

## Principal Investigator

**First Name:** Stefan

**Last Name:** Leucht

**Degree:** MD

**Primary Affiliation:** Klinik für Psychiatrie und Psychotherapie der TU-München Klinikum rechts der Isar

**E-mail:** [Stefan.Leucht@lrz.tum.de](mailto:Stefan.Leucht@lrz.tum.de)

**Phone number:** +49-89-4140-4249

**Address:** Ismaningerstr. 22

**City:** München

**State or Province:** Bavaria

**Zip or Postal Code:** 81675

**Country:** Germany

**SCOPUS ID:** 7003761080

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### General Information

**Key Personnel (in addition to PI):** **First Name:** Myrto

**Last name:** Samara

**Degree:** MD

**Primary Affiliation:** Department of Psychiatry and Psychotherapy TU-München

**First Name:** Stephen

**Last name:** Levine

**Primary Affiliation:** Department of Community Mental Health, University of Haifa

**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):** [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](#)[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 \(6, 9, 12 mg/Day\) and Olanzapine \(10 mg/Day\), With Open-Label Extension, in the T](#)[NCT00590577 - 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](#)[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 3 Fixed Doses \(25 mg eq, 50 mg eq, and 100 mg eq\) of Paliperidone Palmitate in Patients With Schizophrenia](#)[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 Bipola](#)[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](#)[NCT00037674 - A Randomized, Double-Blind, Multicenter, Placebo-Controlled 12-Week Study of the Safety and Efficacy of Two Doses of Topiramate for the Treatment of Acute Manic or Mixed Episodes in Patients With Bipolar I Disorder With an Optional Open-La](#)[NCT00035230 - A Randomized, Double-Blind, Multicenter, Placebo-Controlled 12-Week Study of the Safety and Efficacy of Topiramate in Patients With Acute Manic or Mixed Episodes of Bipolar I Disorder With an Optional Open-Label Extension](#)[NCT00249132 - A Canadian multicenter placebo-controlled study of fixed doses of risperidone and haloperidol in the treatment of chronic schizophrenic patients](#)[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.](#)[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 Mi](#)[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 T](#)[NCT00077714 - A Randomized, Double-blind, Placebo- and Active-controlled, Parallel-group, Dose-response Study to Evaluate the Efficacy and Safety of 2 Fixed Dosages of Paliperidone Extended Release Tablets and Olanzapine, With Open-label Extension, in t](#)[NCT00083668 - 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.](#)[NCT00074477 - 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 Dosages 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 Wit](#)

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

## Research Proposal

### Project Title

Initial severity and efficacy of antipsychotics for schizophrenia and bipolar mania: Individual patient level analyses of placebo-controlled trials

**Narrative Summary:**

The belief that psychiatric drugs are more damaging than helpful has been recently revived based on reports that questioned their efficacy compared to placebo, especially for milder ill patients. In response to that, we intend to assess the antipsychotic efficacy across the full range of symptom severity and compare it to placebo for patients suffering from acute schizophrenia or bipolar mania.

**Scientific Abstract:**

**Background:** Schizophrenia and bipolar disorder are the most serious and debilitating psychiatric diseases affecting each approximately 1% of the population (1). Antipsychotic drugs are used for the treatment of both conditions, but recently their efficacy compared to placebo was questioned, especially for patients with milder symptoms (2). Our research group has recently published an individual participant data meta-analysis examining the influence of baseline severity on the efficacy of antipsychotic drugs in the acute treatment of schizophrenia (3). We found that the interactions between baseline symptom severity and treatment were statistically significant.

**Objective:** Our goal is to replicate these results in a larger sample and also assess whether the same applies to bipolar mania.

**Study design:** We plan to perform meta-analyses of individual participant data to investigate the relationship between baseline symptom severity and subsequent symptom change comparing antipsychotics versus placebo.  
**Participants:** Patients with schizophrenia and bipolar mania, in the acute phase of their illness, will be included in two separate analyses.

**Main outcome measure:** Our main outcome measure will be the change scores on the Positive and Negative Syndrome Scale (PANSS) (4) for patients with schizophrenia and on the Young Mania Rating Scale (YMRS) (5) for patients with bipolar mania.

**Statistical analysis:** The relationship between baseline and change scores for the drug and placebo groups will be examined with mixed-effects models for repeated measures analysis (MMRM).

**Brief Project Background and Statement of Project Significance:**

Antipsychotic drugs are used for the treatment of both schizophrenia and bipolar mania, either in the acute phase for symptoms' control (6, 7) or in the long term for relapse prevention (8, 9). Nevertheless, the efficacy of many psychotropic agents has been recently called into question. Starting with antidepressants, some studies argued they may be less efficacious for the milder spectrum of the disorder compared to placebo leading to a general mistrust towards psychiatry and the efficacy of its treatments (2, 10, 11). The impact on patients' adherence is still unknown but, given the extensive media coverage of the topic, this is a major issue of public health importance. Our research group has recently published an individual participant data meta-analysis in the acute treatment of schizophrenia examining the influence of baseline severity on the efficacy of antipsychotic drugs (3). We found that benefits from antipsychotic drugs are expected for all patients with acute schizophrenia and for highly symptomatic patients with predominant negative symptoms. However, efficacy was lower in less ill patients; thus, clinicians need to take into account that patients with milder symptoms benefit less in terms of symptom improvement but may still experience full side-effects of antipsychotics. On the other hand, clinicians should also bear in mind that antipsychotic action is not limited in the treatment of active symptoms; it also includes relapse prevention among patients in remission.

We intend to replicate our previous findings in a larger sample of patients, including more antipsychotic drugs and also extend the analysis to patients suffering from bipolar mania since the effect of baseline severity on efficacy may constitute a general pattern rather than a confined phenomenon (12). The results of our planned study could have a major impact on future guidelines and everyday clinical practice. We attach our original publication which provides further details of the planned analysis (3).

**Specific Aims of the Project:**

Our primary hypothesis is that antipsychotic drugs have greater efficacy compared to placebo for all patients suffering from acute schizophrenia or bipolar mania, irrespectively of their baseline symptom severity, but also that more severely ill patients do benefit more (3, 13-18). Our objective is either to confirm or refute this hypothesis based on a large sample of patients.

**What is the purpose of the analysis being proposed? Please select all that apply.** Research that confirms or validates previously conducted research on treatment effectiveness

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:**

Individual participant data from randomized controlled trials (RCTs) comparing the efficacy of antipsychotics versus placebo in the acute phase treatment of schizophrenia and bipolar mania will be included. The data from RCTs in schizophrenia and bipolar mania will be analyzed separately. Ideally, all placebo-controlled trials that examine the efficacy of antipsychotic drugs in the acute treatment of these two conditions will be included, irrespectively of the route of drug administration. Six-week duration will be the primary endpoint, but trials with other endpoints ranging from 4 to 12 weeks will be also included. Of all antipsychotic treatment arms in the RCTs, we will include only the arms that are within the US FDA labels (for schizophrenia or bipolar mania) or the target to maximum doses according to the International Consensus Study of Antipsychotic Dosing (for schizophrenia) (22).

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

Symptom change from baseline to 6 weeks (4-12) will be our main outcome. All assessment time points (from baseline to endpoint) will be used in the analysis. Symptom change will be measured by total score reduction in symptom severity scales. We aim to use the same outcome measure across all trials in the field of schizophrenia and perform the meta-analysis using one scale (e.g. PANSS); the same will be attempted for all trials in the field of bipolar mania (e.g. YMRS).

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

Baseline symptom severity will be the main predictor (independent variable) in our study. It will be defined as the total score in symptom severity scales such as PANSS for schizophrenia and YMRS in bipolar mania. We will investigate the relationship between baseline symptom severity and subsequent symptom change comparing antipsychotics versus placebo in the acute treatment of patients with schizophrenia or bipolar mania. The two conditions (schizophrenia and bipolar mania) will be analyzed separately in order to assess whether potential effects of baseline severity on antipsychotic efficacy are restricted to a specific psychiatric disorder or is a more general phenomenon.

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

Sub-scores of the symptom severity scales representing specific groups of symptoms (e.g. positive and negative symptoms in schizophrenia) and single items will be assessed separately to examine whether baseline severity has the same effect on the subsequent symptom reduction.

In addition, patient characteristics such as age, sex, duration of illness, duration of untreated psychosis, number of hospitalizations etc. will be examined for their possible confounding effect on antipsychotic efficacy. As we would like to calculate the number needed to treat (NNT) of achieving a minimally important change for different baseline severity scores, we will conduct a linking analysis between YMRS and CGI-BP scales (e.g. what do the different cutoffs in the YMRS scale mean). Results of the linking analysis are very important both for clinicians and researchers and are necessary for NNT calculation.

Finally, we will use a network analysis to identify a system (network) of schizophrenia and bipolar symptoms and the most central schizophrenia and bipolar symptoms based on the YMRS and PANSS respectively; and Item Response Theory to identify a short YMRS and PANSS if possible.

### **Statistical Analysis Plan:**

We will conduct individual participant data meta-analysis to examine the relationship between baseline symptom severity and the differences in change scores between the antipsychotic drugs and placebo using a mixed-effects model repeated measures (MMRM) analysis with maximum likelihood estimation (20, 21). The number of levels of the MMRM analysis will account for the data structure such as the represented time, the participant, and the trial. The resulting competing models with increasing complexity will be tested unadjusted and adjusted for confounders (e.g. age, sex, duration of illness etc.). The model with the smallest Bayesian Information Criterion (BIC) will be chosen as the most parsimonious (22). We will report results based on the best fitting models.

Sensitivity analyses will be conducted comparing the different competing models as produced by the different levels of the MMRM analysis. To examine whether the overall results observed with the total score hold also for specific groups of symptoms such as the positive and negative symptoms in schizophrenia or specific single items in schizophrenia and mania, we will run the same analyses for the positive/negative symptoms or the single items

separately.

To calculate the number needed to treat of achieving a minimally important change for different baseline severity scores, we will conduct a linking analysis between YMRS and CGI-BP scales. Finally, we will use (i) a network analysis to identify a system (network) of schizophrenia and bipolar symptoms and the most central schizophrenia and bipolar symptoms based on the PANSS and YMRS; and (ii) Item Response Theory to identify a short YMRS and PANSS if possible.

#### **Project Timeline:**

The project is anticipated to start as soon as the data are available to us. Immediately after request approval, the study protocol will be published online (milestone 1). We will then need approximately 6 months to complete the analyses (milestone 2) and additional three months to draft the manuscript (milestone 3). In about one year after obtaining the data, the first paper will be submitted for publication and, at the same time, all results will be reported back to the YODA Project (milestone 4).

#### **Dissemination Plan:**

Beyond publications in major medical journals (American Journal of Psychiatry, JAMA Psychiatry, The Lancet Psychiatry etc.), we plan to organise symposia at major international and psychiatric conferences. Our findings will be implemented in national and international treatment guidelines for some of which Prof. Stefan Leucht is a (co-)editor (among others he is leading the schizophrenia guideline group of the Collegium Internationale Neuropsychopharmacologicum, CINP).

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**Supplementary Material:**  [initial\\_severity\\_jama.pdf](#)

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