Berlin, January 26, 2019

Amendment

This is an amendment for the project proposal 2017-1846. It is intended to describe the individual participant-level analysis in more detail and specifically address 1) abstract, 2) specific aims of the project, 3) main outcome measure, 4) statistical analysis plan, and 5) project timeline.

Scientific Abstract:

Background: Antipsychotics are mainly used in the treatment of schizophrenia and other mental disorders, such as bipolar disorder. Discontinuation and switching the type of substance may lead to relevant symptoms interfering with the safety and adherence of psychiatric treatment. Especially rapid discontinuation of antipsychotics which functionally inhibit or stimulate receptors may lead to psychiatric and other somatic symptoms.
Objective: Our goal is to systematically assess the full range of withdrawal symptoms, also known as discontinuation symptoms.
Study Design: We plan to investigate the relationship between adverse events (AEs) and discontinuation of an antipsychotic by performing meta-analyses of individual participant data in the placebo groups of RCTs following patients with versus without previous medication. The target group consists of patients who discontinued an antipsychotic just before receiving the placebo and the control group consists of patients who had not recently been taking antipsychotics before receiving the placebo.
Participants: Schizophrenia, bipolar disorder, schizoaffective disorder, and children with disruptive behavior disorders.
Main outcome measure: Our main outcome measure will be the frequency of individual withdrawal symptoms, also known as discontinuation symptoms, within 12 weeks after baseline in the target group compared to the control group.
Statistical analysis: A generalized linear mixed model (GLMM) will be used for the primary analysis of the primary objective to compare the frequency of withdrawal symptoms between the target and control group.

Specific Aims of the Project:

Hypothesis: Adverse events in the target group of the placebo arm that fulfill the diagnostic criteria (i. and ii.) of withdrawal symptoms, also known as discontinuation symptoms, are assumed to be withdrawal symptoms:

i. Symptoms occur after discontinuation of the prestudy antipsychotic
ii. Symptoms are not better accounted for by a general medical condition, another mental disorder, or substance use.

All objectives, hypotheses and endpoints are only investigated for participants in the placebo arm and separately for each diagnosis: schizophrenia, schizoaffective disorder, bipolar disorder, and disruptive behavior disorders.

Primary objective:
A. Identify the frequency, duration and severity of withdrawal symptoms and relapse in the group of patients who discontinued the prestudy antipsychotics before entering the placebo arm (target group) compared to the group of patients with no prestudy antipsychotics before entering the placebo arm (control group) within 12 weeks after baseline.
We hypothesize that the frequency, duration and severity of withdrawal symptoms and relapse

is larger in the target group compared to the control group.

Secondary objectives:
B. Identify if abrupt or tapered discontinuation of a prestudy antipsychotic causes a larger frequency, duration, and severity of withdrawal symptoms and relapse in the target group within 12 weeks after baseline.
We hypothesize that abrupt discontinuation of a prestudy antipsychotic causes a larger frequency, duration, and severity of withdrawal symptoms and relapse in the target group compared to the control group.

C. Identify if the receptor affinities (K_i values) of the discontinued prestudy antipsychotic can predict the frequency, duration, and severity of withdrawal symptoms and relapse in the target group within 12 weeks after baseline.
We hypothesize that the receptor affinities (K_i values) of the discontinued prestudy antipsychotic can predict the frequency, duration, and severity of withdrawal symptoms and relapse in the target group

Endpoints
The following three groups of endpoints (1A-12A, 13B-18B and 19C-24C) are clustered according to the three groups of objectives (A, B and C).

Primary endpoint:
1A: The frequency of individual withdrawal symptoms (e.g. nausea, tachycardia, etc.; definition table 1) within 12 weeks after baseline in the target group compared to the control group. All discontinued antipsychotics will be pooled for the primary endpoint.

Secondary endpoints:
2A: The total duration of each withdrawal symptoms within 12 weeks after baseline in the target group compared to the control group. Withdrawal symptoms that occur more than once will be cumulated (e.g. four days and three days of tachycardia result in a total duration of seven days of tachycardia). If a withdrawal symptom is described within 12 weeks after baseline but continues for longer than 12 weeks after baseline, it will be included for the total period of occurrence (e.g. a withdrawal symptom will be included for the total duration of five weeks if it occurs 11 weeks after baseline and continues until 16 weeks after baseline).

3A: The maximum severity of each occurring withdrawal symptom (e.g. 'moderate' tachycardia; definition table 1) within 12 weeks after baseline in the target group compared to the control group.

4A / 5A / 6A: The frequency / duration / severity (as defined above) of relapse (definition table 2) in the target group compared to the control group within 12 weeks after baseline.

7A / 8A / 9A: The frequency / duration / severity (as defined above) of withdrawal symptoms (definition table 1) for each individual prestudy antipsychotic in the target group compared to the control group within 12 weeks after baseline. The discontinued antipsychotics will be assessed individually and not pooled for these endpoints.

10A / 11A / 12A: The frequency / duration / severity (as defined above) of relapse (definition table 2) for each individual prestudy antipsychotic in the target group compared to the control group within 12 weeks after baseline. The discontinued antipsychotics will be assessed individually and not pooled for these endpoints.

13B / 14B / 15B: The frequency / duration / severity (as defined above) of withdrawal symptoms (definition table 1) compared between patients with abrupt discontinuation of a prestudy antipsychotic and patients with tapered discontinuation (definition table 3) of a prestudy antipsychotic in the target group within 12 weeks after baseline. All discontinued antipsychotics

will be pooled for this endpoint.

16B / 17B / 18B: The frequency / duration / severity (as defined above) of relapse (definition table 2) compared between patients with abrupt discontinuation of a prestudy antipsychotic and patients with tapered discontinuation (definition table 3) of a prestudy antipsychotic in the target group within 12 weeks after baseline. All discontinued antipsychotics will be pooled for this endpoint.

19C / 20C / 21C: The frequency / duration / severity (as defined above) of withdrawal symptoms (definition table 1) predicted from the receptor affinities (Ki values) of the discontinued prestudy antipsychotic in the target group within 12 weeks after baseline. The discontinued antipsychotics will be assessed individually and not pooled for these endpoints.

22C / 23C / 24C: The frequency / duration / severity (as defined above) of relapse (definition table 2) predicted from the receptor affinities (Ki values) of the discontinued prestudy antipsychotic in the target group within 12 weeks after baseline. The discontinued antipsychotics will be assessed individually and not pooled for these endpoints.

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

For oral and long-acting application, the main outcome is the frequency of individual withdrawal symptoms within 12 weeks after baseline in the target group compared to the control group. All discontinued antipsychotics will be pooled for the primary endpoint. Oral and long-acting injectable antipsychotics will be calculated separately.

Statistical Analysis Plan:

We will merge individual patient data from the placebo groups in the 45 RCTs provided in the YODA data base. Separate analyses will be made for each diagnosis, i.e. schizophrenia, bipolar disorder, schizoaffective disorder, and disruptive behavior disorders.

A generalized linear mixed model (GLMM) will be used for the primary analysis of the primary objective to compare the frequency of withdrawal symptoms between the target and control group. The dependent variable is withdrawal symptoms (yes/no). Discontinuation of a prestudy antipsychotic (yes/no) will be included as a fixed factor, while a random intercept will be added per study. A random slope for discontinuation of a prestudy antipsychotic will also be added and tested.

The GLMM will be tested unadjusted and adjusted for confounders (fixed effects for e.g. age, sex, weight, duration and dose of antipsychotic application, duration of illness, duration of untreated psychosis, number of hospitalizations, and additional non-antipsychotic medication).

The secondary analyses of the secondary objectives will be analyzed analogous to the primary objective with a generalized linear mixed model. The secondary objectives will be analyzed with a multiple linear regression, an ordinal logistic regression, or binominal logistic regression according to the type of dependent variable (i.e. continuous, ordinal, or dichotomous).

Frequency, duration, and severity of withdrawal symptoms will be predicted with predictive modelling, which includes splitting the dataset into a training and test set.

Missing data will be treated as recommended by Little et al.[49]: First, we will register if reasons for missing data were documented and develop a primary set of assumptions about the cause for missing data[49]. Then the primary set of assumptions will be followed by multiple imputation by chained equations and robustness tested with a sensitivity analysis[49].

Project Timeline:

Milestone 1 at 0 months: Data preparation starts.

Milestone 2 at 6 months: Data preparation is completed and analysis of objective A starts.

Milestone 3 at 12 months: Analysis of objective A is completed and analysis of objective B starts.

Milestone 4 at 18 months: Analysis of objective B is completed and analysis of objective C starts.

Milestone 5 at 24 months: Analysis of objective C is completed.