

**The YODA Project
Research Proposal Review**

The following page contains the final YODA Project review
approving this proposal.

The YODA Project
Research Proposal Review - Final
(Protocol #: 2016-0766)

Reviewers:

- Nihar Desai
- Cary Gross
- Harlan Krumholz
- Richard Lehman
- Joseph Ross

Review Questions:

Decision:

- | | |
|---|----------------------------|
| 1. Is the scientific purpose of the research proposal clearly described? | Yes |
| 2. Will request create or materially enhance generalizable scientific and/or medical knowledge to inform science and public health? | Yes |
| 3. Can the proposed research be reasonably addressed using the requested data? | Yes, or it's highly likely |
| 4. Recommendation for this data request: | Approve |

Comments:

Use of these recommendations is at your discretion:

It is unclear whether all patients in these trials were routinely assessed for a history inflammatory bowel disease or irritable bowel syndrome. As this is one of the main independent variables, it is worth checking on the availability of these data.

I am not sure if the data set will include sufficient levels of detail about GI symptoms to answer this question. For example, constipation may be reported but probably not in enough detail to assess by the Rome criteria. I'm also surprised that the investigators intend to exclude celiac disease which they mention in their Background section, since although it is auto-immune, it can be made manifest by external factors including medication.

**The YODA Project
Research Proposal Review**

Revisions were requested during review of this proposal.
The following pages contain the original YODA Project review and
the original submitted proposal.

The YODA Project
Research Proposal Review - Revisions Requested
(Protocol #: 2016-0766)

Reviewers:

- Nihar Desai
- Cary Gross
- Harlan Krumholz
- Richard Lehman
- Joseph Ross

Review Questions:

Decision:

- | | |
|---|----------------------------|
| 1. Is the scientific purpose of the research proposal clearly described? | No |
| 2. Will request create or materially enhance generalizable scientific and/or medical knowledge to inform science and public health? | Yes |
| 3. Can the proposed research be reasonably addressed using the requested data? | Yes, or it's highly likely |
| 4. Recommendation for this data request: | Not Approve |

Comments:

The classification of gastrointestinal disorders remains unclear. If the authors propose to look at different classes or antipsychotic drugs and GI disorders, I suspect they will be underpowered to make any meaningful observations. I would ask investigators to further develop the definitions, methods, and analysis plan.

Principal Investigator

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2016-0766

General Information

Key Personnel (in addition to PI): **First Name:** Jamie
Last name: Joseph
Degree: PhD
Primary Affiliation: UC San Diego
SCOPUS ID: 0000-0002-1012-722X **ORCID**

Are external grants or funds being used to support this research?: No external grants or funds are being used to support this research.

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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): [NCT00488319 - A 2-Year, Open-Label, Single-Arm Safety Study of Flexibly Dosed Paliperidone Extended Release \(1.5-12 mg/day\) in the Treatment of Adolescents \(12 to 17 Years of Age\) With Schizophrenia](#)
[NCT01009047 - A Randomized, Multicenter, Double-Blind, Active-Controlled, Flexible-Dose, Parallel-Group Study of the Efficacy and Safety of Prolonged Release Paliperidone for the Treatment of Symptoms of Schizophrenia in Adolescent Subjects, 12 to 17 Ye](#)
[NCT00645099 - A Prospective Randomized Open-label 6-Month Head-To-Head Trial to Compare Metabolic Effects of Paliperidone ER and Olanzapine in Subjects With Schizophrenia](#)
[NCT00518323 - A Randomized, Multicenter, Double-Blind, Weight-Based, Fixed-Dose, Parallel-Group, Placebo-Controlled Study of the Efficacy and Safety of Extended Release Paliperidone for the Treatment of Schizophrenia in Adolescent Subjects, 12 to 17 Yea](#)

[NCT01606228 - An Open-Label Prospective Trial to Explore the Tolerability, Safety and Efficacy of Flexibly-Dosed Paliperidone ER among Treatment-Naive and Newly Diagnosed Patients with Schizophrenia](#)

[NCT00645307 - 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](#)

[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](#)

[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](#)

[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](#)

[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](#)

[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](#)

[NCT00034749 - The Efficacy and Safety of Risperidone in Adolescents With Schizophrenia: a Comparison of Two Dose Ranges of Risperidone](#)

[Multiple NCT#s - OPTICS Trial Bundle](#)

[NCT00249132 - A Canadian multicenter placebo-controlled study of fixed doses of risperidone and haloperidol in the treatment of chronic schizophrenic patients](#)

[NCT00216476 - CONSTATRE: Risperdal® Consta® Trial of Relapse Prevention and Effectiveness](#)

[NCT00378092 - A Prospective Study of the Clinical Outcome Following Treatment Discontinuation After Remission in First-Episode Schizophrenia](#)

[NCT00078039 - Trial Evaluating Three Fixed Dosages of Paliperidone Extended-Release \(ER\) Tablets and Olanzapine in the Treatment of Patients With Schizophrenia](#)

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

Research Proposal

Project Title

Gastrointestinal disease impact on antipsychotic induced weight gain and metabolic syndrome in schizophrenia: analysis of randomized controlled trials

Narrative Summary:

Secondary antipsychotic medication effects such as weight gain and metabolic syndrome are associated with chronic illnesses linked to an early mortality in schizophrenia. We will determine the relationship between gastrointestinal disorders and antipsychotic induced weight gain and metabolic syndrome. Understanding this relationship may help improve risk predictions for chronic somatic conditions thereby leading to improved life expectancy. Future studies will then help determine whether gastrointestinal disease influences the relationship between specific genetic markers and incidence of antipsychotic induced weight gain or metabolic syndrome.

Scientific Abstract:

Background: Although atypical antipsychotics are effective in treating psychotic symptoms, secondary effects such as weight gain and metabolic syndrome contribute to poor outcomes and early mortality.

Objective: The aim of this proposal is to meta analyze data from multiple publicly available randomized controlled antipsychotic medication trials in schizophrenia via the OPTICS program (Janssen paliperidone, NIMH Schizophrenia and dbGaP data sets) in order to determine the relationship between gastrointestinal diagnoses and commonly reported secondary effects of antipsychotics including weight gain and metabolic syndrome.

Study Design: Randomized, double-blind, placebo and active comparator antipsychotic monotherapy trials.

Participants: Individuals diagnosed with schizophrenia or schizoaffective disorder with all baseline and post treatment outcome measures available. Any individuals with congenital/childhood gastrointestinal diagnoses or autoimmune disorders will be excluded from all data analyses.

Main Outcome Measure(s): The primary outcome measures are weight gain and metabolic syndrome after accounting for sociodemographic factors.

Statistical Analyses: The relationship between gastrointestinal diagnoses and weight gain or metabolic syndrome at baseline and post antipsychotic medication treatment will be modeled in SAS with PROC MIXED.

Brief Project Background and Statement of Project Significance:

The life expectancy of people with schizophrenia is estimated to be 20% shorter than the general population (Newman & Bland, 1991) and this mortality gap has widened in recent decades (Saha et al., 2007). Unlike certain affective disorders, premature death in schizophrenia is primarily associated with the comorbid somatic conditions (Laursen et al., 2007). Although some atypical antipsychotics have demonstrated tolerability and efficacy in reducing positive symptoms, especially in individuals previously considered to be treatment refractory (Chakos et al., 2001), a significant proportion of schizophrenia patients on antipsychotics are susceptible to antipsychotic induced weight gain and metabolic disturbances. Obesity and metabolic syndrome are highly prevalent in schizophrenia spectrum disorders and exacerbate patient disability resulting in major public health burden. Obesity and metabolic syndrome are also linked to multiple somatic comorbidities associated with early mortality in schizophrenia such as diabetes, stroke, and cardiovascular disease (Hennekens et al., 2005).

Metabolic syndrome is also a well-recognized antecedent of diabetes, cardiovascular disease and stroke. These chronic diseases are linked to the early mortality observed in schizophrenia. We will also determine the relationship between gastrointestinal disease and incidence of antipsychotic induced metabolic syndrome. The primary aim of this study is to meta analyze data from multiple randomized double blind placebo and active comparator antipsychotic medication trials in schizophrenia (Janssen, NIMH CATIE and dbGaP data sets) via the OPTICS Program in order to determine the relationship between gastrointestinal diagnosis and incidence of antipsychotic medication induced weight gain to predict individuals who may be at elevated risk for chronic somatic conditions leading to an early mortality.

Another significant but underexplored comorbidity in schizophrenia is chronic gastrointestinal dysfunction. A postmortem study of 82 patients with schizophrenia demonstrated that 92% had colitis (inflammatory bowel disease) or another inflammatory gastrointestinal diagnosis (Hemmings, 2004). Case studies and clinical reports suggest that some antipsychotics cause weight gain and constipation potentially leading to mortality due to sepsis (Palmer et al., 2007). Therefore, gastrointestinal disease may be linked to antipsychotic induced weight gain in schizophrenia. However, due to conflicting reports and the limited number of comprehensive gastrointestinal studies in schizophrenia, the relationship between gastrointestinal dysfunction and obesity in schizophrenia is not well known.

If significant differences are observed, our follow up studies will determine whether gastrointestinal disease is a potential moderator of the relationship between specific genetic variants and antipsychotic induced weight gain or metabolic syndrome in schizophrenia.

Specific Aims of the Project:

1. Determine the prevalence of functional and inflammatory bowel diseases in the study sample at baseline and at post antipsychotic treatment follow up.
2. Determine differences in body mass index from baseline to last post treatment follow up for each antipsychotic medication treatment group.
3. Determine differences in metabolic syndrome score from baseline to last post treatment follow up for each antipsychotic medication treatment group.
4. Determine the association between functional or inflammatory bowel disorders and change in body mass index and metabolic syndrome score from baseline to last post antipsychotic medication treatment follow up.
5. Determine the potential sociodemographic and clinical factors associated with weight gain, metabolic syndrome, and gastrointestinal disease in schizophrenia.

What is the purpose of the analysis being proposed? Please select all that apply. Participant-level data meta-analysis

Participant-level data meta-analysis uses only data from YODA Project

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:

We are requesting the OPTICS bundle and other randomized controlled monotherapy schizophrenia, schizoaffective disorder, and psychotic trials from the YODA project. We will restrict our analyses within the OPTICS bundle to patients with schizophrenia or schizoaffective disorder from randomized controlled paliperidone monotherapy treatment trials with all baseline and post treatment outcome measures available. These data will be subsequently combined with all of the NIMH schizophrenia and dbGaP datasets that are antipsychotic monotherapy clinical trials. We will exclude individuals from our data analyses who are noted to have congenital/childhood gastrointestinal diagnoses or autoimmune disorders.

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

The outcome measures for this study are change in body mass index (BMI) and metabolic syndrome score. BMI will be computed using weight and height based on the National Heart, Lung, and Blood Institute (NHLBI) guidelines.

A metabolic syndrome score ranging from 0 to 5 will be computed for baseline and post antipsychotic treatment time points also using NHLBI guidelines that are noted below. If a patient has a score of 3 or greater, they will be considered positive for metabolic syndrome:

1. Fasting glucose \geq 100 mg/dL (or receiving drug therapy for hyperglycemia) 0 = absent, 1 = present
2. Blood pressure \geq 130/85 mmHg (or receiving drug therapy for hypertension) 0 = absent, 1 = present
3. Triglycerides \geq 150 mg/dL (or receiving drug therapy for hypertriglyceridemia) 0 = absent, 1 = present
4. HDL-C $<$ 40 mg/dL in men or $<$ 50 mg/dL in women (or receiving drug therapy for reduced HDL-C) 0 = absent, 1 = present
5. Waist circumference \geq 102 cm (40 in) in men or \geq 88 cm (35 in) in women; if Asian American, \geq 90 cm (35 in) in men or \geq 80 cm (32 in) in women 0 = absent, 1 = present

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

There are two independent variables for this study: antipsychotic medication type and gastrointestinal disease.

1. Antipsychotic Medication Type - Since we will only include individuals who are currently receiving antipsychotic monotherapy, each antipsychotic medication type will be considered a separate level for this independent variable.
2. Gastrointestinal Disease - This study will focus on the following functional and inflammatory gastrointestinal bowel disorders based on reported prevalence in the general population: 1) functional bowel disorders - irritable bowel syndrome, abdominal bloating, constipation, diarrhea and unspecified functional bowel disorder based on the Rome III criteria; and 2) inflammatory bowel disorders - ulcerative colitis and Crohn's disease. Each disorder will be considered a separate level for this independent variable.

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

Potential sociodemographic covariates of interest are participant sex, age, race, ethnicity, psychotic illness duration, and marital status. Other functional and inflammatory gastrointestinal disorders such as gastritis and lymphocytic colitis will also be considered for further analyses if we observe a prevalence of greater than 0.5% in the pooled study sample at baseline.

Statistical Analysis Plan:

The prevalence of each gastrointestinal disorder will be computed as a percentage at baseline and post antipsychotic treatment follow up. The absolute change in BMI and metabolic syndrome score based on gastrointestinal diagnosis and antipsychotic medication type will be compared at baseline and post antipsychotic medication treatment follow up by including number of days or weeks since the baseline assessment as a time-varying covariate by modeling with PROC MIXED in Statistical Analysis Software (SAS), SAS Institute Inc., Cary,

NC. A sensitivity analysis will also be conducted to determine if there are any potential effects of concurrent Selective Serotonin Reuptake Inhibitor (SSRI) and lithium treatment using PROC GLIMMIX.

Project Timeline:

After notification of YODA approval, we will seek expedited approval from NIMH, dbGaP, and the Human Subjects Research Office at UC San Diego. The estimated start date for this proposal is March 31, 2016. Once approved, we anticipate that it will take approximately one year to complete the project. Study analyses are expected to be completed by March 31, 2017 as per the OPTICS program participation requirements. A preliminary manuscript of the project findings will then be drafted by the PI. We expect to submit a manuscript for publication by July 1, 2017. Our study findings will then be reported to the YODA project following manuscript acceptance.

Dissemination Plan:

Initial analyses will be presented as an abstract at the OPTICS project meeting that is expected to take place in November 2016. We expect the findings from our data analyses will lead to the subsequent preparation of a manuscript targeted for open access publication (as per the OPTICS program participation requirements) in a reputable professional journal such as NPJ Schizophrenia, Schizophrenia Research and Treatment, or BMC Psychiatry.

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