

INVESTIGATOR INITIATED RESEARCH PROTOCOL

Study Title: Effects of Risperdal Consta versus oral antipsychotic medication on clinical and functional outcome and neurocognition in first-episode schizophrenia

Principal Investigator:

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Primary Institutional Affiliation (if applicable):

Department of Psychiatry and Biobehavioral Sciences, UCLA Neuropsychiatric Institute

Type of Institution:

Medical School Veteran's Administration Facility Private Practice
 Community Hospital Specialty Clinic Other

Site where study will be conducted:

UCLA Aftercare Research Program
UCLA Department of Psychiatry and Biobehavioral Sciences
300 UCLA Medical Plaza
Los Angeles, CA 90095-6869

Institutional Review Board (name, address, contact person):

UCLA Medical IRB #3
Office of the Human Research Protection Program
11000 Kinross Avenue, Suite 211
Box 951694
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Type of Study (check all that apply):

Prospective Retrospective In-vitro Animal
 Efficacy/Safety Clinical Pharmacy (pk) Outcomes/Health Economics

Study Objective:

To determine if Risperdal Consta shows advantages over oral antipsychotic medication (oral Risperdal) in reducing symptom severity, neurocognitive deficits, and side effects and improving medication compliance and functional outcome in outpatients who have recently experienced a first episode of schizophrenia.

Study Design (check all that apply):

Parallel Crossover Open Label Single Blind Double Blind

Lead in period? None Placebo Previous Drug

Controls? None Active Drug Placebo Active and Placebo

Extension phase? No Yes (if yes, blinded open 6 months length)

Single site? **X** Multiple Sites? _____ (List total number) _____

Planned Enrollment: 150
Total Number per arm: 55 (Oral)/55 (Consta)
Number of arms: 2

Length of enrollment period: 1 year after lead-in **Total expected duration of study:** 6 years

Study Subjects: _____ **Normal volunteers** **X** **Outpatients** _____ **Inpatients**

150 **Sample Size** **Age Range** (years, inclusive): 18-45

Will this study be conducted within the approved FDA labeling for Risperdal: **X** **Yes** **No**

Type of Publication: Abstract/Poster (Y/N): **Y** **N** Specify meeting(s): International Congress on Schizophrenia Research
Manuscript (Y/N): **Y** **N** Specify journal: plan to submit paper to the *Archives of General Psychiatry* or the *American Journal of Psychiatry*.

INVESTIGATOR INITIATED RESEARCH PROTOCOL

Project title: Effects of Risperdal Consta versus oral antipsychotic medication on clinical and functional outcome and neurocognition in first-episode schizophrenia

Summary:

The primary objective of this research project will be to determine if there is an advantage of Risperdal Consta over oral antipsychotic medication on selected aspects of clinical and functional outcome and on specific measures of neurocognition, social cognition, and emotion processing during the early course of schizophrenia. The target population is schizophrenia patients who have had a recent first episode of the disorder. Patients will receive treatment and assessments at the UCLA Aftercare Research Program as part of their participation in the NIMH-funded UCLA Center for Neurocognition and Emotion in Schizophrenia. This study will use a randomized design, wherein the first-episode schizophrenia outpatients will be randomly assigned to either the Risperdal Consta or oral Risperdal treatment condition and subsequently followed for 12 months after randomization. The randomization will follow a two-month period of medication stabilization that includes up to six weeks of cross-tapering to oral Risperdal (if the patient is not already on Risperdal), two weeks of baseline treatment with oral Risperdal as the sole antipsychotic medication, and then baseline assessments. Oral medication adherence will be carefully monitored using a number of sources of information, including MEMS caps (pill bottle caps with electronic detection of bottle opening and time/date recording of each opening), risperidone and 9-hydroxyrisperidone plasma concentration assays, pill counts, patient self-reports, collateral information from family members, and clinician judgment. Well-established operational criteria for medication nonadherence will be utilized.

1. Objectives and Hypotheses:

The primary objective of this research grant will be to determine if there is an advantage of Risperdal Consta over oral Risperdal on selected dimensions of clinical and functional outcome and on specific measures of neurocognition and emotion processing during the early course of schizophrenia. Patients will receive treatment and assessments at the UCLA Aftercare Research Program as part of their participation in the NIMH-funded UCLA Center for Neurocognition and Emotion in Schizophrenia. Risperdal will be the standard initial antipsychotic medication prescribed to all Aftercare Research Program patients.

For this investigator initiated research proposal, we propose to examine the following **Specific Aims** that are directly relevant to the comparison of oral Risperdal and Risperdal Consta:

To determine, in recent-onset schizophrenia patients, the impact on schizophrenic symptoms and work outcome of increasing medication adherence through use of an injectable, long-acting second generation antipsychotic medication, as compared to an oral form of the same medication.

- a. To determine the extent to which psychotic relapse rates are reduced.
- b. To determine the extent to which medication adherence is increased.
- c. To determine whether fewer psychotic relapses and better symptom control leads to improved work outcome.
- d. To determine whether functioning on measures of neurocognitive and emotion processing is better on the injectable than on the oral form of Risperdal.
- e. To determine whether the combination of increased medication adherence and cognitive remediation leads to even better cognitive performance and work outcome.

2. Study Design:

To establish a common baseline assessment point, all patients will be 1) cross-tapered from their initial antipsychotic medication to oral Risperdal over a six week period, if their antipsychotic medication is not already oral Risperdal, 2) then placed on oral Risperdal as the sole antipsychotic medication for 2 weeks, and 3) assessed with the baseline battery. The study will use a randomized design, wherein the first-episode schizophrenia outpatients will then be randomly assigned to either the oral Risperdal or Risperdal Consta treatment condition following an initial stabilization period and then followed for 12 months following stabilization. All patients will also be randomly assigned to either Cognitive Remediation or Healthy Behavior Training at the stabilization point, in a fully crossed 2 X 2 research design.

3. Subject Population:

The target population is schizophrenia patients who have had a recent first-episode of the disorder. The patients are participants in the Aftercare Research Program, which is an outpatient research clinic at the UCLA Neuropsychiatric Institute that serves as the clinical site for all studies of first-episode schizophrenia patients that are part of the Translational Research Center for Behavioral Science, entitled the “Center for Neurocognition and Emotion in Schizophrenia”. The Aftercare Research Program will be responsible for the recruitment, clinical interventions, and assessments of symptoms and functional outcome for first-episode patients who are participating in research projects in this Center. Eligible participants will be between 18 and 45 years of age, have a DSM-IV diagnosis of schizophrenia, schizoaffective disorder, mainly depressed type, or schizophreniform disorder, with an onset of psychosis within the last 2 years. Patients for whom treatment with Risperdal is clinically contraindicated (e.g., have had a previous trial of Risperdal with an adequate dosage and duration but did not show an adequate clinical response, or for whom the side effects of Risperdal were clearly intolerable) will be excluded.

4. Study Procedures:

First-episode schizophrenia participants will be provided antipsychotic medication and offered individual case management, group social skills and life skills training, and family education in the Aftercare Research Program. At a typical clinic visit, Aftercare Program patients participate in skills training groups, have an individual medication and clinical evaluation by their psychiatrist, and see their individual case manager for treatment and assessments. At study entry, patients will initially be cross-tapered to oral Risperdal over a six-week period if they are not already on oral Risperdal, placed on oral Risperdal as the sole antipsychotic medication for at least 2 weeks, and then assessed to establish a standardized baseline point. Then they will be randomly assigned to either the oral Risperdal or Risperdal Consta treatment condition and to the Cognitive Remediation or Healthy Behavior Training condition.

For the oral Risperdal condition, a maintenance dosage will be established at a level that the Aftercare Research Program treating psychiatrist believes is appropriate for the individual patient, without a restriction in dosage range. The treating psychiatrist will titrate the dosage in the initial weeks on Risperdal as needed clinically to establish an optimal maintenance dose (typically the initial 8-10 weeks in the Aftercare Research Program). Thus, the dosage of Risperdal that is selected by the treating psychiatrists in the Aftercare Research Program is not dictated by a research protocol, but rather by the psychiatrist’s judgment about the clinically optimal maintenance dosage for individual patients.

Patients randomized into the injectable Risperdal condition will already have had at least a two-week period on oral Risperdal in which any immediate hypersensitivity or some other severe adverse reaction to Risperdal can be detected prior to the injection of the long-acting form

of the drug. Patients with a hypersensitivity to Risperdal during this lead-in period will not be entered into the randomized treatment phase of the protocol. Following the lead-in period, patients in the injectable Risperdal group will receive an injection of 25 mg open label long-acting Risperdal. The choice of initial dosage level of 25 mg of injectable Risperdal was selected based on the published treatment recommendations^{1,2}. Higher dosages of injectable Risperdal are available and will be administered if a higher maintenance dosage is required for control of psychotic symptoms. The 12.5 mg dose will be used if side-effects of the 25 mg dosage are intolerable.

We will follow the strategies recommended by Marder and colleagues² for switching patients from their current antipsychotic medication to long-acting Risperdal. Oral Risperdal will be administered for the first 3 weeks after the first injection of long-acting Risperdal until the first dose of long-acting Risperdal reaches therapeutic levels (typically in 2 to 3 weeks)³. Following this three-week period, the daily dosage of oral Risperdal will be titrated to zero over the subsequent days to weeks². Most patients will require less than one week to titrate to zero mg of oral Risperdal. Subsequent dosage levels of the long-acting Risperdal injections will be determined by clinical need. The patients in this condition will be maintained on injectable Risperdal administered every two weeks for the 12-month longitudinal protocol. The outpatient maintenance dosage of Risperdal Consta will be at a level judged by the treating psychiatrist to provide an appropriate level of protection against psychotic relapse while keeping side effects as low as possible.

The treating psychiatrists at the Aftercare Research Program do attempt to obtain adequate antipsychotic activity without introducing antiparkinsonian medications and are typically successful in doing so. However, they are also free to introduce antiparkinsonian medication if they feel it is clinically indicated to prevent EPS. In addition, our psychiatrists are also free to decide that the trial of Risperdal does not yield an adequate antipsychotic response or involves intolerable side effects. If this occurs after the initial trial of Risperdal, the treating psychiatrist and patient can decide to switch the prescription to any other antipsychotic medication (usually another second generation antipsychotic) and the patient's participation in the medication protocol will be considered to have ended. However, the patient can continue to participate in the remaining research assessments in the planned protocols, and these follow-up data will be used for secondary analyses.

The randomization to Cognitive Remediation (CR) or Healthy Behaviors Training (HBT) in a fully crossed 2 X 2 design is intended to improve cognitive functioning in the CR group and to improve lifestyle habits and well-being in the HBT group. Patients in Cognitive Remediation training will participate in a computer-assisted cognitive training program for six months, two hours/week, followed by one hour/week for another six months. They will also participate in a Bridging Group one hour/week to aid generalization from cognitive training to everyday functioning. The participants in Healthy Behaviors Training will be instructed in relaxation training, developing healthy eating habits, and light exercise for an equal number of hours/week, rotating the topics every three weeks. An employment specialist will work with patients in both conditions to assist in finding employment or return to school using the Individual Placement and Support model.

5. Study Evaluations.

In addition to the tests administered as part of the patients' participation in the Center for Neurocognition and Emotion, the following laboratory tests will be run for clinical monitoring purposes. Fasting blood glucose and Hemoglobin a1c (same as glycosylated hemoglobin) will be tested at study entry, at the one-year follow-up, and at any point during the longitudinal protocol that the patient develops symptoms consistent with diabetes mellitus. A full lipid panel will be run at study entry and at the one-year follow-up point. These tests will be run by the

UCLA Medical Center Clinical Laboratories, in the Department of Pathology and Laboratory Medicine. In addition, clinical monitoring of patients' body weight and determination of body mass indices will occur at study entry and periodically thereafter.

The assays of blood plasma for risperidone and 9-hydroxyrisperidone will allow an examination of the relationship between plasma levels and symptom levels, functional outcome, and deficits in neurocognition and social cognition. For the oral Risperdal patients, monthly draws will allow us to examine how plasma levels and these measures of outcome covary over time in secondary analyses. In addition, by comparing the ratio of the level of risperidone to that of 9-hydroxyrisperidone, we can identify two extreme types of risperidone metabolizers -- ultrafast metabolizers and poor metabolizers for use in secondary analyses. Ultrafast metabolizers will have a low ratio of risperidone to 9-hydroxyrisperidone, whereas poor metabolizers will have a high ratio, are likely to have side effects, and are more likely to respond at lower dosages. Patients are typically instructed to take their oral Risperdal at bedtime, and blood will typically be drawn in the morning.

For patients in the oral Risperdal condition, blood draws for plasma assays will be drawn once per month. For patients in the injectable Risperdal condition, blood will be drawn two times, one month apart, after a stable dosage has been maintained for 2-3 months. Averaging the values for two draws will provide for a more stable ratio of risperidone to 9-hydroxyrisperidone. For patients in the oral Risperdal condition, the assays will also allow monitoring of patient adherence to the prescribed oral medication regimens. They have proven to be very useful in detecting failures to take prescribed medication in some research patients who indicate verbally that they are taking their medication regularly. These assays will also be useful to check levels in cases of potential drug interactions or liver and/or kidney dysfunction⁴.

Prolactin levels will be tested at study entry, at the one-year follow-up, and if the patient develops symptoms consistent with elevated prolactin. Ratings of medication compliance based on all sources of information will be made for every two-week period during study participation, including pill counts every two weeks for subjects in the oral Risperdal condition. Medication Event Monitoring System (MEMS-6®) will be used to provide day-to-day data on medication bottle opening and closing, which is likely to closely conform to medication taking. This day-to-day level adherence information will allow us to make causal interpretations of any temporal relationship observed between medication nonadherence and return of psychotic symptoms. Compliance will be rated on the following scale: (1) never missed medication (100% compliance), (2) missed a couple of times, but essentially took all prescribed doses (76%-99% compliance), (3) missed several times, but took at least half of prescribed doses (50%-75% compliance), (4) took less than half of the prescribed doses (1%-49% compliance), (5) stopped taking medication altogether (0% compliance), (6) left clinic, assume compliant, (7) left clinic, assume noncompliant. Compliance for the Risperdal Consta condition will be based on the proportion of days during the rating period in which the patient delayed an injection.

The patient's case manager will complete the expanded 24-item version of the Brief Psychiatric Rating Scale (BPRS)⁵ will be rated every two weeks, with each item rated from 1 (not present) to 7 (extremely severe). The Scale for the Assessment of Positive Symptoms (SAPS), and the Scale for the Assessment of Negative Symptoms (SANS) will be rated at the initial randomization point, and at the 6- and 12-month follow-up evaluations.

6. Criteria for Efficacy Assessment:

Primary Clinical Outcome

The primary criterion for clinical efficacy will be to determine if Risperdal Consta is statistically superior to oral antipsychotic medication in time to first psychotic exacerbation/relapse. Relapse or exacerbation of psychotic symptoms will be identified based on increases of the BPRS items Unusual Thought Content, Hallucinations, or Conceptual

Disorganization using computer scoring algorithms⁶. The three types of psychotic symptom return: “Remission Followed by Relapse”, “Remission Followed by Significant Exacerbation”, or “Persisting Symptoms Followed by Significant Exacerbation” do not consider other aspects of outcome, such as hospitalization or role functioning.

Secondary Clinical Outcomes

Psychiatric Hospitalizations. Psychiatric hospitalizations occurring during the follow-through period will be examined independently of symptom return. Hospitalizations often occur due to suicidality, aggression, or agitation rather than due to psychotic symptoms, so will be examined independently of the recurrence of a psychotic episode (see psychotic relapse/exacerbation criteria).

Psychotic Symptom Control. The proportion of the follow-through period during which BPRS Hallucinations and Unusual Thought Content ratings were below a “4” on the BPRS (i.e., the nonpathological range) will be used as an index of psychotic symptom control.

Drug Discontinuation. We will tally clinical decisions to discontinue either oral Risperdal or Risperdal Consta due to lack of clinical efficacy, intolerable side effects, and patients’ decisions to withdraw from the program.

Functional and Cognitive Outcomes

Functional Outcome. The primary functional outcome measure will be the Global Functioning Scale: Role⁷, a rating scale that evaluates overall work/school functioning, administered every 3 months. Secondary measures of functional outcome will include the Role Functioning Scale⁸, quality of work based on the Work Behavior Inventory⁹, and maintenance of work/school attendance based on the Work Outcome section of the Social Adjustment Scale^{10,11}. The clinic staff has extensive training in the implementation of these types of research assessments with standardized protocols.

Cognition. The MATRICS Consensus Cognitive Battery (MCCB) will be the primary index of cognitive performance^{12,13}. The MCCB is endorsed by the FDA as the gold standard for use in trials of pharmacological agents that target cognition in schizophrenia. By using the MCCB, the results of our attempts to improve cognition in schizophrenia can be compared to other attempts to do so through pharmacological and learning-based interventions.

7. Safety Evaluations:

The overall risk of this research protocol is low, as the measures are not likely to involve any risks greater than those encountered in routine psychological assessments and psychiatric treatment. The risks of oral Risperdal and Risperdal Consta in this protocol will parallel those of these FDA-approved antipsychotic medications in clinical practice. Direct physical or psychological risks are minimal in the administration of measures of symptoms, neurocognition and social cognition. If any participant feels distressed during a research procedure, the research assessment measures will be immediately terminated at his or her request. If any aspect of the clinical monitoring or routine psychological assessments contributes to feelings of distress or concern, the patient participant may discuss these concerns with his/her psychiatrist, case manager, or any member of the clinical staff of this study. The study staff attempts to provide a supportive atmosphere to encourage patient participants to discuss concerns of any nature.

To provide ongoing monitoring of patient safety for participants in this protocol, we have adopted a combination of clinical observations by the clinical staff and standardized criteria for detecting any significant psychotic exacerbation or relapse. Patients are scheduled for weekly treatment and evaluation visits during the initial months of the trial and then typically to every other week visits during later months. All clinical staff members at the Aftercare Research Program have been instructed to report to the PI and to the Associate Director of the Aftercare Research Program any clinically significant worsening of a patient's condition that may warrant a serious adverse event report. Status of participants is reviewed weekly at a staff meeting that the

PI and Associate Director lead. To enhance the ongoing monitoring of clinical symptom changes, the Aftercare Research Program clinical staff completes the Brief Psychiatric Rating Scale (BRPS) every two weeks during the clinical trial. In addition to regular clinical monitoring of side effects during routine medication visits, medication side effects will be assessed by the treating psychiatrist every three months throughout the one-year protocol using the Abnormal Involuntary Movement Scale (AIMS). Laboratory tests will be used to identify patients at risk for new onset of diabetes mellitus, for elevated prolactin levels, and changes in cholesterol during the first year of treatment.

We will promptly report to the UCLA IRB and to Janssen any serious adverse events that involve a significant psychotic relapse, a suicide attempt, or a hospitalization, if these events are judged to be protocol-related. In addition, we will report to the IRB any unanticipated study-related problems involving risks to participants. The most common adverse event in our experience is not protocol-related, and involves an increase in psychotic symptoms after a patient refuses antipsychotic medication or all psychiatric treatment, despite the attempt to provide ongoing medication and other psychiatric treatment as part of a clinical trial.

8. Statistical Methods:

For evaluation of clinical efficacy, the primary outcome, time to first psychotic exacerbation/relapse, will be analyzed using Kaplan-Meier survival analysis. Survival analyses involving the full 2 X 2 design will utilize Cox regression, which allows multiple dichotomous predictor variables. No adjustment will be made for multiple comparisons because exacerbation/relapse is the only primary clinical outcome. Comparison of exacerbation/relapse rates will be analyzed using chi-square for the medication group comparison, and hierarchical loglinear modeling for the full 2 X 2 design.

Hospitalizations will be analyzed using analyses that parallel those for psychotic exacerbation/relapse.

Psychotic symptom control will utilize multiple BPRS ratings over the follow-up period and will be analyzed using mixed model repeated measures analyses for the medication group comparison, and regression analyses for the full 2 X 2 model.

Group differences in drug discontinuation will be examined using hierarchical loglinear modeling for the full 2 X 2 design.

Side effects will be examined using a General Linear Mixed Model (GLMM) with the medication condition, the psychosocial condition, and their interaction as predictor variables.

9. References:

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2. Marder SR, Conley R, Ereshefsky L, Kane JM, Turner MS. Dosing and switching strategies for long-acting risperidone. *Journal of Clinical Psychiatry*. 2003;64(suppl 16):41-46.
3. Kane J, Eerdekens M, Lindenmayer J-P, Keith S, Lesem M, Karcher K. Long-Acting Injectable Risperidone: Efficacy and Safety of the First Long-Acting Atypical Antipsychotic. *American Journal of Psychiatry*. 2003;160(6):1125-1132.
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