

## Principal Investigator

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### General Information

**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):** [NCT00216580 - An Open-label Trial of Risperidone Long-acting Injectable in the Treatment of Subjects With Recent Onset Psychosis](#)  
[NCT00378092 - A Prospective Study of the Clinical Outcome Following Treatment Discontinuation After Remission in First-Episode Schizophrenia](#)

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

### Research Proposal

#### Project Title

Investigating the construct validity of supersensitivity psychosis: An analysis of data from two antipsychotic discontinuation studies

#### Narrative Summary:

This study aims to investigate whether the entity of “supersensitivity psychosis” could contribute to the very high rates of relapse that have been observed when antipsychotic treatment is discontinued. We plan to combine the

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data from two studies in which patients who were treated for two years for a first-episode of psychosis underwent treatment discontinuation. Patients who experienced early symptom recurrence (<12 weeks) after discontinuation will be compared to those who experienced later symptom recurrence (>12 weeks). The relapse episode will also be compared to the first psychotic episode and the post-relapse treatment response, for the two groups.

**Scientific Abstract:****Background**

It has been suggested that high relapse rates after antipsychotic treatment discontinuation could be explained on the basis of "supersensitivity psychosis" (SSP). However, while diagnostic criteria have been proposed the construct validity of SSP has never been tested.

**Objective**

This study aims to investigate whether SSP could contribute to the high rates of symptom recurrence shortly after antipsychotic treatment discontinuation by comparing the nature of relapse events that occur soon after treatment discontinuation with those that occur later, as well as with previous psychotic episodes.

**Study Design**

Retrospective analysis of data from two studies in which patients were: 1) treated for at least 2 years for a first-episode of psychosis; 2) subsequently underwent treatment discontinuation and followed up until relapse; 3) underwent re-institution of the same treatment after the relapse-event and followed-up for a further 1 to two years.

**Participants**

Aged 16 to 45 years, meeting DSM-IV criteria for schizophrenia, schizophreniform or schizo-affective disorder.

**Main Outcome Measures**

Factor-analysis derived symptom domains will be compared between patients experiencing early relapse and later relapse, and between the first psychotic episode and the relapse episode

**Statistical Analysis**

Analyses will be conducted with the assistance of a biostatistician and will include descriptive statistics, factor analysis, univariate analyses and logistic regression analyses.

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

The effectiveness of antipsychotic medication for preventing relapse in schizophrenia is very well documented (Leucht et al.2012) and treatment discontinuation studies report extremely high rates of relapse, even after a single episode of psychosis (Zipursky et al.2014). For these reasons, long-term antipsychotic treatment has formed the foundation of maintenance treatment. However, recently concerns have been raised about possible harmful effects of long-term antipsychotic treatment (Moncrieff2015). In addition to the side-effect burden there are a few studies suggesting poorer outcome (Harrow et al.2012;Wunderink et al.2013) and greater loss of cerebral grey matter (Ho et al.2011) for patients who have had greater exposure to antipsychotic medication. These findings, together with those of a recent long-term study suggesting that a substantial number of patients stabilise and remain free of symptoms of psychosis without ongoing antipsychotic treatment (Morgan et al.2014), have reopened the debate on the need for maintenance antipsychotic treatment in schizophrenia. Based on these findings, Moncrieff proposes that the time has come to reconsider the need for long-term antipsychotic maintenance treatment in schizophrenia (Moncrieff2015).

It has been argued that antipsychotic withdrawal studies are fundamentally flawed and that symptom exacerbation may be caused by the process of drug withdrawal itself, rather than representing the course of the underlying illness (Moncrieff2006). The concept of neuroleptic-induced supersensitivity psychosis (SSP) was originally introduced by Chouinard (Chouinard et al.1978). According to the hypothesis, SSP is similar to tardive dyskinesia insofar as it is thought to be caused by alteration of dopamine receptors secondary to prolonged neuroleptic blockade. It has been proposed that receptor changes in the dopaminergic pathways of the mesolimbic or other non-striatal dopaminergic regions of the brain could explain the disorder in the same way that changes in the neostriatum are thought to be responsible for tardive dyskinesia (Davis and Rosenberg1979).

While the validity of SSP has not been established as a diagnostic entity some researchers have conducted studies using the proposed criteria of Chouinard (Chouinard1991). For example, an association between abnormal involuntary movements and psychotic was reported in patients meeting SSP criteria (Fallon and Dursun2011), and a checklist derived from the Chouinard criteria applied to a patients experiencing a psychotic relapse reported the presence of SSP in 39% of patients (Fallon et al.2012). Also, SSP is proposed to be a cause of treatment-resistant schizophrenia (Kimura et al.2014;Suzuki et al.2015). However, the actual construct validity of SSP has not been tested.

Assumptions that SSP could explain the high relapse rates associated with treatment discontinuation have major

clinical complications. The present study proposes to investigate whether SSP could contribute to the high rates of symptom recurrence shortly after antipsychotic treatment discontinuation.

### Specific Aims of the Project:

Using the combined dataset we aim to:

1. Compare the clinical characteristics of the relapse episode of the patients who relapsed early (within 12 weeks of treatment discontinuation) with those of the patients who relapsed later (after 12 weeks of treatment discontinuation).

2. Compare the clinical characteristics of the first psychotic episode with that of the relapse episode.

Research questions:

1. Can the very high rates of relapse shortly after antipsychotic treatment discontinuation be explained on the basis of phenomena such as SSP related to the process of drug withdrawal itself, rather than recurrence of the underlying illness?

2. And if so, can the condition be distinguished from illness recurrence on the basis of symptomatology?

**What is the purpose of the analysis being proposed? Please select all that apply.** New research question to examine treatment effectiveness on secondary endpoints and/or within subgroup populations  
New research question to examine treatment safety

## Research Methods

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

We will analyse the combined datasets of two studies we conducted. The first had two components – a 2yr outcome study (Emsley et al.2008) in 50 patients (NCT00216580), and an extension (Emsley et al.2012) in which 31 patients underwent discontinuation (NCT00378092). We are applying to YODA to use the full datasets for these two studies.

(The second study involves patients who were treated with flupenthixol decanoate for 2yrs (Chiliza et al.2014) and an extension (Emsley et al.2014) in which 33 patients underwent discontinuation. These data are in our possession.)

According to the proposed criteria (Chouinard et al.1978;Fallon et al.2012;Moncrieff2015) SSP should be characterised by:

- Rapid relapse shortly after antipsychotic discontinuation (<12wks for depot antipsychotics)
- Symptom expression of the relapse episode should differ from the first episode
- Greater frequency of dyskinesia
- High levels of serum prolactin
- Tolerance, with higher doses of antipsychotics required
- Emergent refractoriness

Groups to be compared:

1. Early Relapse Group (<12wks) vs. Late Relapse Group
2. Early Relapse Group relapse episode vs. Early Relapse Group first episode

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

The main outcome measure will be early relapse vs. later relapse. This will be defined as <12weeks after discontinuation and ? 12 weeks after discontinuation.

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

Symptom expression, defined according to the Positive and Negative Syndrome Scale (PANSS) factor-analysis derived symptom domains of positive, negative, disorganised, excitement/hostility and depression/ anxiety (Emsley et al.2003).

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

1. Demographics (age, sex, ethnicity, age of onset of illness)
2. Clinical Global Impression Severity (CGI-S)
3. Social and Occupational Functioning Assessment Scale (SOFAS) (DSM-IV)
4. Calgary Depression Scale for Schizophrenia (CDSS)
5. Extrapyramidal Symptoms Rating Scale (ESRS) total and subscales for dyskinesia and parkinsonism

**Statistical Analysis Plan:**

Analyses will be conducted with the assistance of a biostatistician and will include descriptive statistics; factor analysis (using varimax rotation and selection of factors by eigenvalues greater than one, scree plot inspection, and forced five-factor models); depending on the nature of the data, parametric or no-parametric statistics will be used to compare continuous and categorical variables between the groups; backward step-wise logistic regression will be conducted with early/late relapse as the dependent variable and selection of predictors according to the univariate analyses. Treatment response will be compared between the groups by linear mixed-effect models for repeated measures.

The study will be limited by its small sample size. However, the strength of the study lies in the uniqueness of this dataset which enables us address the research question. To our knowledge no other datasets exist in which first-episode patients were treated according to standard protocols, followed by treatment discontinuation, and were subsequently treated and assessed for the second (relapse) episode.

**Project Timeline:**

Projected start date: February 2016

Completion of analysis: July 2016

Manuscript completion: Dec 2016

**Dissemination Plan:**

Scientific publication(s); presentation at scientific meetings

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