The following page contains the final YODA Project review approving this proposal.
The YODA Project
Research Proposal Review - Final
(Protocol #: 2016-1005 )

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

Review Questions:

1. Is the scientific purpose of the research proposal clearly described?  
   Decision: Yes

2. Will request create or materially enhance generalizable scientific and/or medical knowledge to inform science and public health?  
   Decision: Yes

3. Can the proposed research be reasonably addressed using the requested data?  
   Decision: Yes, or it's highly likely

4. Recommendation for this data request:  
   Decision: Approve

Comments:

No additional comments.
Revisions were requested during review of this proposal.
The following pages contain the original YODA Project review and the original submitted proposal.
Reviewers:

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

Review Questions:

1. Is the scientific purpose of the research proposal clearly described?  
   Decision: Yes

2. Will request create or materially enhance generalizable scientific and/or medical knowledge to inform science and public health?  
   Decision: Yes

3. Can the proposed research be reasonably addressed using the requested data?  
   Decision: Unsure, further clarification from requestor is needed

4. Recommendation for this data request: Not Approve

Comments:

Can the authors provide additional details about the sample size? They report that 20-30% of subjects do not achieve a therapeutic response and propose to develop a predictive model to identify features associated with lack of efficacy. How many subjects will they have between all of the studies requested? Do they have adequate statistical power to test all of the variables they propose to include? How can they determine whether the lack of efficacy is due to non-adherence to study medications?
Principal Investigator

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State or Province: CT
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Country: USA

2016-1005

General Information

Key Personnel (in addition to PI):  First Name: Nikolaos
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Degree: MD
Primary Affiliation: Department of Psychiatry and Psychotherapy, Ludwig-Maximilians-University Munich, Munich, Germany.

First Name: Alkomiet
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Degree: MD
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First Name: John
Last name: Krystal
Degree: MD
Primary Affiliation: Yale

First Name: Ralitza
Last name: Gueorguieva
Degree: PhD
Primary Affiliation: Yale
First Name: Martin
Last name: Paulus
Degree: MD
Primary Affiliation: Laureate Institute for Brain Research

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

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 Ye
- 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
- NCT00334126 - 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
- NCT00650793 - A Randomized, DB, PC and AC, Parallel Group, Dose-Response Study to Evaluate the Efficacy and Safety of 3 Fixed Dosages of Extended Release OROS Paliperidone (6, 9, 12 mg/Day), With Open-Label Extension, in the T
- 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
- NCT00590577 - A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Dose Response Study to Evaluate the Efficacy and Safety of 3 Fixed Doses of Extended Release Paliperidone (25 mg eq., 100 mg eq., and 150 mg eq.) of Paliperidone Palmitate 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
- 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
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
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
NCT00101634 - A Randomized, Double-blind, Placebo-controlled, Parallel-group, Dose-response Study to Evaluate the Efficacy and Safety of Risperidone Long-acting Injectable (LAI) for the Prevention of Mood Episodes in the Treatment of Subjects With Bipolar I
NCT00034749 - The Efficacy and Safety of Risperidone in Adolescents With Schizophrenia: a Comparison of Two Dose Ranges of Risperidone
NCT00076115 - Research on the Effectiveness of Risperidone in Bipolar Disorder in Adolescents and Children (REACH): A Double-Blind, Randomized, Placebo-Controlled Study of the Efficacy and Safety of Risperidone for the Treatment of Acute Mania in Bipolar
NCT00132678 - A Randomized, Double-blind, Placebo-controlled Study to Explore the Efficacy and Safety of Risperidone Long-acting Intramuscular Injectable in the Prevention of Mood Episodes in Bipolar 1 Disorder, With Open-label Extension
NCT00397033 - A Randomized, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy and Safety of Two Dosages of Paliperidone ER in the Treatment of Patients With Schizoaffective Disorder
NCT00412373 - A Randomized, Double-blind, Placebo-controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Flexible-dose Paliperidone ER in the Treatment of Patients With Schizoaffective Disorder
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
NCT00216580 - An Open-label Trial of Risperidone Long-acting Injectable in the Treatment of Subjects With Recent Onset Psychosis
NCT00253162 - The Efficacy and Safety of Flexible Dose Ranges of Risperidone Versus Placebo or Haloperidol in The Treatment Of Manic Episodes Associated With Bipolar I Disorder
NCT00378092 - A Prospective Study of the Clinical Outcome Following Treatment Discontinuation After Remission in First-Episode Schizophrenia
NCT00299715 - A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Dose-Response, Multicenter Study to Evaluate the Efficacy and Safety of Three Fixed Doses of Extended-Release Paliperidone in the Treatment of Subjects With Acute Manic and Mixed Episode Schizophrenia
NCT00309699 - A Randomized, Double-blind, Active- and Placebo-Controlled, Parallel-Group, Multicenter Study to Evaluate the Efficacy and Safety of Flexibly-Dosed, Extended-Release Paliperidone Compared With Flexibly-Dosed Quetiapine and Placebo in the Treatment of Acute Manic
NCT00309686 - A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study to Evaluate the Efficacy and Safety of Flexibly-Dosed Extended-Release Paliperidone as Adjunctive Therapy to Mood Stabilizers in the Treatment of Acute Manic
NCT00752427 - 24 week extension of NCT00085748: 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 Subjects With Acute Manic
NCT00083668 - A Randomized, Double-blind, Placebo- and Active-controlled, Parallel-group, Dose-response Study to Evaluate the Efficacy and Safety of 3 Fixed Doses of Paliperidone Extended Release (ER) Tablets and Olanzapine, With Open-label Extension
NCT0074477 - 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
NCT00078039 - Trial Evaluating Three Fixed Doses of Paliperidone Extended-Release (ER) Tablets and Olanzapine in the Treatment of Patients With Schizophrenia
NCT00085748 - 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
NCT01529515 - A Randomized, Multicenter, Double-Blind, Relapse Prevention Study of Paliperidone Palmitate 3 Month Formulation for the Treatment of Subjects With Schizophrenia
NCT01193153 - A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study of Paliperidone Palmitate
Research Proposal

Project Title

Identification of multivariate, clinical patterns predicting treatment response to paliperidone in schizophrenia

Narrative Summary:
The response to existing pharmacological interventions in patients with schizophrenia is highly heterogenous. Overall, it is estimated that between 20 and 30% of patients do not respond sufficiently to medication. Currently, clinicians have no way of predicting whether a specific medication will work for a specific patient. Consequently, patients frequently undergo multiple unsuccessful treatments. This is associated with a prolonged duration of illness episodes, repeated hospitalizations and increased financial and medical costs. We plan to develop tools that can help clinicians choose better treatments, and ultimately help patients get better faster.

Scientific Abstract:
Background:
Only a subset of patients with schizophrenia respond sufficiently to the currently available pharmacological interventions. There exists no clinical marker to predict treatment response in individual patients. This inefficacy leads to prolonged illness episodes and suffering in affected patients, repeated hospitalizations and a substantial socio-economic burden.

Objective:
To use clinical data from existing clinical trials to generate multivariate models for the prediction of treatment response to paliperidone in patients with schizophrenia.

Study Design:
Clinical and demographic variables of individual patients will be used to generate prediction models. We will employ a cross-validation scheme (leave-one-trial-out cross-validation) to estimate the generalizability of the generated models.

Participants:
All participants of the requested trials will be included in the analysis.

Main Outcome Measure(s):
The main outcome measure of our analysis will be the balanced accuracy ((sensitivity + specificity)/2) of the generated multivariate statistical models when predicting early responders vs. early non-responders (week 6-7) and late responders vs. late non-responders (week 12-13). Response to paliperidone will be defined as a reduction on the PANSS total of >20% relative to baseline.

Statistical Analysis:
All continuous variables will be mean centered and scaled. A wrapper method will be used to generate models based on a minimal set of highly predictive variables.

Brief Project Background and Statement of Project Significance:
The clinical response to pharmacological interventions in patients with schizophrenia is highly heterogenous. Despite significant scientific efforts, there exists currently no reliable biomarkers to predict treatment response. As a consequence, patients frequently undergo multiple unsuccessful pharmacological interventions until they respond sufficiently. This leads to prolonged illness episodes and suffering in affected patients, repeated hospitalizations...
and a significant socio-economic burden. In the absence of more effective treatment options, it has been suggested that a stratification prior to treatment initiation could be a valuable strategy to improve treatment outcome in psychiatric patients (Chekroud & Krystal 2016, BMJ). In their recent work Chekroud et al. (2016, Lancet Psychiatry) demonstrated that merely based on clinical and demographic data, a multivariate statistical model could be used to predict treatment response in patients with major depression. In this study, we are planning to apply this approach to existing data from pharmacological trials in patients with schizophrenia. Multivariate pattern analysis (MVPA) will be employed to generate statistical models to predict treatment response to paliperidone. The analysis will identify a minimal subset of highly predictive variables. Those could be used to create a MVPA-based clinical questionnaire to be used in the clinical setting to assess patients and acquire the necessary data for response prediction. In this way, our work could significantly contribute to the efficacy of existing pharmacological treatments in psychiatry. If applied in the clinical setting, patients could be assessed prior to treatment initiation and their treatment response could be predicted using the generated models. Treatment with paliperidone could then be restricted to only those patients with sufficient response while other patients could be treated with other compounds.

Specific Aims of the Project:
To generate multivariate statistical models based on clinical data to predict treatment response to paliperidone in patients with schizophrenia on the level of individual subjects.

What is the purpose of the analysis being proposed? Please select all that apply. New research question to examine treatment effectiveness on secondary endpoints and/or within subgroup populations
Participant-level data meta-analysis
Participant-level data meta-analysis uses only data from YODA Project
Other

Research Methods

Data Source and Inclusion/Exclusion Criteria to be used to define the patient sample for your study:
Multivariate pattern analysis (MVPA) is a new statistical method that allows the identification of predictive patterns in high-dimensional data sets. In comparison with traditional univariate statistical approaches, MVPA is particularly suited to be applied to a large number of variables. The approach allows prediction with high accuracy on the level of individual subjects. In this way, models can be applied to answer practical questions in the clinical context such as the prediction of the disease course or potential differential diagnosis of an individual patient. Thus, the aim of the present project is to apply MVPA to identify patterns in clinical data to predict treatment response to paliperidone in patients with schizophrenia.

In addition, we will apply trajectory-based statistical methods to these data. Trajectory-based models (e.g. latent class models, and growth mixture models) capture heterogeneity in the development of clinical outcomes during an intervention, and this more sensitive approach can result in trial outcomes that differ from traditional endpoint measures.

Main Outcome Measure and how it will be categorized/defined for your study:
The main outcome measure of our analysis will be the balanced accuracy ([sensitivity + specificity]/2) of the generated multivariate statistical models when predicting early responders vs. non-responders (week 6-7) and late responders vs. non-responders (week 12-13) (http://www.ncbi.nlm.nih.gov/pubmed/14662555). Response to paliperidone will be defined as a reduction on the PANSS total of >20% relative to baseline. For trajectory based approaches, we will use trajectories of PANSS-based outcome measurements over time.

Main Predictor/Independent Variable and how it will be categorized/defined for your study:
In the current project, we plan to employ a data-driven approach. All variables shared between the available clinical trials will be entered in our analysis. Using cross-validation and penalized statistical methods we will aim to avoid overfitting and generate reliable estimated of the generalizability of the models predictions.

Other Variables of Interest that will be used in your analysis and how they will be categorized/defined for your study:
We will test the specificity of our results to paliperidone by applying the generated models to predict early and late treatment response (reduction in PANSS total score >20% relative to baseline) in patients treated with quetiapine, olanzapine, aripiprazole and placebo.
**Statistical Analysis Plan:**

We will employ a multivariate approach to generate statistical models to predict treatment response to paliperidone. The main outcome measure will be the binary variables early treatment response (week 6-7) and late treatment response (week 12-13) whereas treatment response will be defined as a reduction in the PANSS total score of >20% with respect to baseline. From all trials only participants with available data of at least one of the main outcome measures will be included. Based on those participants we will define maximum set of clinical and demographic variables that is shared between all trials. Prior to analysis all continuous variables will be mean centered and scaled. In order to improve predictive power of the modes, variables with low predictive value as well as highly correlated variables will be removed from the analysis to retain a subset of n=25 highly predictive variables (Chekroud et al., 2016). This will be accomplished by a elastic net regression which includes a linear combination of a L1- as well as a L2-regularization term. Subsequently, we will fit a gradient-boosting machine to classify patients into responders and non-responders. Most importantly, all data processing steps will be embedded in a nested cross-validation scheme. At the outer level of the cross-validation we will successively hold out one entire trial and use the remaining data to generate the predictions models. Then the models will be applied to the hold-out data to estimate the generalizability of the model. This procedure will be repeated until each trial has been held out once. At the inner cross-validation loop, we will employ a 10-fold cross-validation with 10 permutations to optimize the multivariate prediction models. The main outcome measure of the prediction models will be the balance accuracy.

In order to test the specificity of our results to paliperidone, the models will be applied also to participants receiving other drugs (risperidone, quetiapine, olanzapine, aripiprazole) or placebo. In this way, we will test whether the identified predictive patterns relate to a specific paliperidone response, a general trait to respond to any medication or a general subtype of patients with a spontaneous remission. For trajectory-based approaches we will explore whether similar or different trajectory classes exist for patients who take active treatments or placebo, and test whether there were clinical predictors of trajectory class membership.

**Project Timeline:**

We plan to initiate the project at the 1st of October 2016. At the initial stage of the project, data will be merged and processed to prepare analysis. At the 1st of November we will begin the analysis of the prepared data and expect results at the 1st of January 2017. In the following period the draft will be written and prepared for publication. We expect the first submission of the manuscript at the 1st of March 2017.

**Dissemination Plan:**

We plan to submit the finalized manuscript to one of the leading, peer-reviewed journals in the field of schizophrenia and psychiatry (e.g. Molecular Psychiatry, Biological Psychiatry, American Journal of Psychiatry, Schizophrenia Bulletin, JAMA Psychiatry, Lancet Psychiatry). Furthermore, we plan to create a clinical questionnaire to specifically provide the required information to predict treatment response based on our multivariate models, and make this available to clinicians online. This will allow this research to reach its maximum potential for improving patient care.