A Molecular Approach to Treat Cognition in Schizophrenia: Ca2+ Channel Blockade
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Mount Sinai	Protocol Title:	A Molecular Approach to Treat Cognition in Schizophrenia: Ca2+ Channel Blockade
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MSSM Protocol Template HRP-503a

Instructions:

1. *Prepare a document with the following sections. Note that, depending on the nature of your research, certain sections below may not be applicable. Indicate N/A as appropriate, explaining where possible.*
2. *For any items described in the sponsor's protocol, grant application or other source documents submitted with the application, you may reference the title and page numbers of these documents rather than cutting and pasting into this document.* ***Do NOT refer to any derived documents, such as the Sample Consent document, or other internal documents required with the submission.***
3. *If you reference page numbers, attach those pages to this protocol.*
4. *When you write a protocol, keep an electronic copy. You will need to modify this copy when making changes.*

1) Objectives:

In this project we propose to conduct a 4-week open label cognitive enhancement trial of isradipine in up to 80 stable outpatients with schizophrenia and schizoaffective disorder.

The primary aim of this study is to evaluate the effects of the calcium channel antagonist, isradipine on cognitive dysfunction in patients with schizophrenia and schizoaffective disorder. Incomplete treatment response is common. Cognitive impairment and negative symptoms persist in a majority of patients even when positive psychotic symptoms are well-controlled, and they account for a large proportion of the variance in explaining functional disability (Keefe et al. 2007). This has led to a focused effort to target the specific treatment of cognition in patients with schizophrenia (Green and Nuechterlein, 2004), with somewhat limited success to date.

Novel treatment options have been limited by an incomplete understanding of the biological etiology of schizophrenia; however, recent data from the field of genomics have provided insights into the molecular underpinnings of schizophrenia and its associated symptoms. The majority of genetic risk loci identified to date show trans-disorder effects, increasing susceptibility across a broad range of neuropsychiatric disorders including schizophrenia and bipolar disorder (Williams et al. 2011; Purcell 2009). One possible explanation for this overlap is that several of these genes are influencing risk via their effects on shared phenotypes such as neurocognitive dysfunction. One such example is a single nucleotide polymorphism (SNP; rs1006737) in the calcium channel gene, CACNA1C; initially associated with bipolar illness (Sklar et al. 2008; 2011; Ferriera et al 2008) but also linked with schizophrenia (Green et al. 2009; Nyegaard et al. 2010) and recurrent major depression (Green et al, 2009). The strength of

the association signal for CACNA1C in major mental illness is unambiguous and several subsequent studies have evaluated the effects of CACNA1C variation on neurocognitive capacity.

2) Background

CACNA1C rs1006737 has been shown to affect neural networks underlying reward and emotional processing (Bigos et al. 2010; Wessa et al. 2010), verbal fluency (Krug et al. 2010), alerting and orienting aspects of attention (Thimm et al. 2011), and executive functions (Bigos et al. 2010). CACNA1C is responsible for coding the L-type voltage-gated calcium channel Cav1.2, which has been shown to be involved in synaptic plasticity, learning and memory in an NMDA-independent manner (Woodside et al. 2004; Moosmang et al. 2005; White et al. 2008) and CACNA1C knock-out mice show notable deficits in long term potentiation (Striessnig et al. 2006). These convergent data suggest that variation within CACNA1C may play a critical role in the development of neurocognitive deficits associated with schizophrenia and may point toward a novel treatment strategy targeting calcium channel dysfunction for these disabling symptoms.

Dysregulation of intracellular Ca^{2+} homeostasis and excess calcium signaling have been hypothesized to underlie multiple pathogenic processes in schizophrenia, including dopaminergic hyperactivity and hypofunction of the N-methyl-D-aspartate (NMDA) receptor (Bojarki et al. 2010). In selecting an intervention, we considered the numerous calcium-channel blockers that are widely utilized as anti-hypertensives; however, we chose isradipine for its specificity for the CaV1.2 channel subtype and its superior blood-brain barrier penetrance.

3) Setting of the Human Research

The Icahn School of Medicine at Mount Sinai (ISMMS) site has ideal facilities for the proposed study. The research activities will be conducted in the Laboratory of Neurocognition located at 53-55 E. 96th Street, 1st floor suite. This space, completely renovated in 2014, consists of a seven-room suite with ample space for research staff, interview rooms, and an exam room.

4) Resources Available to Conduct the Human Research

The current study will be performed in the Department of Psychiatry, located at the Icahn School of Medicine at Mount Sinai (ISMMS). Referrals will primarily come from Manhattan based Mount Sinai Health System Outpatient Psychiatry Departments. These will include the Mount Sinai Hospital, Beth Israel, and St. Luke's Roosevelt.

5) Study Design

a) Recruitment Methods

Subjects will be recruited from the outpatient clinical services of the Mount Sinai Health System as described above. Potentially eligible patients are identified by the patient's clinical care provider (nurse practitioner and/or physician), who would then ask the patient's permission for our research team to approach and explain the protocol. A research team member will approach that individual and explain the study objectives, procedures, risks and benefits, and begin the informed consent process if the patient wishes to. We will also utilize IRB approved community based advertisements.

b) Inclusion and Exclusion Criteria

Inclusion criteria: **1.** Age 18-60; **2.** DSM-IV schizophrenia or schizoaffective diagnosis; **3.** Residual phase of illness criteria met at screen and baseline as defined by item scores of $\leq$ 4 on each of the Brief Psychiatric Rating Scale (BPRS) hallucinatory behavior, unusual thought content, and conceptual disorganization items; **4.** Hamilton Rating Scale for Depression (HRSD) $\leq$ 12; **5**. Baseline Clinician Administered Ratings Scale for Mania (CARS-M) score of <5; **6.** Simpson Angus Scale (SAS) total score of $\leq$ 6; **7.** Treatment with at least one but no more than two stably-dosed second-generation antipsychotic medication (other than clozapine) for $\geq$ 2 months and no changes planned over the 4-week study period. First generation antipsychotics and clozapine are thought to cause significant cognitive impairment. Initial baseline cognitive functioning will not be evaluated as inclusion/exclusion criterion because schizophrenia/schizoaffective disorder have a relatively cognitively homogeneous patient sample. We do not anticipate any subjects without cognitive impairment. We will cover for baseline performance to determine if degree of cognitive impairment at baseline is responsible for any change noted.

Exclusion criteria: **1.** History of CNS trauma, neurological disorder, ADHD, mental retardation, learning disability, or other non-schizophrenic cause of cognitive impairment; **2.** DSM-IV diagnosis of substance abuse/dependence within 3 months or positive urine toxicology at screening that is not consistent with what participant reported. Substance abuse and dependence are determined based on an extremely comprehensive interview (the SCID), which evaluates lifetime history and current history of all substance use disorders. As per the protocol, DSM-IV diagnosis of substance abuse or dependence within 3 months will be exclusionary (not substance use); **3.** Pregnant women or women of child bearing potential who are not using a medically accepted means of contraception (including oral contraceptive or implant, condom, diaphragm, spermicide, intrauterine device, tubal ligation, or partner with vasectomy) **4.** Women who are breastfeeding; **5.** Active, unstable medical problem that may interfere with cognition; **6.** Current treatment for hypertension; **7.** Uncontrolled hypertension; **8.** History of heart

disease; **9.** Any drug known to interact with isradipine. **10.** History of GI strictures; **11.** Abnormal lab or ECG at screen. **12.** Significant suicidal ideation at baseline (HRSD item 3 > 2). Concomitant Medications: Practical and ethical considerations prevent an exclusive focus on medication-free patients; however, we will limit participation to individuals taking at least one and no more than 2 concomitant antipsychotic medications and we will exclude subjects who have received ECT within 12 months. Medication load will be incorporated as covariates in statistical analyses using chlorpromazine (CPZ) equivalents.

c) Number of Subjects

Up to 80 stable schizophrenia and schizoaffective patients will be recruited from the Mount Sinai Health System Outpatient Departments, and community advertisements.

d) Study Timelines

The recruitment and enrollment process will be active for approximately 24 months. The anticipated final date for this study is 7/2017. The patients will be informed of the length of the study, which will include 8 visits in total. There will be a screening visit, baseline visit when they will receive the study medication, a visit eight hours after the first dose of medication is taken (baseline) where blood pressure will be checked, 4 weeks of medication administration and weekly monitoring, and a visit eight hours after the dosage of the medication is increased (week 2) where blood pressure will be checked. They will be informed of all of the study procedures for each week, including assessments and medical tests.

e) Study Endpoints

The primary endpoint related to the efficacy of isradipine will be cognitive enhancement measured by the MATRICS Consensus Cognitive Battery (MCCB). The MCCB is accepted by the FDA as a primary outcome measure for registry trials of cognitive enhancement in schizophrenia.

f) Procedures Involved in the Human Research

All eligible subjects will undergo visits at screening, baseline (week 0), visit 8 hours after week 0, week 1, week 2, visit 8 hours after week 2, week 3, and week 4 (end of study). The parameters of study drug dosing are as follows: isradipine as utilized in this trial will be administered twice daily. Isradipine will be titrated as follows: baseline (week 0) 5 mg/day BID; Week 2 increase to 10 mg/day BID if 5 mg was well-tolerated. Dosing will be flexible based on side effects with a maximum=10 mg/day. If 5 mg cannot be tolerated, the subject will be discontinued. Dosing was based on package labeling for hypertension and prior studies in Parkinson's disease (Simuni et al. 2010).

Measures described in detail below:

Safety Outcome Measures

- The Side Effects Checklist (SEC; physician administered) and side effect self-report form – (all visits)
- Vital signs including blood pressure (standing/supine – all visits)
- Blood pressure check within 8 hours of first dose. Staff contact number will be given to subject in case there are any problems before the 8 hour BP check (week 0). An additional blood pressure check 8 hours after increased dosage (week 2).
- Electrocardiogram (ECG); chemistry panel and CBC via blood draw (approximately 2 TSP blood drawn); urinalysis (screening & week 4)
- Urine toxicology (screening)
- Urine pregnancy test for women of childbearing potential (baseline)
- Abnormal Involuntary Movement Scale (AIMS) and Simpson Angus Scale (SAS) (all visits)
- Beck Scale for Suicidal Ideation (SSI) and Columbia Suicide Severity Rating Scale (C-SSRS) (all visits)

Clinical/Symptom Measures

- Structured Clinical Interview for the DSM-IV (SCID-IV) (screening)
- Symptom rating scales including the Brief Psychiatric Rating Scale (BPRS), the Scale for the Assessment of Negative Symptoms (SANS), the Hamilton Rating Scale for Depression (HRSD), the Clinical Global Impression Scale (CGI), the Clinician Administered Rating Scale for Mania (CARS-M) (all visits)

Neurocognitive/Functional Measures

- MATRICS Consensus Cognitive Battery* (baseline & week 4)
- UCSD Performance Skills Assessment (UPSA) (baseline & week 4)
- Quality of Life Scale (QoL) (baseline & week 4)

*** Table 1.**

The MATRICS Consensus Cognitive Battery	**Domain**	**Note/Description**
Category Fluency	Speed of Processing	Total animals in 60 seconds
BACS Symbol Coding	Speed of Processing	Matching numbers to symbols
Trail Making Test Part A	Speed of Processing	Dot-to-dot: Numbers only
CPT-Identical Pairs	Attention/Vigilance	Computerized numeric stimuli
Letter-Number Span	Working Memory	Recoding numbers and letters in order
WMS-III Spatial Span	Working Memory	Visual sequence forward and backward
Hopkins Verbal Learning (HVLT)	Verbal Learning	12 word list x 3
Brief Visuospatial Memory Test (BVMT)	Visual Learning	6 designs to be drawn from recall
NAB Mazes	Reasoning & Prob Solving	Pencil-paper maze solutions
MSCEIT Managing Emotions	Social Cognition	Situational social judgments
Additional Measures ("Plus")	---	---
Affective Go-no-go	Affective Neuroscience	Emotional modulation of inhibition
Emotional Stroop	Affective Neuroscience	Affective Bias/Cognitive Control

g) Specimen Banking

N/A

h) Data Management and Confidentiality

If a participant agrees to be in this study, we will collect health information that identifies them, "Protected Health Information" (PHI). We may collect the results of tests, questionnaires and interviews. We may collect information from a patient's medical record. We will only collect information that is needed for the research. This information is described in the consent form. By signing the consent form a participant gives us permission (authorization) to collect, use and share their health information.

Data collected will include questionnaires and assessments as described above in section (5f). Labs and tests will be done at the ISMMS laboratory and information sent to the PI, data for these will be stored in a binder which will be secured in a double locked fashion. Blood samples will be labeled with de-identified codes, which cannot be associated with individual subjects. PHI, such as patient name and DOB, will only be included in a separate file including the consent documents. All other data collected for the study will be de-identified and stored apart from PHI, identified by study number linked to PHI in a secure file. This data will be stored indefinitely.

The PI will be responsible for receipt and transmission of study data and specimens. Quality control of the data collected will include double data entry and data quality check by investigators after each 5 subjects completed.

Study staff will have access to data and records may be reviewed by the Mount Sinai School of Medicine Institutional Review or government agencies (i.e. NIH) in order to meet federal or state research regulations. Please be aware that once private information is disclosed, it is subject to re-disclosure by the recipient and can no longer be considered protected. If research records are used for decisions related to clinical care, then a participant has the right to review this information and to request changes. This is limited to information about their treatment, and does not include information related to procedures or tests that are for research purposes only. Participants may access this information only after the study analysis is complete.

Data from this study may be used in medical publications or presentations. The information will be de-identified so that individual subjects cannot be recognized and the information will no longer be considered PHI. The information that is collected for research will be analyzed for many years and it is not possible to know how long this analysis and follow-up will take. Therefore, participants are allowing access to this information indefinitely.

Subjects will only be identified with a numerical code in compliance with HIPAA regulations. Raw subject data will be secured in double locked physical control. Digitized raw data will be similarly de-identified using coding and will be secured on an MS SQL server with Windows integrated security.

Data analysis plan is included below. All analyses will be based on an intent-to-treat sample of subjects who received at least one dose of isradipine. Since the missing values may be dependent on the observed outcomes, we assume the missing data mechanism to be missing at random, and hence a mixed models analysis will be used to assess the treatment effect of isradipine with fixed effects for week and first order autoregressive covariance structure to evaluate change over time for all of the primary outcome measures. Cognitive measures will be handled differently, as these will only be collected at two time points – if missing data are substantial (or a complete visit is missing), subjects' data will not/cannot be meaningfully analyzed.

Primary Analyses will test the following hypotheses based on our specific aims:

To determine the feasibility of 4 weeks of isradipine on cognitive outcomes in SZ.
Hypothesis: We will successfully recruit up to 80 stable schizophrenia and schizoaffective patients

To determine the safety of 4 weeks of isradipine on cognitive outcomes in SZ.
Hypothesis: The frequency of new or worsened side effects (clinician-rated; self-reported; lab-based) will not be significantly different from baseline to end of study visit.

A Fisher exact test will compare time-points by frequencies of new or worsened (compared with baseline) side effect severity ratings – this will be done for all side effects assessed by the SEC.

Differences on laboratory measures (chemistry panel, etc.) will be tested using repeated measures ANCOVA (baseline and week 4) and changes in vital signs (specifically blood pressure) will be assessed using mixed model ANCOVA, to incorporate data at each weekly visit.

Differences on SAS and AIMS total scores will be examined by calculating the τ-b rank correlation between score and week for each subject and comparing the distribution of these trend scores with the Conover-Salsburg rank test.

i) Provisions to Monitor the Data to Ensure the Safety of subjects

Safety monitoring will be done on a patient by patient basis by the PI and the study physician on weekly visits. Side effects will be monitored closely and all AEs recorded. To increase safety, a blood pressure check will be done within 8 hours of this first dose (baseline). Staff contact number will be given to subject before the first dose in case there are any problems before the 8 hour BP check. Additionally, a blood pressure check will be done within 8 hours of increasing the dosage (week 2).

The PI will summarize all safety related outcomes after each set of 5 patients have completed the study and discuss these results with study physicians. This monitoring will be applied sooner than 5 patients if indicated, or if a SAE or unanticipated event occurs. All SAEs will be reported to the IRB within 24 hours and documented as per protocol. In the case that there are safety concerns from the PI or the IRB, this will be addressed in an ongoing manner. Independent of any SAEs, a Data Safety Monitoring Plan will be submitted to the IRB after the first 15 participants have been enrolled.

j) Withdrawal of Subjects

If they choose to consent to the study and are eligible to begin the trial, they will be closely monitored and will visit with the study coordinator and study physician. Side effects will be rated weekly at each visit using an adverse events checklist completed by a study physician. Subjects with an exacerbation of psychosis/depression/mania on a 2-point CGI-change score will be discontinued and treated appropriately by the study physician. Suicidal ideation will be assessed at each visit with the Beck (SSI) and the Columbia Suicide Severity Rating Scale (C-SSRS). Significant suicidal ideation will be addressed immediately using the standard clinical response at ISMMS (evaluation at the walk-in clinic/psychiatric emergency room for potential need to hospitalize). Subjects at risk for suicidal behavior will be discontinued. Subjects with any other clinical worsening as noted by study physician, and any instance of an SAE will be discontinued. In addition, subjects who exhibit any inability to follow the protocol with be discontinued and withdrawn from the study.

To ensure orderly termination from the study, the study physician would meet with the subject to discuss termination and discontinuation of medication. Safety measures would be collected and a follow-up visit by phone would be scheduled to further ensure safe discontinuation. Discontinuing isradipine does not require a taper. We will schedule an in-person visit if necessary after the follow-up visit by phone to address any remaining concerns the subject may have.

Subjects may withdraw from the study for any reason at any time by contacting the principal investigator or any of the research staff. It is also possible to withdraw permission for the use and disclosure of any protected information for research, but it must be done in writing to the principal investigator. In the event permission is withdrawn, information that was already collected may still be used if that information is necessary to complete the research study.

6) Risks to Subjects

During the informed consent process, subjects will be informed of the potential risks associated with the study. Isradipine has not been shown to induce or worsen psychosis in any of the published human data; nonetheless, symptoms may worsen in the course of the study. We will very closely monitor psychotic and affective symptoms on a weekly basis

throughout the study period using standardized rating scales described above in 5f). At each weekly visit the study physician will meet with the patients and conduct a thorough review of symptoms including psychosis, mood, and suicidal/homicidal ideation. If there is an acute worsening of symptoms the study clinicians will review the case with the PI (or will make an emergency decision as needed) to ensure that the subject receives emergency care or hospitalization. Participation in the study will be discontinued in any case of clear symptom worsening. Between weekly visits, the patients will have emergency contact information.

Along with closely monitoring for symptom exacerbation, each visit with the study physician will entail a detailed side effect evaluation, which will include vital signs and a side effect checklist. The most common side effects of isradipine include hypotension, edema, headache, dizziness, palpitations, fatigue, flushing, and constipation. Patients will be educated about the potential for hypotension and its symptoms, and blood pressure and symptoms will be measured at every visit. If the patient develops clinically significant hypotension (e.g., systolic blood pressure equal to or less than 90 mm Hg or diastolic equal to or less than 60 mm Hg, or if they experience significant associated symptoms), or if at any point in the study subsequent to baseline there is a blood pressure drop of 20% or more from blood pressure at baseline, they will be discontinued from the study medication and excluded from the protocol. Rare side effects have also been reported including arrhythmias, syncope, severe hypotension or myocardial infarction. The informed consent process will alert subjects to these potential risks and close monitoring will ensure prompt response to any adverse effects with appropriate treatment and/or study discontinuation, as indicated.

Additional risks are minimal and involve the completion of questionnaires, interviews and paper-pencil/computerized tests. Some of the questions may be distressing to the individual and subjects will be told that they may refuse to answer any questions that they so choose. The testing procedure can sometimes cause fatigue but we will ensure plenty of resting periods during the session and will instruct subjects to notify staff if they would like an additional break. Pain and bruising may be associated with the blood draw for screening labs; however, a trained phlebotomist will perform the procedure to avoid any additional discomfort.

7) Provisions for Research Related Injury

In accordance with Federal Regulations, if anyone is injured from being in the study, they will receive medical care and treatment as needed from the Mount Sinai Medical Center. However, participants are responsible for the costs of such medical treatment, directly or through their medical insurance and/or other forms of medical coverage. No money shall be given to them.

8) Potential Benefits to Subjects

There may be no immediate potential benefit to the subject from participation in this research study; however, the results may provide the bases for larger scale, pivotal trials designed to move toward new indications for the study agent and therefore, lead to novel options for treating these disabling symptoms. Moreover, although there is no guarantee, it is possible that subjects taking isradipine may experience some improvement in cognitive deficits associated with SZ.

9) Provisions to Protect the Privacy Interests of Subjects

Subjects are free to refuse to answer any of the questions that are asked of them in the study. If the withheld information is critical to study eligibility the patient may not be enrolled. While enrolled in the study, all tests and procedures will be done in a research office at ISMMS ensuring privacy. All research staff will be open to answering any questions and will address any concerns of the subjects throughout the duration of the study.

10) Economic Impact on Subjects

There is no cost to participants for participating in the study.

11) Payment to Subjects

Subjects will be informed during the informed consent process of the study compensation. [redacted]

12) Consent Process

A potential subject will be approached by a member of the study team after she/he has been given permission to do so by the patient's clinician. The research team member will explain the study objectives, procedures, risks and benefits, and answer all questions the potential subject may have. Subjects are advised that they can withdraw at any time during the study. Subjects will receive a copy of the consent form for the study. Informed consent will be documented when the subject signs the consent form that has been approved by ISMMS PPHS.

13) Process to Document Consent in Writing

All participants must provide written informed consent. The consent form will be documented in writing. The consent form has been derived from the standard PPHS consent template.

14) Vulnerable Populations

The following vulnerable population types will be excluded from the study: adults unable to consent, individuals who are not yet adults, wards of the state, pregnant women, and prisoners.

15) Multi-Site Human Research (Coordinating Center)

N/A

16) Community-Based Participatory Research

N/A

17) Sharing of Results with Subjects

If any preliminary results arise from this study or any related studies are published that change the risks associated with this protocol, we will notify all subjects who have participated. Otherwise, results from the analyses will be published in peer-reviewed journal articles but will not be transmitted directly to the subjects involved in the research.

18) IRB Review History

N/A

19) Control of Drugs, Biologics, or Devices

Note: The IDS has its own forms that must be completed and a review process that must be followed before the IDS representative will sign off on Appendix B for submission to the PPHS.

The study drug will be stored in secure, temperature-controlled offices on the [redacted] Street within the Laboratory of Neurocognition under the supervision of the PI. The principal investigator will be authorizing the study physician to handle and control the study drug.

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	Primary Contact Name/Contact Info	Megan Shanahan [redacted]
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