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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?: Other

Conflict of Interest

https://yoda.yale.edu/wp-content/uploads/2019/05/conflictform_ae.pdf
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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

1. NCT00044681 - A Study to Evaluate the Efficacy, Safety and Maintenance Effect of Risperidone Augmentation of SSRI Monotherapy in Young and Older Adult Patients With Unipolar Treatment-Resistant Depression
2. NCT02417064 - A Randomized, Double-blind, Multicenter, Active-controlled Study to Evaluate the Efficacy, Safety, and Tolerability of Fixed Doses of Intranasal Esketamine Plus an Oral Antidepressant in Adult Subjects With Treatment-resistant Depression
3. NCT02418585 - A Randomized, Double-blind, Multicenter, Active-controlled Study to Evaluate the Efficacy, Safety, and Tolerability of Flexible Doses of Intranasal Esketamine Plus an Oral Antidepressant in Adult Subjects With Treatment-resistant Depression
4. NCT02422186 - A Randomized, Double-blind, Multicenter, Active-controlled Study to Evaluate the Efficacy, Safety, and Tolerability of Intranasal Esketamine Plus an Oral Antidepressant in Elderly Subjects With Treatment-resistant Depression
5. NCT01998958 - A Double-Blind, Doubly-Randomized, Placebo-Controlled Study of Intranasal Esketamine in an Adaptive Treatment Protocol to Assess Safety and Efficacy in Treatment-Resistant Depression (SYNAPSE)
6. NCT03039192 - A Double-blind, Randomized, Placebo-controlled Study to Evaluate the Efficacy and Safety of Intranasal Esketamine in Addition to Comprehensive Standard of Care for the Rapid Reduction of the Symptoms of Major Depressive Disorder, Including Suicidal Ideation, in Adult Subjects Assessed to be at Imminent Risk for Suicide
7. NCT02918318 - A Randomized, Double-blind, Multicenter, Placebo-controlled Study to Evaluate the Efficacy, Safety and Tolerability of Fixed Doses of Intranasal Esketamine in Japanese Subjects With Treatment Resistant Depression
8. NCT00095134 - A Double-Blind Study Comparing Adjunctive Risperidone Versus Placebo in Major Depressive Disorder That Is not Responding to Standard Therapy
9. NCT01627782 - A Double-blind, Randomized, Placebo-controlled, Parallel Group, Dose Frequency Study of Ketamine in Subjects With Treatment-resistant Depression
10. NCT01640080 - A Double-Blind, Double-Randomization, Placebo-Controlled Study of the Efficacy of Intravenous Esketamine in Adult Subjects With Treatment-Resistant Depression

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

Research Proposal

Project Title

Role of clinical, historical and demographic factors in the response to antidepressants versus placebo

Narrative Summary:

Little is known about whether clinical or demographic variables differentially predict treatment outcome. Information gained on this question would further our understanding of the impact and relevance of non-traditional antidepressant mechanisms of action, may help select patients who may optimally respond to one treatment or the other, or guide the development of future novel medicines. We will address this question using meta analyses of clinical and demographic data from

randomised clinical trials treating MDD. Pooling datasets will allow high statistical power, should reduce bias from specific site / study effects, and allow a broad exploration of different drugs and drug classes.

Scientific Abstract:

Background: Antidepressant selection is presently a trial-and-error process. This unguided process of treatment selection results in substantial morbidity, increased mortality (including risk of suicide), tremendous patient and provider frustration, and a high risk of the patient dropping entirely out of treatment. As such, the need to establish which treatments are most effective for a patient with MDD is a deeply pressing clinical and societal issue.
Objectives: (i) Determine the relationship between pre-treatment clinical and demographic variables. (ii) Establish a multivariate composite of clinical and demographic measures that best predict outcome. (iii) Identify subtypes of subjects that may potentially show superior response to drug vs placebo
Study design: We will conduct analyses using randomized, double-blind, placebo-controlled datasets in which one or more antidepressants are compared to placebo. We will address this question using aggregated analyses of clinical and demographic data from randomised clinical trials treating MDD. Pooling datasets will allow high statistical power, should reduce bias from specific site / study effects, and allow a broad exploration of different drug classes versus placebo.
Participants: Thousands of subjects with a diagnosis of Major Depressive Disorder
Main outcome measures: Treatment response defined by MADRS, and HDRS
Statistical Analysis: Analyses of treatment response will make use of linear mixed models to capture variance across multiple studies, drug classes and placebo. Independent variables will be clinical scales, historical data and demographics available at baseline. Predictors may include: age, sex, body mass index, anhedonia, medication and treatment history, comorbidities, quality of life. Sub-typing analyses will utilise semi-supervised cluster analysis. We will test whether the relationships identified in the training subset (70% of subjects) are replicated in a holdout dataset (30% of patients, matched to the training subset).

Brief Project Background and Statement of Project Significance:

Antidepressant selection is presently a trial-and-error process. Data from seminal clinical trials, such as the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial, demonstrates that after failure of a selective serotonin reuptake inhibitor (SSRI), there is an equal probability of response to another SSRI, a serotonin norepinephrine reuptake inhibitor (SNRI), or bupropion [1]. As such patients may go through many successive trials of antidepressant medications (ADMs) before finding an effective one for them, without any information to guide this process. This unguided process of treatment selection results in substantial morbidity, increased mortality (including risk of suicide), tremendous patient and provider frustration, and a high risk of the patient dropping entirely out of treatment. As such, the need to establish which treatments are most effective for a patient with MDD is a deeply pressing clinical and societal issue.
Little is known about whether clinical or demographic variables differentially predict treatment outcome. Information gained on this question would further our understanding of the impact and relevance of non-traditional antidepressant mechanisms of action, may help select patients who may optimally respond to one treatment or the other, or guide the development of future novel medicines. We will address this question using aggregated analyses of clinical and demographic data from randomised clinical trials treating MDD. Pooling datasets will allow high statistical power, should reduce bias from specific site / study effects, and allow a broad exploration of different drugs and drug classes. Our statistical methods will be ones common to clinical trial research, as well as those more closely related to simple forms of machine learning. Given the broad relevance of the proposed analyses, meaningful impact is expected for the general population of depressed patients (22M in the US alone), as well as patients with anxiety or trauma-related disorders in which antidepressant treatment is also a mainstay (10M's in the US). Indeed, at present it is estimated that one in eight in the US is on an antidepressant at any given time, thus illustrating both the breadth and need for a precision approach such as that described herein.

Specific Aims of the Project:

1. Determine the relationship between pretreatment clinical and demographic variables in a training subset (70% of patients) with respect to clinical outcome pooling drug classes and placebo in a meta analysis spanning multiple studies
Hypothesis: Greater drug-placebo differences in depressive symptoms will be predicted by later age of onset, smaller difference between current age and age of onset, lower somatic symptoms, and less anhedonia.
2. Test if the relationships identified in the training subset are replicated in a holdout dataset (30% of patients, matched to the training subset)
Hypothesis: Greater drug-placebo differences in MDD symptoms will be predicted by later age of onset, less difference between current age and age of onset, lower somatic symptoms, and less anhedonia.
3. Establish a multivariate composite of clinical and demographic measures that best predict outcome in the training subset and determine its replication in the holdout subset
Hypothesis: The resulting model will explain at least 10% of variance in treatment-related change in MDD symptoms
4. Identify subtypes of subjects that may potentially show superior response to drug vs placebo
Hypothesis: Groups split by BMI, along with other baseline clinical information will be associated with response

Research Methods

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

We are interested in the differences between baseline predictors of response to antidepressants and placebo, as well as possible differences in sub-types for responders and non-responders. This will be an analysis where we are interested in global treatment response (pooling drugs), with exploratory analyses of drug-specific response (versus placebo).

Primary and Secondary Outcome Measure(s) and how they will be categorized/defined for your study:

Primary analyses will focus on treatment response defined by MADRS, and HDRS where available, and if not measured, auxiliary response measures could include CGI, QIDS, PHQ.
Treatment response for each scale will be defined as change from baseline for continuous variables, and for categorical outcomes as response (50% decrease from baseline) or remission (scale-dependent thresholds).

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

We aim to make predictions for treatment response using measures available at baseline. Across studies this could entail a large number of variables, which we would expect to include:
Age and Sex
Body mass index (BMI)
Baseline MADRS, CGI, HAM-A, HDRS, QIDS, PHQ, SHAPS etc (at the total scale, subscale and individual item levels)

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

Clinical scales for quality of life, social function, anxiety Comorbidities
Previous treatment duration, number of prior medications failed Previous treatment type (SNRI, SSRI, etc)

Lifetime history of episodes
Lifetime of treatment resistance / response if applicable/available Age of onset, time since onset

Statistical Analysis Plan:

Statistical Analyses
We will aim to predict treatment associated changes from baseline in clinical measures using baseline demographics and clinical information. These analyses will pool data from many trials. Measurement intervals for response variables will vary between trials however we will for each trial seek to define at least baseline and a treatment time-point at 6 weeks (or 8 weeks if data were not collected at six weeks). Primary analyses will use response and remission defined by HDRS or MADRS, while a secondary analysis will pool other clinical scales based on availability.
Mixed effects modelling
(i) For a pooled analysis across all (active) treatments we will use linear mixed regression models with MADRS/HAM-D change from baseline as the dependent variable, random effects for study, drug, study*drug, drug-class, a continuous covariate for ?week of response measurement?, then predictors of interest will the largest possible set of appropriate common baseline variables, including: age, sex, baseline clinical scales, BMI, etc, as described in the ?Predictors of treatment response? section. If there is insufficient overlap to test some predictors we will consider splitting analyses into separate models for each related predictor set, rather than including all predictors in tandem. Non significant terms and predictors will be removed from models in a step-wise fashion. We will furthermore use mixed effects logistic regression to test the same predictors and interactions with response as the dependent variable.
(ii) For a pooled analysis of all placebo groups the same analysis will be performed without the terms for drug (and other drug-related model terms).
(iii) Depending on the composition of studies obtained, similar analyses will be conducted pooling for drug-classes (e.g, SSRI, SNRI); or for (iv) drugs of interest (e.g, Vortioxetine, Esketamine, etc). These models would be of the same form as above, although; drug class analyses would include random drug/drug-interaction terms; while specific drug analyses would only include study as a random term and utilize dose as a continuous predictor.
The aim in these analyses will be to identify significant baseline predictors of treatment response at the p

Project Timeline:

Target Analysis Start Date: January 03, 2022
Estimated Analysis Completion Date: January 03, 2024

Dissemination Plan:

The dissemination plan will include publications, posters in relevant conferences, pending knowledge of the strength of the findings. Anticipated suitable journals, and in which the research team has previously published multiple papers, include the American Journal of Psychiatry [1], JAMA Psychiatry [2], Biological Psychiatry [3] and Lancet Psychiatry [4].

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