

Principal Investigator

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2016-0880

General Information

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

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SCOPUS ID: 55602634300

Are external grants or funds being used to support this research?: External grants or funds are being used to support this research.

Project Funding Source: German ministry of education and research

 [conflicts_of_interest_stefan_leucht.pdf](#)

 [conflicts_of_interest_johannes_schneider_thoma.pdf](#)

 [conflicts_of_interest_maximilian_huhn.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

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](#)
[NCT00645307 - A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study With an Open-Label Extension Evaluating Extended Release OROS® Paliperidone in the Prevention of Recurrence in Subjects With Schizophrenia - Open Label Phase](#)
[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](#)
[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](#)
[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](#)
[NCT00391222 - A Randomized, Double Blind, Placebo and Active Controlled Parallel Group 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](#)
[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](#)
[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](#)
[NCT00094926 - A Prospective, Randomized, Double-blind, Placebo-controlled Study of the Effectiveness and Safety of RISPERDAL CONSTA Augmentation in Adult Patients With Frequently-relapsing Bipolar Disorder](#)
[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](#)
[NCT00236444 - Risperidone in the Prevention of Relapse: a Randomized, Double-blind, Placebo-controlled Trial in Children and Adolescents With Conduct and Other Disruptive Behavior Disorders](#)
[NCT00250354 - The Safety And Efficacy Of Risperidone Versus Placebo In Conduct Disorder In Mild, Moderate And Borderline Mentally Retarded Children Aged 5 To 12 Years](#)
[NCT00266552 - The Safety And Efficacy Of Risperidone Versus Placebo In Conduct Disorder and Other Disruptive Behavior Disorders In Mild, Moderate And Borderline Mentally Retarded Children Aged 5 To 12 Years](#)
[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](#)
[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](#)
[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](#)
[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](#)
[NCT00249158 - Risperidone in the Treatment of Behavioural and Psychological Signs and Symptoms in Dementia \(BPSSD\): a Multicentre, Double-blind, Placebo-controlled Parallel-group Trial](#)
[Risperidone in the treatment of behavioural disturbances in patients with Alzheimer's dementia: a double-blind placebo-controlled trial](#)
[NCT00261508 - Efficacy And Safety Of Risperidone In The Treatment Of Children With Autistic Disorder And Other Pervasive Developmental Disorders: A Canadian, Multicenter, Double-Blind, Placebo-Controlled Study](#)
[NCT00249236 - The Efficacy And Safety Of Flexible Dosage Ranges Of Risperidone Versus Placebo In The Treatment Of Manic Or Mixed Episodes Associated With Bipolar I Disorder](#)
[NCT00249145 - Risperidone in the Treatment of Behavioral Disturbances in Demented Patients: an International, Multicenter, Placebo-controlled, Double-blind, Parallel-group Trial Using Haloperidol as Internal Reference](#)
[NCT00250367 - The Safety And Efficacy Of Risperdal \(Risperidone\) Versus Placebo As Add-On Therapy To Mood Stabilizers In The Treatment Of The Manic Phase Of Bipolar Disorder](#)
[Efficacy and safety of a flexible dose of risperidone versus placebo in the treatment of psychosis of Alzheimer's disease. A double-blind, placebo-controlled, parallel-group study.](#)
[NCT00088075 - A Randomized, Double-Blind, Placebo-Controlled Clinical Study of the Efficacy and Safety of Risperidone for the Treatment of Schizophrenia in Adolescents](#)
[Risperidone versus haloperidol versus placebo in the treatment of schizophrenia](#)
[NCT00253149 - The Safety And Efficacy Of Risperdal \(Risperidone\) Versus Placebo Versus Haloperidol As Add-On Therapy To Mood Stabilizers In The Treatment Of The Manic Phase Of Bipolar Disorder](#)
[NCT00253136 - Risperidone Depot \(Microspheres\) vs. Placebo in the Treatment of Subjects With Schizophrenia](#)
[A double-blind, placebo-controlled study of risperidone in children and adolescents with autistic disorder](#)
[NCT00034762 - Efficacy And Safety Of A Flexible Dose Of Risperidone Versus Placebo In The Treatment Of Psychosis Of Alzheimer's Disease](#)
[NCT00257075 - The Efficacy And Safety Of Flexible Dosage Ranges Of Risperidone Versus Placebo In The Treatment Of Manic Episodes Associated With Bipolar I Disorder](#)
[The efficacy and safety of flexible dose ranges of risperidone vs. Placebo or divalproex sodium in the treatment of manic or mixed episodes associated with bipolar 1 disorder](#)
[NCT00253123 - A Randomized, Double-Blind, Placebo-Controlled Study of Risperidone for Treatment of Behavioral Disturbances in Subjects With Dementia](#)
[The safety and efficacy of risperidone 8 mg qd and 4 mg qd compared to placebo in the treatment of 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, Parellel-Group Study of Paliperidone Palmitate Evaluating Time to Relapse in Subjects With Schizoaffective Disorder](#)
[NCT01662310 - Paliperidone Extended Release Tablets for the Prevention of Relapse in Subjects With Schizophrenia: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study](#)
[NCT00490971 - A Randomized, Double-Blind, Active- and Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Efficacy and Safety of Extended-Release Paliperidone as Maintenance Treatment After an Acute Manic or Mixed Episode Associated Wi](#)
[NCT00524043 - 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](#)
[NCT00105326 - A Double-blind, Placebo-controlled, Randomized Study Evaluating the Effect of Paliperidone ER Compared With Placebo on Sleep Architecture in Subjects With Schizophrenia](#)

What type of data are you looking for?: Full CSR

Research Proposal

Project Title

Incidence of death and other SAEs related to second generation antipsychotic or placebo treatment in RCTs - a systematic review and meta-analysis

Narrative Summary:

Antipsychotic drugs are the mainstay for the treatment of schizophrenia, but are also very important and widely used therapeutic options for the treatment of several other psychiatric diseases and disorders. In the community of patients, professionals and scientists it is currently a highly discussed topic, if their application is associated with a decreased or increased risk of serious side effects including death.

Since these serious outcomes are fortunately rare, this can only be answered by analyses including high numbers of patients. We are tackling this issue therefore by a big size meta-analysis comparing antipsychotic drugs as a group to placebo in RCTs over all indications.

Scientific Abstract:

Background: Antipsychotic drugs are the mainstay for the treatment of schizophrenia, but are also very important and widely used therapeutic options for the treatment of several other psychiatric diseases and disorders. In the community of patients, professionals and scientists it is currently a highly discussed topic, if their application is associated with a decreased or increased risk of serious adverse events including death. Up to date analysis are based on observational studies with inherent methodological problems.

Study Design: We are working on a systematic review including a large meta-analysis of randomized controlled trials to evaluate and differentiate the risk of death and other serious adverse events related to antipsychotic drug treatment or no treatment of mental disorders.

Participants: Participants of randomized placebo-controlled trials of second generation antipsychotic drugs irrespective of indication, age or gender.

Main Outcome Measures: incidence rates of serious adverse events including death.

Statistical Analysis: Odds ratios and their 95% confidence intervals will be calculated and combined in pairwise meta-analysis.

Please find attached our successful application to the German ministry of education and research (BMBF) and the PROSPERO protocol for further information.

Brief Project Background and Statement of Project Significance:

Antipsychotic drugs are the mainstay for the treatment of schizophrenia, but are also very important and widely used therapeutic options for the treatment of several other psychiatric diseases and disorders. In the community of patients, professionals and scientists it is currently a highly discussed topic, if their application is associated with a decreased or increased risk of serious adverse events including death.

Up to date analysis are based on observational studies with inherent methodological problems.

To reach a high level of precision and confidence about these rare but very important outcomes, analyses on the basis of randomized populations and high number of participants are required. We are planning to achieve this goal by conducting by a big size meta-analyses of RCT comparing SGAs as a groups to placebo over all indications.

Please find attached our successful application for a grant from the German ministry of education and research (BMBF) for further details concerning the relevance of our project and references to prior work.

Specific Aims of the Project:

The aims of this project are to examine whether antipsychotic drugs increase the risk for death and other serious adverse events, to further evaluate the differential incidence of specific serious adverse events in pharmacologically treated (SGA-drug-group) and non treated (placebo-group) patients suffering from mental disorders and to find out which patient or treatment related factor are associated with their occurrence.

Main hypothesis (two sided): There is an overall significant difference in mortality and incidence of serious adverse events in antipsychotic drug trials between the verum and the placebo group.

The same two sided hypothesis will be used for all identified specific serious adverse events.

Subgroup analysis will include antipsychotic drug used, diagnostic subgroup, age, gender, drug combination, dosage.

We expect the state of treatment (active antipsychotic treatment or placebo) to be the main predictor.

Other potential predictors that will be addressed in subgroup analysis are specific antipsychotic drug, diagnostic subgroup, age, gender, combination of drugs, dosage.

Please find attached our successful application to the German ministry of education and research (BMBF) and the PROSPERO protocol for further information.

What is the purpose of the analysis being proposed? Please select all that apply. New research question to examine treatment safety

Research that confirms or validates previously conducted research on treatment safety

Summary-level data meta-analysis

Summary-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:

Systematic review and meta-analysis:

Search strategy: We ran electronic searches in the databases MEDLINE, EMBASE, Cochrane Central Register of Randomised Trials (CENTRAL), BIOSIS, CINAHL, Dissertation Abstracts, LILACS, PSYINDEX, PsycINFO). Additionally we contacted all SGA-marketing pharma companies for missing relevant data.

inclusion criteria: Participants of randomized placebo-controlled clinical trials of second generation antipsychotic drugs irrespective of underlying mental disease, age or gender.

Included SGAs are amisulpride, aripiprazole, asenapine, brexpiprazole, cariprazine, clozapine, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, sertindole, ziprasidone and zotepine. First generation antipsychotics will only be evaluated if they are used as additional active comparator.

Please find attached our successful application to the German ministry of education and research (BMBF) and the PROSPERO protocol for further information.

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

The main outcome measure is the incidence of serious adverse events in the drug group and the placebo group. The effect size measure will be the odds ratio (OR) and its 95% confidence intervals (CIs). We will calculate the number needed to treat to provide benefit /to induce harm, and its 95% confidence intervals (CIs). Analyses will be carried out in accordance to the 'intention-to-treat' principal when possible ('once randomized always analyze'). As all outcomes of interest (serious adverse events) are rare we will assume for those who have been lost to follow-up that they will not have had the outcome (unless it occurred before dropping out), because other strategies would overestimate the risk because the outcomes are rare.

If data is available, we will calculate incidence rates per mean time in study to control for different periods of observation in the drug and the placebo group.

Please find attached our successful application to the German ministry of education and research (BMBF) and the PROSPERO protocol for further information.

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

We expect the state of treatment (active antipsychotic treatment or placebo) to be the main predictor.

Please find attached our successful application to the German ministry of education and research (BMBF) and the PROSPERO protocol for further information.

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

Other potential predictors that will be addressed in subgroup analysis are specific antipsychotic drug, diagnostic subgroup, age, gender, combination of drugs, dosage.

Please find attached our successful application to the German ministry of education and research (BMBF) and the PROSPERO protocol for further information.

Statistical Analysis Plan:

Pairwise meta-analyses within a Bayesian framework will be used to estimate the summary comparative effect sizes. All outcomes will be dichotomous and be primarily analysed as odds ratios, supplemented by NNT/NNH. Special statistical attention in terms of data synthesis and heterogeneity assessment will be paid to the fact that events will be rare. Predefined subgroups analyses will address: diagnostic subgroup, age, gender, antipsychotic drug used, antipsychotic combinations, dose. Publication bias will be examined with funnel-plot methods, recommendations will be made with GRADE.

The following sensitivity analyses of the primary outcome are planned a priori: a) random-effects instead of fixed effects model, b) exclusion of open RCTs, c) exclusion of studies that used doses higher than in the official labels ("off-label doses").

Please find attached our successful application to the German ministry of education and research (BMBF) and the PROSPERO protocol for further information.

Project Timeline:

Start of project: 09/2015

First contact of data holders: 11/2015

Actual state of the project: identification of included RCTs from literature search and data extraction.

It is planned to finish data extraction and to start data analysis by 07/2016

First data presentations and publications are planned for the following month.

According to the framework of our grant, there is a deadline for data presentation in 03/2017.

Dissemination Plan:

We will produce a very large review with approximately 50000 participants. The research question is a priority for patients with schizophrenia and it is important for many other psychiatric patient groups for which antipsychotics have indications or are used "off-label". Therefore, it is likely that we will be able to publish the results in a general medicine journal with high visibility such as the BMJ or the Lancet in which other reviews of our group have already been published [29, 30, 31, 32]. It can be expected that our findings will be rapidly implemented in national and international treatment guidelines. For example, Stefan Leucht is a member of the group producing the schizophrenia and depression guidelines of the German national psychiatric association (DGPPN) and of the British Association of Psychopharmacology, and he is leading the schizophrenia guideline group of the Collegium Internationale Psychopharmacologicum (CINP).

For references and further information please find attached our successful application for a grant from the German ministry of education.

Bibliography:

For references and further information please find attached our successful application for a grant from the German ministry of education.

Supplementary Material:  [successful application for bmbf grant.doc](#)

 [prospero_protocol.pdf](#)