

## Principal Investigator

**First Name:** Mark  
**Last Name:** Weiser  
**Degree:** MD  
**Primary Affiliation:** Sheba Medical Center, Psychiatry Dep.  
**E-mail:** [mweiser@netvision.net.il](mailto:mweiser@netvision.net.il)  
**Phone number:** +97235303773  
**Address:** Tel Hashomer

**City:** Ramat Gan  
**State or Province:** Ramat Gan  
**Zip or Postal Code:** 52561  
**Country:** Hamerkaz

## General Information

### Key Personnel (in addition to PI):

**First Name:** Daphna  
**Last name:** Fenchel  
**Degree:** MSc  
**Primary Affiliation:** Sheba Medical Center, Psychiatry Dep.  
**SCOPUS ID:**

**First Name:** John  
**Last name:** Davis  
**Degree:** MD  
**Primary Affiliation:** Psychiatric Institute, University of Illinois at Chicago; Maryland Psychiatric Research Center  
**SCOPUS ID:**

**First Name:** Daisy  
**Last name:** Zamora  
**Degree:** PhD  
**Primary Affiliation:** Department of Psychiatry, University of North Carolina-Chapel Hill  
**SCOPUS ID:**

**First Name:** Jinyoung  
**Last name:** Park  
**Degree:** MA  
**Primary Affiliation:** UNC  
**SCOPUS ID:**

**First Name:** Keturah  
**Last name:** Faurot  
**Degree:** PA, MPH, PhD  
**Primary Affiliation:** UNC  
**SCOPUS ID:**

**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?:** Conference

## Conflict of Interest

<http://yoda.yale.edu/system/files/photograph34.pdf>  
<http://yoda.yale.edu/system/files/png2pdf.pdf>  
[http://yoda.yale.edu/system/files/coi\\_2017-1521\\_zamora.pdf](http://yoda.yale.edu/system/files/coi_2017-1521_zamora.pdf)  
[http://yoda.yale.edu/system/files/coi\\_2017-1521\\_davis.pdf](http://yoda.yale.edu/system/files/coi_2017-1521_davis.pdf)  
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[http://yoda.yale.edu/system/files/yoda\\_project\\_coi\\_form\\_for\\_data\\_requestors\\_2017\\_jin\\_0.pdf](http://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_2017_jin_0.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):

1. [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](#)
2. [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](#)
3. [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](#)
4. [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](#)
5. [NCT00378092 - A Prospective Study of the Clinical Outcome Following Treatment Discontinuation After Remission in First-Episode Schizophrenia](#)
6. [NCT01529515 - A Randomized, Multicenter, Double-Blind, Relapse Prevention Study of Paliperidone Palmitate 3 Month Formulation for the Treatment of Subjects With Schizophrenia](#)
7. [NCT01193153 - A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study of Paliperidone Palmitate Evaluating Time to Relapse in Subjects With Schizoaffective Disorder](#)
8. [NCT01662310 - Paliperidone Extended Release Tablets for the Prevention of Relapse in Subjects With Schizophrenia: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study](#)
9. [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 With](#)

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

## Research Proposal

### Project Title

Predictors of Relapse following Maintenance Treatment of Antipsychotic Drug or Placebo in patients with SCZ, schizoaffective disorder and BPD

### Narrative Summary:

Many patients with schizophrenia and bipolar disorder receive ongoing maintenance drug treatment, however, the dose necessary for maintenance is not always clear, and it is conceivable that a sub-set of patients can have maintenance doses lowered or even discontinued. The aims of this proposal are 1) to establish a dose-response curve for antipsychotic drug treatment in relapse prevention 2) to identify characteristics of patients who were allocated to drug or placebo in maintenance antipsychotic RCTs, who did or did not relapse during the follow-up

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period.

### **Scientific Abstract:**

**Background:** Many patients with schizophrenia or bipolar disorder relapse despite maintenance medication. Although treatment guidelines suggest administering antipsychotics indefinitely to patients who had two or more exacerbations, the optimal treatment dose for stabilized patients is unknown. Moreover, several recent studies indicate that some patients might do reasonably well in the long run without maintenance treatment, and placebo controlled maintenance trials indicate that a significant proportion of patients remain in remission for many months or more while on placebo.

**Objective:** To utilize data from J&J maintenance trials of Risperidone and Paliperidone (oral and LAI) to identify dose-response curves for antipsychotic treatment in non-acute patients with schizophrenia or bipolar disorder, and to identify baseline characteristics of patients who received placebo and did or did not relapse on medication.

**Participants:** Patients diagnosed with schizophrenia, schizoaffective disorder and bipolar disorder who participated in J&J antipsychotic maintenance trials.

**Study Design:** We will utilize data from patients who received placebo or study medication in nine clinical trials.

**Main Outcome Measure:** "recurrence of symptoms/episode/exacerbation" or "no relapse".

**Statistical Analysis:** Analyses will be performed for each trial separately, and then pooled by disorder and by antipsychotic drug. Analyses will mainly use Cox models to examine predictors of the relapse rate and the dose response curve.

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

An overview of available treatment guidelines would suggest administering psychoactive treatment indefinitely to patients with schizophrenia (Buchanan et al., 2010) or bipolar disorder (Grunze et al., 2004) who had several exacerbations. While maintenance treatment prevents many exacerbations in comparison to placebo, some patients relapse despite antipsychotic prophylaxis, while others fail to relapse on placebo. We propose to explore whether antipsychotic dose, and demographic and illness characteristics at baseline may be associated with relapses on medication and/or failure to relapse on placebo.

**Aim 1.** While some information is available on the dose-response curve of antipsychotics given for the treatment of an acute episode, very little is known about the dose-response relationship when antipsychotics are used to prevent relapse. If too low a dose is used a patient may not achieve as much protection for relapse as could be achieved with a higher dose when receiving maintenance treatment, whereas a dose above the threshold for optimal response would cause unnecessary side effects. Maintenance dose is often based on acute dose, but opinion differs widely. Some advocate that dose be reduced substantially for maintenance, but others suggest that the maintenance dose should be the same as the acute dose. We will determine the dose-response relationship for maintenance for oral and LAI risperidone and paliperidone available from YODA.

**Aim 2.** We will explore where early relapses are associated with background variables, e.g., severity of disease at baseline and frequency of past relapses, as special support could be given to patients predicted to relapse early.

**Aim 3.** It is conceivable over time that there might be changes in the course of the illness (Harvey & Davidson, 2002) which will allow some patients to stop medication. We will identify characteristics that predict which patients do not relapse on placebo. Several studies indicate that some patients might do reasonably well in the long run without maintenance treatment, suggesting that discontinuation of antipsychotics was associated with better outcome (Harrow et al., 2014, Wunderink et al., 2013). Also, it has been suggested that patients who were allocated to placebo and were classified as relapsing, were actually experiencing withdrawal symptoms from antipsychotics, and not an actual psychotic episode (Moncrieff, 2015). In addition, placebo-controlled maintenance trials indicate that a proportion of patients remain in remission for a year or more while on placebo (Berwaerts et al., 2015, Fu et al., 2014). Antipsychotic treatment is associated with serious side effects (e.g., weight gain, diabetes, sexual dysfunction, extrapyramidal symptoms, sudden cardiac death), hence it is important to identify patients who might benefit from discontinuation of antipsychotic treatment. By identifying baseline demographic and clinical characteristics of patients who received placebo for extended periods of time and did not relapse, we will attempt to build an algorithm to predict which patients might do well without indefinite antipsychotic medication, or who might relapse early.

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

We will determine the dose-response relationship of risperidone and paliperidone compared with placebo on the

rate of relapse of patients with schizophrenia and bipolar disorder in the maintenance trials.

The second aim of this project is to attempt to recognize which patients relapse despite maintenance medication; or (aim 3) which patients (on placebo) will not relapse when discontinued from antipsychotic treatment. We hypothesize that patients with fewer hospital admissions, with no recent hospitalization, with longer duration of illness, with fewer positive and more negative symptoms (in patients with schizophrenia), less manic symptoms (in patients with bipolar and schizoaffective disorders), and good family or caregiver support would be less likely to relapse on drug or will be more likely to stay remitted when antipsychotic drugs are discontinued. It has been suggested that some patients classified as relapsed might actually have experienced withdrawal symptoms from antipsychotics. We will examine differences in symptomatology in patients who relapsed soon after initiation of placebo maintenance treatment, hence might be considered as having withdrawal symptoms, and in patients who relapsed late during maintenance treatment, which might be considered "true" relapses.

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

Preliminary research to be used as part of a grant proposal  
Participant-level data meta-analysis  
Participant-level data meta-analysis uses only data from YODA Project  
Other

## **Research Methods**

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

Our focus is on the maintenance studies for all three aims. We will utilize data from patients who received study medication or placebo in J&J antipsychotic maintenance trials with schizophrenia (NCTs 01529515, 0086320 , 00111189, 01662310, 00378092), schizoaffective disorder (NCT 01193153), and bipolar disorder (NCTs 00490971, 00132678, 00391222). This analysis will be on individual participant data only from YODA. We have previous experience in analyzing pooled individual datasets (Davis, 1974, 1975, 1976; Davis & Chen, 2004; Gibbons et al., 2012; Marder et al., 1997).

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

The main outcome measure in this study will be the intent to treat "recurrence of symptoms/episode/exacerbation" or "no relapse" according to the term used by the authors of the publication on the specific clinical trial. In our analyses, we will consider the different criteria used in each study for recurrence or relapse. We will model both the time to relapse and also the rate of relapse over different periods of time.

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

Independent variables included (where available)

- Treatment dose
- Demographics: age, gender, marital status
- Illness duration: age of onset, age of first antipsychotic use, duration of untreated psychosis
- Concomitant medications: yes/no, type of medication (antidepressants, mood stabilizers, anti EPS-drugs, etc.)
- Prior hospitalizations: number, frequency of relapse, time from last discharge
- Diagnostic subtype (categorical)
- Double-blind phase baseline symptoms:
  - ? PANSS: positive symptoms score, negative symptoms score and total score
  - ? YMRS total score
  - ? MADRS/HDRS-21 scores
  - ? CGI score
- Antipsychotic use prior to beginning of trial: number of previous drug switches, dosage of last antipsychotic used prior to trial
- Presence of permanent caregiver/support
- Symptom presentation at relapse
- Plasma levels

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

Type of medication used (long lasting injection or oral treatment) will be examined separately in light of different pharmacokinetics. Slower clearance of LAIs from the body might influence relapse rates and characteristics. We

hypothesize that if there were withdrawal symptoms, there might be (1) a transitory increase in psychotic or other symptoms as measured by the PANSS/YMRS in the first month following the discontinuation of oral medication in comparison to these relapses per unit time observed at later months and (2) an increase in the relapse rate in the first month after discontinuation of oral medication compared to increase in relapse after discontinuation of depot medication. We would take into account the pharmacokinetics data in our modeling of the relapse rates at different periods of time.

### **Statistical Analysis Plan:**

Analyses will be performed for each trial separately, and then pooled by disorder (schizophrenia, schizoaffective disorder and bipolar disorder) and by type of antipsychotic drug (paliperidone ER, paliperidone 1M, paliperidone 3M, oral Risperdal, Risperdal Consta).

Dose response:

We will use Cox models to calculate the time to relapse of placebo of three different drug doses in the various formulations. We will then compare the dose response curves to determine the dose that best prevents relapse.

Predictors of relapse:

We will use Cox modeling to evaluate the effect of baseline variables on time to relapse. We will randomly split each study into two groups, identify predictors in the first group, and test their accuracy in the second group. We will identify patients who relapse faster despite drug treatment. We will examine rate of relapse in the placebo arms and if the rate of relapse slows down in certain subgroups, this might help identify characteristics of people who might not relapse without treatment.

Are there withdrawal symptoms from antipsychotics?

Moncrieff (2015) hypothesizes that there is an antipsychotic withdrawal syndrome characterized by psychotic symptoms which is mischaracterized as a relapse of disease. If true, there should be an exacerbation of psychotic symptoms following discontinuation of oral medication, in the first month versus in comparison to that observed over the next 5 months. This can be tested by comparing exacerbation of PANSS/YMRS total scores (or individual items) during the first month after discontinuing oral medication, in comparison to that observed after discontinuation of depot formulations.

### **Project Timeline:**

Anticipated project start date: Immediate with approval of project and granted with desired data.

Analysis completion date: 6 months from start date.

Date manuscript drafted and first submitted for publication: 9 months from analysis completion.

Date results reported back to the YODA Project: 9 months from analysis completion.

### **Dissemination Plan:**

The results of this project as well as the results of the planned future clinical trial might provide preliminary information to guide clinicians in dosing during the maintenance phase of schizophrenia or bipolar disorder, and on decisions to continue or discontinue antipsychotic drug treatment after achieving stabilization. We expect at least one study manuscript stemming from this project and deem "The American Journal of Psychiatry" as a suitable journal for publication.

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