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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?: Colleague

Conflict of Interest

https://yoda.yale.edu/system/files/000069_001.pdf
https://yoda.yale.edu/system/files/singh.coiform.pdf
https://yoda.yale.edu/system/files/ugayodacoiform.pdf
https://yoda.yale.edu/system/files/yoda_project_coi_form_mahmoud_alnsour_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. NCT01606228 - R076477SCH3033 - 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
2. NCT00334126 - R076477SCH3015 - A Randomized, Double-blind, Placebo-controlled, Parallel Group Study to Evaluate the Efficacy and Safety of Paliperidone ER Compared to Quetiapine in Subjects With an Acute Exacerbation of 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. NCT00589914 - R092670PSY3006 - 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
5. NCT00604279 - R092670PSY3008 - 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
6. NCT00590577 - R092670PSY3007 - 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
7. 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
8. NCT00210717 - R092670PSY3002 - 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 Weeks in Subjects With Schizophrenia
9. NCT00119756 - R092670PSY3005 - 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
10. NCT00210548 - R092670PSY3003 - 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
11. NCT00101634 - R092670PSY3004 - 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
12. NCT00083668 - R076477-SCH-305 - A Randomized, Double-blind, Placebo- and Active-controlled, Parallel-group, Dose-response Study to Evaluate the Efficacy and Safety of 3 Fixed Dosages of Paliperidone Extended Release (ER) Tablets and Olanzapine, With Open-label Extension, in the Treatment of Patients With Schizophrenia
13. NCT00074477 - R092670-SCH-201 - 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
14. NCT00085748 - R076477-SCH-302 - A Randomized, 6-Week Double-Blind, Placebo-Controlled Study With an Optional 24-Week Open-Label Extension to Evaluate the Safety and Tolerability of Flexible Doses of Paliperidone Extended Release in the Treatment of Geriatric Patients With Schizophrenia
15. NCT01529515 - R092670PSY3012 - A Randomized, Multicenter, Double-Blind, Relapse Prevention Study of Paliperidone Palmitate 3 Month Formulation for the Treatment of Subjects With Schizophrenia
16. NCT00524043 - R076477SCH4012 - A Randomized, Double-Blind, Placebo- and Active-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of a Fixed Dosage of 1.5 mg/Day of Paliperidone Extended Release (ER) in the Treatment of Subjects With Schizophrenia
17. NCT01081769 - R092670SCH3005 - A 24-month, Prospective, Randomized, Active-Controlled, Open-Label, Rater-Blinded, Multicenter, International Study of the Prevention of Relapse Comparing Long-Acting Injectable Paliperidone Palmitate to Treatment as Usual With Oral Antipsychotic Monotherapy in Adults With Schizophrenia
18. NCT01281527 - R092670SCH3010 - A 6-month, Open Label, Prospective, Multicenter, International, Exploratory Study of a Transition to Flexibly Dosed Paliperidone Palmitate in Patients With Schizophrenia

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Previously Unsuccessfully Treated With Oral or Long-acting Injectable Antipsychotics
19. NCT01051531 - R092670SCH3009 - Safety, Tolerability, and Treatment Response of Paliperidone Palmitate in Subjects With Schizophrenia When Switching From Oral Antipsychotics
20. NCT01527305 - R092670SCH4009 - An Open-Label, Prospective, Non-Comparative Study to Evaluate the Efficacy and Safety of Paliperidone Palmitate in Subjects With Acute Schizophrenia
21. NCT01299389 - PALM-JPN-4 - A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Fixed-Dose, Multicenter Study of JNS010 (Paliperidone Palmitate) in Patients With Schizophrenia
22. NCT01258920 - PALM-JPN-5 - A Long-Term, Open-Label Study of Flexibly Dosed Paliperidone Palmitate Long-Acting Intramuscular Injection in Japanese Patients With Schizophrenia
23. NCT01515423 - R092670PSY3011 - A Randomized, Multicenter, Double-Blind, Non-inferiority Study of Paliperidone Palmitate 3 Month and 1 Month Formulations for the Treatment of Subjects With Schizophrenia
24. NCT02713282 - R092670SCH3015 - A 52-Week, Open-Label, Prospective, Multicenter, International Study of a Transition to the Paliperidone Palmitate 3-Month Formulation In Patients With Schizophrenia Previously Stabilized on the Paliperidone Palmitate 1-Month Formulation

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

Research Proposal

Project Title

Estimation of Geographic and Demographic Variabilities Associated with Schizophrenia Age of Onset and Duration of Untreated Psychosis

Narrative Summary:

Epidemiological data on the age of onset of psychosis, and duration of untreated psychosis (DUP) are limited. To date, most of the estimates from epidemiologic literature are based on individual patient and family interviews. Large scale epidemiological surveys on mental illness have been performed in the past. But these datasets are limited because participants are mainly North American and estimates from other countries are limited in scope. The objective of this study is to estimate the age of onset based on a pooled sample of patients with confirmed schizophrenia from large scale worldwide clinical trials. Patient data from 24 clinical trials comprising 11,740 patients will be pooled.

Scientific Abstract:

Background: Current epidemiologic literature is limited regarding age of onset of psychosis and duration of untreated psychosis. In particular, information on the variability in the distribution, and impact of any demographic or regional factors are lacking.

Objective: to estimate the age of onset based on a pooled sample of patients with confirmed schizophrenia from large scale worldwide clinical trials.

Study design: This is a retrospective pooled analysis of clinical trial data from patients with schizophrenia. In this analysis, we hope to verify the distribution for age of onset of psychosis. Baseline data only will be used, so treatment effect will not be analyzed.

Participants: Patient level data from 24 clinical trials comprising 11,740 patients will be pooled.

Main outcome measure: age of onset of schizophrenia (distribution).

Statistical Analyses: Descriptive statistics and histograms for distribution of average age of onset and duration of untreated psychosis (DUP) will be estimated (mean, median, and 95% CI). Exploratory analyses for differences by potential explanatory factors (gender, substance use and region) will also be performed. Assumptions for normality

will be examined (histograms, QQ Plots, Shapiro-Wilk test, etc.)

Brief Project Background and Statement of Project Significance:

Epidemiological data on the age of onset of psychosis, and duration of untreated psychosis (DUP) are limited (Kessler 2008). To date, most of the estimates from epidemiologic literature are based on individual patient and family interviews. Large scale epidemiologic surveys on mental illness have been performed in the past (Bourdon 1992). But these datasets are limited because participants are mainly North American and estimates from other countries are limited in scope. These surveys have limited generalizability by the fact that they rely on participants to willingly provide information. Due to stigmatization of mental illness, it is possible that estimates obtained by interview are underreported. The validity of the diagnoses obtained from these interviews are also subject to scrutiny because they are based on self-report, or family report. Diagnoses confirmed by a psychiatrist or using standardized criteria (APA 2013) would be preferred. Information on variation by age, sex, or geographic region are also not well characterized.

The age of onset in schizophrenia differs for males and females. Based on past literature, the age of onset for schizophrenia approximates a bimodal distribution for males at 21.4 and 39.2 years old, whereas for females a trimodal distribution is seen at 22.4, 36.6, and 61.5 years old (Castle 1998). The findings of bimodal and trimodal distributions are unusual and could simply be due to chance, skewness of data, improper binning technique or too small of a sample size. It is important to understand if these age distributions for schizophrenia still hold true for both male and female patients. The clinical significance behind this research will help provide quantifiable predictors for when the prevalence of schizophrenia is most common based on the statistical analysis.

Several large global clinical trial programs in schizophrenia have recently been completed and access to the underlying datasets have been made available to the public through the Yale Open Data Initiative (YODA). These clinical trial datasets each contain information on the demographic information of each patient enrolled in large scale worldwide clinical trials. During trial entry procedures the diagnosis of each patient was verified by a mental health professional according to the Diagnostic and Statistical Manual of mental disorders (DSM) (APA 2013). The demographic information contained within these datasets could be of vital importance to future efforts to understand the origins and typical clinical presentations of patients with newly developed psychosis. Reduction of DUP has positive effects on long-term outcomes, and so any factors to help clinicians understand the natural course of the disease would be important for the scientific community. Similarly, estimation of the average age of onset, with understanding of the low and high ends of distribution would be useful from a clinician’s perspective as part of the differential diagnosis.

Specific Aims of the Project:

Primary Hypothesis: The average age of onset of schizophrenia is in late teens or early adulthood
Objective: Estimate age of onset of psychosis from a pooled sample of global clinical trial data in patients with diagnosis confirmed schizophrenia
Endpoints: Diagnosis age, Descriptive statistics (n, mean, median, SD, SE) and histograms

Secondary: The average age of onset of schizophrenia varies among geographic region
Objective: Estimate age of onset by geographic region (N America, Latin America, Europe, Asia-Pac)
Endpoints: Diagnosis age. Descriptive statistics (n, mean, median, SD, SE) and histograms along with 95% confidence intervals

Secondary: The average age of onset of schizophrenia varies by sex
Objective: Estimate age of onset by sex (male vs female). Verify whether bimodal or trimodal distributions exist.
Endpoints: Diagnosis age, Descriptive statistics (n, mean, median, SD, SE) and histograms along with 95% confidence intervals

Secondary: Cannabis use is associated with earlier onset of psychosis and longer DUP
Objective: Estimate age of onset by prior cannabis use
Endpoints: Diagnosis age, descriptive statistics (n, mean, median, SD, SE) and histograms along with 95% confidence intervals

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

Summary-level data meta-analysis using only data from YODA Project
Participant-level data meta-analysis
Participant-level data meta-analysis using only data from YODA Project
Develop or refine statistical methods
Research on clinical trial methods
Research on comparison group

Research Methods

Data Source and Inclusion/Exclusion Criteria to be used to define the patient sample for your study:

The data source for this study will be from the aforementioned studies that are posted on YODA. All available YODA studies with schizophrenia patients were reviewed. Studies with adolescent, pediatric, or phase 1 studies were excluded. Only studies with access to patient-level data were included, as we need to pool the samples together for an accurate estimate of the sample distribution. Studies with only access to the clinical study report were excluded for this reason.

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

The main outcome measured will be the age of onset for schizophrenia in male and females. The proposed research objectives do not involve any statistical modeling, summary statistics will be provided for each of the primary and secondary endpoints. Variables of interest for the primary and secondary endpoints will be combined. Pooled summary statistics will be generated after combining the patient level datasets together. Duplicate patients will be removed (based on patient identification number). Assumptions underlying normal distribution for each of the continuous variables will be examined graphically. If normality conditions are met, then for continuous variables, histograms and summary statistics (n,mean, median,SD,SE) along with 95% confidence intervals will be presented. No adjustments of alpha for multiple comparisons will be performed. For ordinal or binary variables percentages or proportions within each category (along with a total %) will be calculated and presented. If skewed data are found, these will be presented accordingly in the manuscript and publications as a limitation. Patient level data from the clinical trial datasets will be pooled together using R Studio.

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

No predictor variables

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

Other variables of interest: age, sex, substance abuse, region.

Statistical Analysis Plan:

Since the proposed research objectives do not involve any statistical modeling, summary statistics will be provided for each of the primary and secondary endpoints. Variables of interest for the primary and secondary endpoints will be combined. Pooled summary statistics will be generated after combining the patient level datasets together. Duplicate patients will be removed (based on patient identification number). Assumptions underlying normal distribution for each of the continuous variables will be examined graphically. If normality conditions are met, then for continuous variables, histograms and summary statistics (n, mean, median, SD, SE) along with 95% confidence intervals will be presented. No adjustments of alpha for multiple comparisons will be performed. For ordinal or binary variables percentages or proportions within each category (along with a total %) will be calculated and presented. If skewed data are found, these will be presented accordingly in the manuscript and publications as a limitation.

Patient level data from the clinical trial datasets will be pooled together using R Studio. Due to the nature of the objectives, no formal statistical hypothesis testing or p values will be generated. Since the research objectives are descriptive in nature, no adjustment using propensity score matching is needed; other more advanced modeling methods (logistic regression, multivariable regression, non-linear methods, non-parametric) are not necessary.

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Information regarding patient identifying variables will not be examined including: name, initials, zip code, address, primary treating physician or other factors. The anonymized patient identification number from the clinical trial will be used to pool patients together and to avoid duplicates.
Software Used:
RStudio
Project Timeline:

Apr 16, 2021: Start Date -- Gather authors, agree upon analysis plan, present plan to YODA
Apr 30, 2021: Start Analysis -- Obtain datasets from YODA, perform analyses
May 28, 2021: Complete Analyses -- Perform statistical analyses, quality control check
June 30, 2021: Draft manuscript and posters -- Draft manuscript and posters. Submit abstracts to conferences
July 30, 2021: Submit manuscript -- Submit manuscript to first journal choice
Aug 30, 2021 Revise/resubmit Revise manuscript based on reviewers' comments and/or submit to second choice journal
Dec 30, 2021 Results reported back to YODA Results of primary manuscript and abstracts reported to YODA

Dissemination Plan:

Submission as Abstract/Poster: US Psych Congress Oct 2021; American Psychiatric Association Annual Meeting 2022; Society for Biological Psychiatry Annual Meeting; Schizophrenia International Research Society 2022

Publication: Peer reviewed journal options include: Neuropsychiatric Disease & Treatment, Schizophrenia Bulletin, Journal of Psychopharmacology, CNS Drugs

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Supplementary Material:

https://yoda.yale.edu/sites/default/files/schizophrenia_age_of_onset_-_project_proposal.docx