March 2018
- First manuscript draft: By April 2018
- Submission of manuscript: By June 2018

### **Dissemination Plan:**

The initial product that we expect to develop is a publication of the IPD MA. We believe that this research would be of interest of a higher tier publication in psychiatry, given the significance of the problem being studied, the innovation of the methods, and the potential advancement to the field of the evidence that will be generated. In addition to publication in peer reviewed journals, we expect to be able to present the findings of this study in various research forums, (conference of the American College of Neuropsychopharmacology, the American Society of Clinical Psychopharmacology, or the International Congress on Schizophrenia Research). Furthermore, we expect that the data generated from this project will inform the design of our own study with primary data, that will study the biological correlates of BAMM, in order to enrich our understanding of this phenomenon. We believe that this publication would serve as the main reference for clinical studies on BAMM, which would then be followed by a whole body of literature on this topic, ranging from its biological to its public health implications.

### **Bibliography:**

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**Supplementary Material:**

 [covariates\\_into\\_the\\_model\\_yoda\\_proposal.docx](#)