Principal Investigator

First Name: Jamie
Last Name: Joseph
Degree: PhD
Primary Affiliation: UC San Diego
E-mail: jamiemjoseph@gmail.com
Phone number: 973-727-7611
Address: 9500 Gilman Drive
Mail Code 0993
City: La Jolla
State or Province: CA
Zip or Postal Code: 92093
Country: United States

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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
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
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 overall incidence of major gastrointestinal disorders and the relationship between gastrointestinal bowel disorders and antipsychotic induced weight gain and metabolic syndrome in schizophrenia. Future studies may help determine whether gastrointestinal disease influences the relationship between specific genetic markers and incidence of antipsychotic induced weight gain or metabolic syndrome. In the long term, these studies may lead to improved illness prediction and life expectancy in schizophrenia.

Scientific Abstract:
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 publicly available randomized controlled antipsychotic medication trials in schizophrenia via the OPTICS program (Janssen paliperidone, NIMH CATIE and dbGaP data sets) in order to determine the overall incidence of major gastrointestinal disorders and the relationship between gastrointestinal bowel disorders and the 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 including celiac disease will be excluded from all data analyses. Main Outcome Measure(s): The primary outcome measures are change in body mass index and metabolic syndrome score after accounting for significantly correlated 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 using PROC MIXED since the duration between baseline and post antipsychotic medication treatment follow up time points are expected to vary.

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/or 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 bowel diseases and incidence of antipsychotic medication induced weight gain and metabolic syndrome 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 an increased incidence of celiac disease and gluten sensitivity in schizophrenia (Cascella et al., 2011). Previous studies also suggest that some antipsychotics such as clozapine result in significant weight gain and constipation leading to significant fecal impactation and fatality due to sepsis (Palmer et al., 2007; Hibbard et al., 2009; De Hert et al., 2011). Therefore, gastrointestinal disease may be linked to antipsychotic induced weight gain in schizophrenia. Although there are a few reports on the incidence of psychiatric disorders in individuals diagnosed with irritable bowel syndrome (Lee et al., 2015), peptic ulcer (Hsu et al., 2015; Liao et al., 2014), ulcerative colitis (O'Connor et al., 1966), Crohn’s disease (Cucino &, Sonnenberg, 2001), and celiac disease (Ludvigsson et al., 2007), the number of studies that have determined the overall incidence of various gastrointestinal disorders in people who have

Specific Aims of the Project:
1. Determine differences in body mass index from baseline to last post treatment follow up for each antipsychotic medication treatment group.

2. Determine difference in metabolic syndrome score from baseline to last post treatment follow up for each antipsychotic medication treatment group.

3. Determine the estimated prevalence of gastrointestinal disorders in schizophrenia spectrum populations at baseline and at post antipsychotic treatment follow up. Primary analyses are aimed at major functional and inflammatory bowel disorders including ulcerative colitis, Crohn’s disease, irritable bowel syndrome, constipation and diarrhea. Secondary analyses will determine the prevalence of other gastrointestinal disorders such as lymphocytic colitis, gastritis, etc. Any disorders previously suggested to have an autoimmune origin, such as celiac disease will not be analyzed. These study subjects will be excluded from all data analyses.

4. Determine the association between gastrointestinal bowel disorders and change in body mass index and metabolic syndrome score from baseline to last post antipsychotic medication treatment follow up.

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:
There are two outcome (dependent) measures for this study: 1) change in body mass index (BMI) and 2) metabolic syndrome score. BMI will be computed at baseline and post antipsychotic treatment 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 ?100 mg/dL (or receiving drug therapy for hyperglycemia) 0 = absent, 1 = present

2. Blood pressure ?130/85 mmHg (or receiving drug therapy for hypertension) 0 = absent, 1 = present

3. Triglycerides ?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 ?102 cm (40 in) in men or ?88 cm (35 in) in women; if Asian American, ?90 cm (35 in) in men or ?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. Antipsychotic medications include Paliperidone from the Janssen trials and Clozapine, Olanzapine, Quetiapine, Risperidone and Ziprasidone from the NIMH CATIE trials. We will create binary (2-level) independent variables for each antipsychotic medication for initial univariate analyses. Medications that suggest significant associations from our univariate analyses will then be considered for subsequent multivariate analyses.
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, constipation, and diarrhea based on the Rome III criteria; and 2) inflammatory bowel disorders - ulcerative colitis and Crohn’s disease.

Other Variables of Interest that will be used in your analysis and how they will be categorized/defined for your study:
Potential sociodemographic covariates that will be included in our mixed models if significant correlations are observed with BMI or metabolic syndrome score are: participant sex (0 = Female, 1 = Male), age (Years), race (Asian/Pacific Islander = 1, Black = 2, Native American = 3, White = 4) ethnicity (Non-Hispanic = 0, Hispanic = 1), psychotic illness duration (Years), and marital status (Single, Never Married = 1, Married = 2, Divorced = 3, Widowed = 4). Other functional and inflammatory gastrointestinal bowel disorders such as lymphocytic colitis may also be considered for secondary analyses if we observe a prevalence of greater than 10% in the pooled study sample at baseline.

Statistical Analysis Plan:
The prevalence of each gastrointestinal disorder will be computed as a percentage of the total eligible study sample 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. If significant associations are observed between antipsychotic medication type

and our outcomes, a sensitivity analysis will also be conducted to determine if there are potential confounding effects of concurrent Selective Serotonin Reuptake Inhibitor (SSRI) or lithium treatment using PROC GLIMMIX. Irritable bowel syndrome (IBS) is the most common functional gastrointestinal (GI) disorder with U.S prevalence rates of 10–15%. http://www.aboutibs.org/site/what-is-ibs/facts/statistics. In addition, the inflammatory bowel disorders noted above are also prevalent in the U.S. (Sandler et al., 2002). Therefore, we expect the prevalence of these disorders to be significant in the pooled data set. We will create binary (2-level) independent variables for each gastrointestinal disorder for initial univariate analyses. For example, if an individual is noted to meet the Rome III criteria for constipation, the variable will be coded as 1 = presence of constipation and 0 = absence of constipation. Only gastrointestinal disorders that suggest significant associations from our univariate analyses will then be considered for subsequent multivariate analyses. Each significant disorder will represent a separate level for the gastrointestinal disorder independent variable for the subsequent multivariate analyses.

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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Supplementary Material: yodaprojectproposalsubmission3.25.2016.pdf