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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?:** Colleague

## Conflict of Interest

[http://yoda.yale.edu/system/files/coi\\_heinz.pdf](http://yoda.yale.edu/system/files/coi_heinz.pdf)  
[http://yoda.yale.edu/system/files/coi\\_brandt.pdf](http://yoda.yale.edu/system/files/coi_brandt.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

### Associated Trial(s):

1. [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](#)
2. [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](#)
3. [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](#)
4. [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](#)
5. [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](#)
6. [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](#)
7. [NCT00086320 - A Randomized, Double-blind, Placebo-controlled, Parallel-group Study With an Open-label Extension Evaluating Paliperidone Extended Release Tablets in the Prevention of Recurrence in Subjects With Schizophrenia](#)
8. [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](#)
9. [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](#)
10. [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](#)
11. [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](#)
12. [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](#)
13. [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](#)
14. [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](#)
15. [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](#)
16. [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](#)
17. [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](#)
  18. [NCT00034749 - The Efficacy and Safety of Risperidone in Adolescents With Schizophrenia: a Comparison of Two Dose Ranges of Risperidone](#)
  19. [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](#)
  20. [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](#)
  21. [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](#)
  22. [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](#)
  23. [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](#)
  24. [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](#)
  25. [NCT00236470 - Risperidone in the Treatment of Children and Adolescents With Conduct and Other Disruptive Behavior Disorders - an Open Label Follow-up Trial of CR002020](#)
  26. [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](#)
  27. [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](#)
  28. [Multiple NCT#s - OPTICS Trial Bundle](#)
  29. [NCT00249132 - A Canadian multicenter placebo-controlled study of fixed doses of risperidone and haloperidol in the treatment of chronic schizophrenic patients](#)
  30. [NCT00216476 - CONSTATRE: Risperdal® Consta® Trial of Relapse Prevention and Effectiveness](#)
  31. [NCT00216580 - An Open-label Trial of Risperidone Long-acting Injectable in the Treatment of Subjects With Recent Onset Psychosis](#)
  32. [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.](#)
  33. [NCT00378092 - A Prospective Study of the Clinical Outcome Following Treatment Discontinuation After Remission in First-Episode Schizophrenia](#)
  34. [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](#)
  35. [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](#)
  36. [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](#)
  37. [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 T](#)
  38. [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](#)
  39. [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.](#)

40. [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](#)
41. [NCT00078039 - Trial Evaluating Three Fixed Dosages of Paliperidone Extended-Release \(ER\) Tablets and Olanzapine in the Treatment of Patients With Schizophrenia](#)
42. [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](#)
43. [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](#)
44. [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](#)
45. [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](#)
46. [NCT00088075 - A Randomized, Double-Blind, Placebo-Controlled Clinical Study of the Efficacy and Safety of Risperidone for the Treatment of Schizophrenia in Adolescents](#)
47. [Risperidone versus haloperidol versus placebo in the treatment of schizophrenia](#)
48. [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](#)
49. [NCT00253136 - Risperidone Depot \(Microspheres\) vs. Placebo in the Treatment of Subjects With Schizophrenia](#)
50. [A double-blind, placebo-controlled study of risperidone in children and adolescents with autistic disorder](#)
51. [NCT00257075 - The Efficacy And Safety Of Flexible Dosage Ranges Of Risperidone Versus Placebo In The Treatment Of Manic Episodes Associated With Bipolar I Disorder](#)
52. [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](#)
53. [The safety and efficacy of risperidone 8 mg qd and 4 mg qd compared to placebo in the treatment of schizophrenia](#)
54. [NCT01529515 - A Randomized, Multicenter, Double-Blind, Relapse Prevention Study of Paliperidone Palmitate 3 Month Formulation for the Treatment of Subjects With Schizophrenia](#)
55. [NCT01193153 - A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study of Paliperidone Palmitate Evaluating Time to Relapse in Subjects With Schizoaffective Disorder](#)
56. [NCT01662310 - Paliperidone Extended Release Tablets for the Prevention of Relapse in Subjects With Schizophrenia: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study](#)
57. [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](#)
58. [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](#)
59. [NCT00105326 - A Double-blind, Placebo-controlled, Randomized Study Evaluating the Effect of Paliperidone ER Compared With Placebo on Sleep Architecture in Subjects With Schizophrenia](#)
60. [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](#)
61. [NCT00246246 - A Randomized, Open-label Trial of RISPERDAL® CONSTA™ Versus Oral Antipsychotic Care in Subjects With Bipolar Disorder](#)

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

## Research Proposal

### Project Title

Discontinuation symptoms in antipsychotics: Individual patient level analyses of randomized controlled trials

### Narrative Summary:

Avoiding the recurrence of major symptoms and rebound phenomena after discontinuation or switching of antipsychotics is a key factor when planning a safe and successful therapy. Rebound phenomena and recurrence of major symptoms like psychotic or manic symptoms or disruptive behaviour are among the known risks when discontinuing antipsychotics but the systematic evaluation have been scarcely studied<sup>1</sup>.

We intend to assess the complete spectrum of discontinuation symptoms in patients with schizophrenia, schizoaffective disorder, bipolar disorder and children with disruptive behaviour disorders treated with antipsychotics in the placebo group of randomized controlled trials.

### **Scientific Abstract:**

**Background:** Antipsychotics are mainly used in the treatment of schizophrenia and other mental disorders, such as bipolar disorder or disruptive behaviour disorders (main indication for antipsychotics in children<sup>2</sup>). 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<sup>1,3</sup>.

**Objective:** Our goal is to systematically assess the full range of 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.

**Participants:** Schizophrenia, bipolar disorder, schizoaffective disorder and children with disruptive behaviour disorders.

**Main outcome measure:** Our main outcome measure will be total AEs and recurrence of major symptoms (psychotic or manic symptoms or disruptive behaviour) in two placebo subgroups. 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.

**Statistical analysis:** The relationship between T0 and T1 scores for the two placebo subgroups will be examined with a mixed model of repeated measures and Kaplan-Meier estimator.

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

Antipsychotic drugs are a heterogeneous group of compounds with a wide range of receptor affinities and diverse functional effects<sup>4</sup>. These substances may cause a variety of side effects in patients<sup>5</sup>. Therefore, providing the appropriate antipsychotic substance is a complex process<sup>1</sup>. The process frequently includes discontinuation and switching of compounds and may be accompanied or even initiated by AEs comprising cholinergic, dopaminergic, serotonergic, histaminergic and adrenergic rebound phenomena<sup>3</sup>. During switching, AEs may be caused by the current drug but could also be related to the cessation of a prior drug. Differentiating the cause for the AEs requires knowledge of the discontinuation symptoms caused by the specific compound. Additionally, there is a large number of patients who show poor adherence of antipsychotic substances especially during stable phases of illness or at the beginning of relapse (e.g. 43% of schizophrenic patients had at least one year of poor adherence over four years)<sup>6</sup>. Therapeutic strategies and treatment adherence could be significantly optimized if clinicians and patients were well

informed about potential discontinuation symptoms. This study could have a major impact on health of patients as systematic analyses of discontinuation symptoms in antipsychotics could help to identify discontinuation symptoms and may help to promote the development of innovative therapeutic strategies and guidelines in this field. This would have very practical implications for the individual patient as rapid discontinuation of an antipsychotic without professional supervision is very frequent in clinical routine<sup>7</sup>. The importance of this study is highlighted by the lack of systematic assessment of discontinuation symptoms in RCTs after rapid and complete discontinuation of antipsychotic treatment<sup>1</sup>. This study will be a first step to implement further research into which factors are predictive for occurrence of discontinuation symptoms in an individual and in long term develop treatment strategies for discontinuation syndromes.

### **Specific Aims of the Project:**

Primary objective:

a. Evaluate whether discontinuation symptoms occur after rapid discontinuation of the prestudy antipsychotic.

Secondary objectives:

- b. Evaluate whether discontinuation symptoms are linked to the type of discontinued antipsychotic (e.g. olanzapine, amisulpride, risperidone, etc.)
- c. Evaluate whether discontinuation symptoms can be predicted by specific receptor affinities ( $K_i$  values) of the discontinued antipsychotic<sup>3</sup>.
- d. Evaluate whether discontinuation symptoms can be differentiated from early recurrence of major symptoms (i.e. are certain AEs especially predictive before recurrence of psychotic or manic symptoms or disruptive behaviour?)

Primary endpoint:

- a. Total AE rate and recurrence of major symptoms (psychotic or manic symptoms or disruptive behaviour).

Secondary endpoints:

- b. Association between type of discontinued antipsychotic and AE rates and recurrence of major symptoms respectively.
- c. Interdependence network<sup>8</sup> between receptor affinities and AE rates and recurrence of major symptoms respectively.
- d. Most predictive AEs before recurrence of major symptoms.

**What is the purpose of the analysis being proposed? Please select all that apply.**

Confirm or validate previously conducted research on treatment safety  
Participant-level data meta-analysis  
Participant-level data meta-analysis using only data from YODA Project

## Research Methods

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

We will merge data from the placebo groups in RCTs on antipsychotic treatment of patients with schizophrenia, bipolar disorder and schizoaffective disorder. Children with disruptive behaviour disorders will be included in the analysis as a separate group to investigate discontinuation symptoms in children<sup>9</sup>.

For oral antipsychotics, the placebo group will be divided into two subgroups:

- A. Target group: Patients who have just stopped taking the antipsychotic no longer than 3 days before entering the placebo group will be compared with B.
- B. Control group: All patients who have not been taking medication for more than 1 month before entering the placebo group.

For long-acting injectable antipsychotics, the placebo group will also be divided into two subgroups:

- C. Target group: Patients who should have had their last scheduled injection no longer than 1 week before entering the placebo group will be compared with D.
- D. Control group: Patients who have not been receiving long-acting injectables in the last 3 months (and no oral antipsychotic for more than 1 month) before entering the placebo group.

Primary target: total AE rate during the first 12 weeks.

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

For oral application, the main outcome is change in the total AE rate and recurrence of major symptoms (psychotic or manic symptoms or disruptive behaviour) from baseline (T0) to four weeks (T1). All assessment time points in this timeframe will be included (i.e. the primary target is total AE rate and recurrence of major symptoms during the first 4 weeks).

For long-acting injectables, the main outcome is change in the total AE rate and recurrence of major symptoms from baseline (T0) to twelve weeks (T1). All assessment time points in this timeframe will be included (i.e. the primary target is total AE rate and recurrence of major symptoms during the first twelve weeks).

Oral and long-acting injectable antipsychotics will be calculated separately. All detected AEs will be included in the

analyses. General AEs (e.g. vegetative dysregulation) and recurrence of psychotic or manic symptoms or disruptive behaviour will be calculated separately.

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

The main predictor will allow us to investigate the relationship between antipsychotic treatment (substance taken before entering the placebo group) and discontinuation symptoms. The main predictor is the rapid discontinuation of an oral or long-acting injectable antipsychotic.

Rapid discontinuation of the oral application will be defined as discontinuation less than three days before entering the placebo group<sup>10</sup>.

Rapid discontinuation of a long-acting injectable application will be defined as the next scheduled injection less than one week before entering the placebo group (e.g. 28 days after a four week depot antipsychotic)<sup>11</sup>.

These two groups will be compared to patients in the placebo group without rapid discontinuation of antipsychotics as described in the previous section "Data Source and Inclusion Criteria to be used to define the patient sample for your study".

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

We will include additional variables/characteristics associated with occurrence of AEs and examine them for their possible confounding effect including age, sex, weight, duration and dose of antipsychotic application, previous medication, measures of psychopathology (PANSS/YMRS/Conduct Problem Subscale/etc.), duration of illness, duration of untreated psychosis, number of hospitalizations, etc. The Ki values were previously summarized (summary by Correll, p. 15, table 2)<sup>3</sup> and will be implemented according to this study. Receptor types and corresponding rebound syndromes were also defined (definition by Correll, p. 18, table 3)<sup>3</sup> and these definitions will be used in our study. The number needed to harm (NNH) and network analysis<sup>8</sup> of receptor affinities will be calculated separately for both types of application (oral and long-acting injectable).

**Statistical Analysis Plan:**

A mixed model of repeated measures (MMRM) and Kaplan-Meier estimator will be used to investigate the relationship between rapid discontinuation of an antipsychotic and the total AE rate and recurrence of major symptoms (psychotic or manic symptoms or disruptive behaviour) in an individual participant data meta-analysis. Baseline score (T0) of AE rates will be determined at the time when the participant is included in the study and the post-baseline score (T1) is determined at the last time point of the included timeline. Recurrence of psychotic or manic symptoms or disruptive behaviour will be determined between T0 and T1 (measured as change in score PANSS/YMRS/Conduct Problem Subscale/etc.) The within-subject factor is "time" and the between-subjects factor is "rapid discontinuation of an antipsychotic" (Yes/No) and the model will be tested adjusted and unadjusted for confounders (e.g. age, sex, duration of application, etc.).

The relationship between type of antipsychotic and the AE rates and recurrence of major symptoms will be assessed with multinomial logistic regression. The relationship between Ki values and the AE rate of the corresponding rebound syndrome and recurrence of major symptoms will be investigated with network analysis<sup>8</sup> and ordinal logistic regression. Ki values will be treated as independent variables and the AE rate of the corresponding rebound syndrome and recurrence of major symptoms as dependent variable. The potential predictive value of an AE for a consecutive psychotic relapse will be investigated with multinomial logistic regression.

Missing data will be treated as recommended by Little et al.<sup>12</sup> We will register if reasons for missing data were documented and develop a primary set of assumptions about the cause for missing data<sup>12</sup>. The primary set of assumptions will be followed by a matching statistically valid analysis (e.g. estimating-equation methods) and robustness tested with a sensitivity analysis<sup>12</sup>.

**Project Timeline:**

Immediately after the data is available the project will start and the study plan will be published online (8/2017). The analysis will be completed six months later (2/2018). The manuscript will be drafted and submitted after four months (06/2018). The publication is planned for 08/2018. The YODA project will be informed about the completion of each milestone and reports will be made available.

**Dissemination Plan:**

To benefit both health professionals and patients we will present the study at internationally accredited conferences (e.g. symposia at the WPA) and make the study available in major medical journals (e.g. JAMA Psychiatry, American Journal of Psychiatry, Lancet Psychiatry). Based on our results we will develop and validate a questionnaire to assess the risk of discontinuation symptoms. Patients will be directly affected as national and international treatment guidelines will be influenced.

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