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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?: PubMed

Conflict of Interest

https://yoda.yale.edu/system/files/yoda_schoretsanitis_1.pdf
https://yoda.yale.edu/system/files/yoda_rubio_0.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. 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
2. 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
3. NCT00378092 - CR011992, RISSCH3024 - A Prospective Study of the Clinical Outcome Following

Treatment Discontinuation After Remission in First-Episode Schizophrenia
4. NCT01529515 - R092670PSY3012 - A Randomized, Multicenter, Double-Blind, Relapse Prevention Study of Paliperidone Palmitate 3 Month Formulation for the Treatment of Subjects With Schizophrenia
5. NCT01193153 - R092670SCA3004 - A Randomized, Double-Blind, Placebo-Controlled, Parellel-Group Study of Paliperidone Palmitate Evaluating Time to Relapse in Subjects With Schizoaffective Disorder
6. 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
7. NCT00645307 - R076477-SCH-701 - A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study With an Open-Label Extension Evaluating Extended Release OROS® Paliperidone in the Prevention of Recurrence in Subjects With Schizophrenia - Open Label Phase

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

Research Proposal

Project Title

Placebo relapse after antipsychotic withdrawal: an individual participant meta-analysis

Narrative Summary:

Placebo-controlled withdrawal studies in stabilized patients are standard for seeking a maintenance or relapse prevention claim for medications used for patients with schizophrenia related disorders. This type of trials are crucial for making long-term treatment recommendations for schizophrenia. Therefore, these evidence allow for assessment of the relapse risk after antipsychotic discontinuation. Here, we propose to study the factors involved in relapse after discontinuation of antipsychotics. Addressing underlying patterns related to increased risk for relapse after antipsychotic discontinuation can help to disentangle treatment withdrawal-related phenomena from illness recurrence.

Scientific Abstract:

Background: Antipsychotic discontinuation has been associated with increased risk of psychosis relapse, yet a subgroup of individuals is able to not relapse despite being off antipsychotic treatment long-term.
Objective: To study the incidence and predictors of relapse after antipsychotic discontinuation in individuals previously stabilized with oral or long acting injectable (LAI) antipsychotics.
Study Design: Two-Stage individual participant data meta-analysis (IPDMA) of randomized controlled trials (RCTs) with at least one arm of placebo treatment.
Participants: Individuals with schizophrenia-spectrum disorders treated and stabilized for at least 12 weeks with an oral or LAI antipsychotic, and followed up on placebo treatment for at least 12 weeks.
Main Outcome Measure(s): Time to study-defined relapse.
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 for individuals with residual symptoms at the time of allocation to placebo.

Brief Project Background and Statement of Project Significance:

While most individuals with acute psychosis respond to antipsychotics,1 the course of illness is characterized by a relapse-remitting pattern.2 Psychosis relapse interferes with recovery, is associated with personal and societal costs, and potentially involves danger to self and/or others. Therefore, relapse prevention is crucial for the long-term management of schizophrenia. Current recommendations involve long-term antipsychotic maintenance treatment in schizophrenia,3,4 given the high risk of psychosis relapse,5 medical comorbidity and mortality6,7 associated with antipsychotic non-adherence over the long-term. Furthermore, the strong relapse-prevention effect

of antipsychotic maintenance8, has raised ethical concerns about using placebo-controlled relapse-prevention studies.9 Despite all of these issues, it is also true that a small proportion of individuals with schizophrenia does not relapse even off antipsychotic treatment,10 to the point of several authors advocating against the indiscriminate use of long-term antipsychotics.11 Unfortunately, the factors protect individuals with schizophrenia from not relapsing off antipsychotic maintenance are not well understood. Clarifying these issues is critical to inform long-term recommendations for the maintenance treatment of schizophrenia. The availability of individual participant data of placebo controlled relapse-prevention studies in schizophrenia offers a unique opportunity to identify the factors that at an individual level are associated with lower risk of relapse off antipsychotic maintenance using an individual participant level meta-analysis, which overcomes limitations of traditional meta-analyses resulting from study-level meta-analyses.12
In this proposal we aim to study factors involved in relapse after antipsychotic withdrawal using an individual participant data meta-analysis in a two stage approach. We will study the cumulative incidence of relapse, and its independent clinical predictors separately in individuals randomized to placebo after stabilization with oral or LAI antipsychotics, given the different pharmacokinetic properties of withdrawal between these formulations. The literature on relapse after treatment discontinuation limited. To our knowledge, only post-hoc secondary analyses of one trial have examined some sociodemographic and clinical variables involved in this phenomenon.13 In this recent study, Emsley and colleagues reported a median time-to-relapse of 163 days in patients randomized to placebo. When compared to the maintenance treatment-assigned patients relapsing, patients relapsing on placebo were slightly older, whereas men were overrepresented in the maintenance treatment-assigned patients relapsing.13 Further, no differences regarding number of previous hospitalizations, illness duration, and symptom profiles were detected between groups. By meta-analyzing patient-level data we aim to consistently identify sociodemographic and clinical protective factors that inform clinical care and future research on maintenance treatment in schizophrenia.

Specific Aims of the Project:

For this project we have 4 exploratory specific aims:
Aim 1: To measure the risk of relapse over time in antipsychotic-treated individuals after discontinuation of oral and long acting injectable antipsychotics, in an IPD MA of multiple RCTs.
Aim 2: To identify protective factors of time to relapse among a comprehensive set of covariates.
Aim 3: To examine the consistency of the independent predictors by comparing pooled within-study risk vs pooled between study risk.
Aim 4: To study the differences in time to event and predictors associated with residual symptoms at the time of treatment discontinuation, as well as the effect on formulation used upon discontinuation (i.e., LAI versus oral antipsychotic).

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

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 to placebo however defined by the study
• Treatment with an antipsychotic for at least 12 weeks prior to allocation to placebo.
• Data is available for our primary or secondary outcome measures
• Follow-up period while on placebo for at least 23 weeks
The source of data will be IPD provided by the YODA project for RCT on oral or long-acting risperidone and paliperidone.

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

The main outcome measure will be relapse after allocation to placebo, however defined by each study.

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

As provided by each trial:
• 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 placebo
• Dates of study defined relapse
• 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:

The general analytic approach will be to conduct a IPD MA comparing placebo-assigned individuals with relapse as defined above without relapse through trial course, following the recommendations stated in the PRISMA-IPD Statement.14 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.15 In this proposal, we aim to conduct a MA using IPD from the industry sponsored RCTs on risperidone long acting injectable and paliperidone palmitate provided by the YODA project. 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.16 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 for individuals allocated to placebo.. 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. 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.17 We will measure heterogeneity using the I2. We will also conduct subgroup analysis for individuals with residual psychotic symptoms; measuring incidence and predictors in this sub-group, and also comparing it to the subgroup of no residual symptoms.
Software Used:
RStudio
Project Timeline:

The proposed dates for completion of the key milestones of the project would be:
• Initiation: By February 2020
• Data cleaning and harmonization: By April 2020
• Completion of analyses: By June 2020
• First manuscript draft: By August 2020
• Submission of manuscript: By September 2020

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 that will address the biological correlates of relapse, in order to enrich our understanding of this phenomenon. We believe that this publication would serve as the main reference for clinical studies on relapse after treatment discontinuation, which would then be followed by a whole body of literature on this topic, ranging from its biological to its public health implications.

Bibliography:

1. Leucht S, Leucht C, Huhn M, Chaimani A, Mavridis D, Helfer B, et al. Sixty Years of Placebo-Controlled Antipsychotic Drug Trials in Acute Schizophrenia: Systematic Review, Bayesian Meta-Analysis, and Meta-Regression of Efficacy Predictors. Am J Psychiatry. 2017 May 25;appi.ajp.2017.1.
2. Robinson D, Woerner MG, Alvir JM, Bilder R, Goldman R, Geisler S, et al. Predictors of relapse following response from a first episode of schizophrenia or schizoaffective disorder. Arch Gen Psychiatry. 1999 Mar;56(3):241–7.
3. Goff DC, Falkai P, Fleischhacker WW, Girgis RR, Kahn RM, Uchida H, et al. The Long-Term Effects of Antipsychotic Medication on Clinical Course in Schizophrenia. Am J Psychiatry. 2017 Sep;174(9):840-849.
4. Correll CU, Rubio JM, Kane JM. What is the risk-benefit ratio of long-term antipsychotic treatment in people with schizophrenia? World Psychiatry. 2018 Jun;17(2):149-160
5. Robinson D, Woerner MG, Alvir JM, Bilder R, Goldman R, Geisler S, et al.Predictors of relapse following response from a first episode of schizophrenia or schizoaffective disorder.
Arch Gen Psychiatry. 1999 Mar;56(3):241-7
6. Taipale H, Tanskanen A, Mehtälä J, Vattulainen P, Correll CU, Tiihonen J.20-year follow-up study of physical morbidity and mortality in relationship to antipsychotic treatment in a nationwide cohort of 62,250 patients with schizophrenia (FIN20). World Psychiatry. 2020 Feb;19(1):61-68.
7. Olfson M, Gerhard T, Huang C, Crystal S, Stroup TS. Premature Mortality Among Adults With Schizophrenia in the United States. JAMA Psychiatry. 2015 Dec;72(12):1172-81.
8. Leucht S, Tardy M, Komossa K, Heres S, Kissling W, Salanti G, et al. Antipsychotic drugs versus placebo for relapse prevention in schizophrenia: a systematic review and meta-analysis. Lancet. 2012 Jun 2;379(9831):2063-71
9. Lawrence RE, Appelbaum PS, Lieberman JA. Are Placebo-Controlled, Relapse Prevention Trials in Schizophrenia Research Still Necessary or Ethical? JAMA Psychiatry. 2019 Jul;76(7):673-674
10. Wunderink L, Nieboer RM, Wiersma D, Sytema S, Nienhuis FJ. Recovery in remitted first-episode psychosis at 7 years of follow-up of an early dose reduction/discontinuation or maintenance treatment strategy: long-term follow-up of a 2-year randomized clinical trial. JAMA Psychiatry. 2013 Sep;70(9):913-20
11. Murray RM, Di Forti M. Increasing expectations and knowledge require a more subtle use of prophylactic antipsychotics. World Psychiatry. 2018 Jun; 17(2): 161–162

12. Riley RD, Lambert PC, Abo-Zaid G.Meta-analysis of individual participant data: rationale, conduct, and reporting. BMJ. 2010 Feb 5;340:c221
13. Emsley R, Nuamah I, Gopal S, Hough D, Fleischhacker WW. Relapse After Antipsychotic Discontinuation in Schizophrenia as a Withdrawal Phenomenon vs Illness Recurrence: A Post Hoc Analysis of a Randomized Placebo-Controlled Study. J Clin Psychiatry. 2018 Jun;79(4). pii: 17m11874.
14. Stewart LA, Clarke M, Rovers M, Riley RD, Simmonds M, Stewart G, et al. Preferred Reporting Items for a Systematic Review and Meta-analysis of Individual Participant Data: The PRISMA-IPD Statement. JAMA. 2015 Apr 28;313(16):1657.
15. Rubio JM, Correll CU, Inczedy-Farkas G, Birnbaum ML, Kane JM, Leucht S. Efficacy of 42 Pharmacologic Cotreatment Strategies Added to Antipsychotic Monotherapy in Schizophrenia: Systematic Overview and Quality Appraisal of the Meta-analytic Evidence. JAMA Psychiatry. 2017 Jul 1;74(7):675.
16. Burke DL, Ensor J, Riley RD. Meta-analysis using individual participant data: one-stage and two-stage approaches, and why they may differ. Stat Med. 2017 Feb 28;36(5):855–75.
17. Higgins JPT, Green S (editors). Chapter 18. In: Cochrane Handbook for Systematic Reviews of Interventions Version 510 [updated March 2011] The Cochrane Collaboration, 2011 Available from http://handbook.cochrane.org