Detailed Protocol Title: 1/2-Pramipexole in Bipolar Disorder: Targeting Cognition (PRAM-BD)
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I. BACKGROUND AND SIGNIFICANCE

Data suggest that, as in schizophrenia (SZ), bipolar disorder (BD) patients' everyday functioning is directly influenced by persistent symptomatology and cognitive dysfunction (Bowie et al. 2010; Burdick et al. 2010). A recent meta-analysis indicated significant correlations (mean r=.27) between cognition and functional measures in BD (Depp et al. 2012), with little evidence for differences across cognitive domains. These data strongly support the role of cognition in quality of life in BD and highlight the need for treatment and prevention efforts targeting this domain (Burdick et al. 2007). There are several ongoing large-scale clinical trials targeting cognition in SZ, with a parallel need existing in BD. We recently completed one of the first controlled trials of cognition as a treatment target in BD (Burdick et al. 2012). We approached the initial question of which agent to test based upon prior evidence that enhancing dopamine may result in improvements in neurocognition in other clinical samples.

Although the neurobiological basis of persistent cognitive impairment in BD is not well-understood, convergent evidence suggests that the enhancement of DA activity may be a useful remediation strategy. Neuroimaging studies highlight structural brain abnormalities in BD in regions rich in DA receptors, including anterior cingulate, dorsolateral, orbital, and subgenual cortex (Drevets et al. 1998; Lopez-Larson et al. 2002) and the basal ganglia (Baumann et al. 2001). Abnormal activation in these regions has been reported in BD during cognitive tasks using fMRI (Blumberg et al. 2000; Gruber et al. 2004). Moreover, in previous studies of healthy subjects increasing levels of DA via agents such as pergolide, a D1 agonist (Kimberg et al. 2003) or bromocriptine, a D2 agonist, (Kimberg et al. 1997; Luciana et al. 1998) improves cognition, particularly in cognitive domains linked to prefrontal cortex (PFC) functions. Finally, molecular genetic studies support the importance of DA in normal cognitive functions. Several cognitive studies have focused on the gene coding for catechol-o-methyl transferase (COMT), an enzyme responsible for the degradation of catecholamines, including DA, in the PFC (Dickinson et al. 2009). Convergent results demonstrate an association between genetic variation within *COMT* and cognitive function in SZ (Bilder et al. 2002; Egan et al. 2001) and healthy controls (Malhotra et al. 2002; Tsai et al. 2003). *COMT* has also been implicated in the susceptibility for BD (Kirov et al. 1998; Papolos et al. 1998), including work by our group (Burdick et al. 2007). In a sample of 52 Caucasian BD probands and 102 Caucasian healthy controls, we detected a modest but significant association between SNP rs165599 and BD, with the g allele being over-represented in cases vs. controls (OR=2.41; genotypic p=0.04; allelic p=0.02). We found a relationship between the risk allele at this SNP and poorer performance on verbal memory tasks (California Verbal Learning Test; CVLT Trials 1-5; p=0.005; eta^2=0.07) particularly with regard to PFC aspects of learning (CVLT semantic cluster; p=0.037; eta^2=0.04) in BD patients and in healthy controls (Burdick et al. 2007). In addition to these lines of evidence supporting the use of a DA agent to enhance cognition, recent evidence suggests that pramipexole, a

novel D2/D3 agonist, may be an effective adjunctive anti-depressant in BD. Pramipexole (Mirapex®) is an FDA-approved medication for Parkinson's disease (PD) and restless leg syndrome.

II. SPECIFIC AIMS

Converging evidence suggests that patients with bipolar disorder suffer from deficits in neurocognitive functioning that persist, despite remission of acute affective symptoms. These impairments contribute directly to functional disability, highlighting the need for interventions above and beyond standard treatments in order to achieve a full inter-episode recovery. The current study aims to investigate the safety and efficacy of a dopamine agonist (pramipexole), on these persistent cognitive abnormalities in euthymic bipolar patients using a placebo-controlled, adjunctive, 14-week trial design.

Aim 1: Baseline to Week 6
a) To determine the short-term efficacy of pramipexole on neurocognitive functioning in stable BD patients. b) To determine the short-term safety of pramipexole on neurocognitive functioning in stable BD patients.

Aim 2: Week 6 to Week 12
a) To determine the long-term efficacy of pramipexole on neurocognitive functioning in stable BD patients. b) To determine the long-term safety of pramipexole on neurocognitive functioning in stable BD patients.

Exploratory Aim: To integrate results from multiple dopamine-based domains (cognition; affect; reward processing) to evaluate the main and interactive effects of pramipexole on these factors in stable BD patients.

III. SUBJECT SELECTION

a. ***Inclusion criteria: 1.*** Age 18-65. ***2.*** DSM-V BD I or II diagnosis. ***3.*** Affective stability, defined by a Young Mania Rating Scale (YMRS) rating of < 8 and a Hamilton Depression Rating Scale (HRSD) rating of ≤ 16 at screening and baseline. We will further require that any subsyndromal depression has not significantly worsened in the 4 weeks prior to randomization so as to avoid enrolling subjects who are on the verge of a full depressive episode. ***4.*** Evidence of clinically-significant neurocognitive impairment at screening. This will be formally assessed using a short battery of tests including Trails B, Wechsler Adult Intelligence Scale (WAIS-IV) Digit Symbol, WAIS-IV Digit Span Forward and Backward, Wisconsin Card Sorting Test (WCST), and California Verbal Learning Test – Second Edition (CVLT-II). Clinically-significant impairment will be defined as scoring ≥ 1 SD below normative means on at least one of these measures. ***5.*** Clinically-acceptable, stably-dosed, mood stabilizing medication regimen for ≥ 1 month prior to enrollment, with no medication changes planned over the 14-week study period.

Exclusion criteria: 1. History of CNS trauma, neurological disorder, ADHD, or learning disability. ***2.*** Positive urine toxicology or DSM-V diagnosis of substance abuse/dependence within 3 months. ***3.*** Active, unstable medical problem that may interfere with cognition. ***4.*** Recent history of rapid-cycling. ***5.*** Abnormal lab or ECG

result at screen. ***6.*** History of heart failure. ***7.*** Significant suicidal risk (HRSD item 3 > 2 or by clinical judgment). ***8.*** Estimated IQ in MR range as per Wide Range Achievement Test (WRAT) standard score of less than 70. ***9.*** 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) ***10.*** Women who are breastfeeding. ***11.*** Participation in any other investigational cognitive enhancement study within 30 days.

Concomitant Medications*:* Practical and ethical considerations prevent a focus on medication-free patients. Medications with known adverse cognitive effects will be disallowed (i.e., topiramate, anticholinergics), as will agents that may enhance cognition (e.g., amphetamine, other DA agonists). Benzodiazepines will not be allowed within 6 hours of testing. ECT in the past 12 months will be disallowed, as will any drug known to interact with pramipexole. With regard to antipsychotic medications specifically, only half of the sample will be allowed to be taking any antipsychotics. Recruitment efforts will be adjusted to ensure 50% of the sample is antipsychotic-free at baseline. Further, we will exclude any subject who is taking more than 4 concomitant psychotropic medications. Older generation neuroleptics will be specifically disallowed due to their high binding potential at the D2 receptor (Kapur et al. 1999). Although some of the standard treatments for BD (e.g. lithium) may influence cognition, it is impractical to exclude these medications given their widespread use; therefore, data will be coded for medication classes and dosages to determine a load score (as per Hassel et al. 2008) to be included as a covariate in statistical analyses.

b. Subjects will be recruited from the BWH outpatient psychiatry department per guidelines of PHRC.

IV. SUBJECT ENROLLMENT

a. Enrollment will be done through the outpatient psychiatry department at BWH (see section III.b. above for detail on recruitment). Randomization is done from one list, created by Co-I at Icahn School of Medicine at Mount Sinai. The list is evenly spread across sites. Subjects will be randomized on a 1:1 ratio with stratification for concomitant antipsychotic status and depression at baseline (Hamilton Rating Scale for Depression score <8 vs ≥ 8).

b. Potential subjects are given general information about the research through or discussion with their treating physicians, and if they are interested in learning more about the study, they contact or agree to be contacted by study staff. One of the study staff then meets with the potential subject to review and to discuss the details of the research study using the informed consent document as a guide. Potential subjects are then given a copy of the informed consent document to take home so they can carefully read the document and discuss the research with their family, friends and/or physician and develop questions to ask at their next meeting with the research staff. Once they have read the consent document and their questions are answered by a study physician, if they agree to participate in the research, they sign and date the informed consent document, which will then also be signed by the study physician.

c. Randomization will be conducted via a computer generated program and all study staff will be blinded unless un-blinding is required for safety reasons. Subjects will be randomized on a 1:1 ratio with stratification for concomitant antipsychotic status and depression at baseline (HRSD <8 vs ≥ 8). Study drug will be blinded and matched to placebo.

V. STUDY PROCEDURES

a. All eligible participants will undergo study visits at screening, baseline (week 0), week 1, week 2, week 3, week 4, week 6, week 8, and week 12, (end of study). Co-Investigators Jessica Harder, MD, and Timothy Mariano, MD, PhD, MSc will be responsible for consenting subjects, administering drug, and ensuring safety outcome measures at each study visit.

Measures are described in detail below:

Safety Outcome Measures

- Side Effects Checklist (SEC; physician administered) – (*all visits*)
- Columbia Suicide Severity Rating Scale – *(all visits)*
- Iowa Gambling Task – (*baseline, week 6, week 12*)
- Vital signs including blood pressure (standing/supine) – (*all visits*)
- Electrocardiogram (ECG) – (*screening, week 6, week 12*)
- Liver function tests; chemistry panel; CBC; (9 mL blood sample); urinalysis – (*screening, week 12*)
- Pregnancy test for women of childbearing age – (*screening, week 12*)
- Urine toxicology – (*screening, week 12*)
- Medication log of current medications and all medications administered during previous week – (*all visits*)

Clinical/Symptom Measures

- Structured Clinical Interview for the DSM-V (SCID–V) – (*screening*)
- Symptom rating scales: Young Mania Rating Scale (YMRS); Hamilton Rating Scale for Depression (HRSD); Brief Psychiatric Rating Scale (BPRS) – (*all visits*)
- Smoking questionnaire – *(screening, baseline, week 6, week 12)*

Neurocognitive/Functional Measures

- Screening cognitive battery (see inclusion criteria 4.) – (*screening*)
- Cognitive assessment: MATRICS Consensus Cognitive Battery (MCCB- plus; see description below) – (*baseline, week 6, week 12*)
- The Probabilistic Stimulus Selection Task – (*baseline, week 6, week 12*)
- UCSD Performance Skills Assessment (UPSA) – (*baseline, week 12*)
- The World Health Organization Disability Assessment Schedule (WHODAS 2.0) – (*baseline, week 12*)

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 & Problem 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

b. Adapting from our previous work in BD and according to package labeling, the dosage titration schedule will be slow and flexible. Dosing will be initiated at 0.25 mg QHS on night one, followed by 0.25 mg BID day two onward, and ideally increased as follows to a target of 4.5 mg/day:
day 2-week 1 0.25 mg BID;
week 1-2 0.25 mg QAM/0.50 mg QHS;
week 2-3 0.75 BID;
week 3-4 1.0 mg QAM/1.5 mg QHS;
week 4-5 1.75 mg BID;
week 5-6 1.5 mg QAM/3.0 mg QHS.
The dosing stated above is ideal titration, dosing will be flexible at the discretion of the study physicians. If subjects can reach a titration of 1.5mg/day by week 4 they will be allowed to continue in the study. As compared with our previous maximum 1.5 mg/day (Burdick et al. 2012), we opted to allow up to 4.5 mg/day (the maximum approved dosage in Parkinson's disease) to ensure adequate target engagement. We are familiar

with this dose range, as 4.5 mg/day was allowed in our study in BD depression (Goldberg et al. 2004). As stated above, dosing will be flexible based on side effects; however, if 1.5 mg/day cannot be tolerated, the subject will be discontinued. Titration will occur up to week 6 and then efforts will be made to maintain the same dose until the completion of the trial (week 12). Upon week 12/end of study visit, study drug will be tapered over a 7-10 day period, depending on the dose at week 12/end of study, decreasing by 0.25mg to 0.75mg daily per the pramipexole package insert instructions.

c. Devices to be used: N/A

d. Procedures/surgical interventions, etc.: N/A

VI. BIOSTATISTICAL ANALYSIS

Statistical Methods: *Preliminary analyses*: Groups will be compared on demographics, baseline symptom ratings, and concomitant medication load; if necessary, covariates will be included in subsequent models. MCCB data are standardized using the MCCB program, scores are age- and sex- corrected and reported on a t-score scale (Mean=50, SD=10). Any study focusing on improving cognition must consider practice effects (Goldberg et al. 2008). The placebo arm will provide estimates of expected practice so that we are able to calculate a reliable change index (RCI) to determine the meaningfulness of change (Goldberg et al. 2009).
Primary hypothesis testing: 100 participants will be randomized in a 1:1 allocation to treatment with pramipexole or placebo. The primary assessment of safety will be based on the incident of adverse event rates and standardized mood ratings at each visit. Differences in the incidence of individual adverse events will be compared between randomization arms using Poisson regression. Exact 95% confidence intervals (based on the Poisson distribution) for the risk ratios for individual adverse events for treatment with pramipexole versus placebo will be computed and may incorporate an estimated overdispersion parameter if observed variability exceeds that determined by the Poisson distribution. Performance on the IGT will also be used to track potential changes in impulse-control (baseline, weeks 6 and 12). We will test for correlations between IGT performance and mania symptoms at the times of testing (simultaneous measurements). Moreover, we will use IGT change scores as predictors in regression models to evaluate changes in mania ratings at concurrent time points as well as future time points. This will directly address the question of whether or not changes in IGT strategy serve as markers of current mania and/or impending affective destabilization.

The relative specificity of pramipexole in binding to D2/D3 receptors allows for a unique opportunity to enhance DA in neural networks associated with specific aspects of cognition as well a reward processing, which will be carefully assayed in this study so that exploratory analyses will be able to test questions related to the role for these receptors across several interacting domains in BD, at least at the level of behavior. Exploratory analyses will include specific domains and individual tasks which will be modeled to account for main effects and interactions (as described in primary analyses below).

The primary outcome for efficacy is change in cognition from baseline to week 6 (MCCB Composite). The null hypothesis is that there is no difference in this change between patients on pramipexole vs. patients on placebo. This will be tested in an intent-to-treat analysis using a 0.05 level two-tailed test based on a mixed effects regression model, with patients considered to be a random effect, and randomization group a fixed effect. In order to preserve statistical power, change in MCCB Composite will be used as the dependent variable; however, secondary analyses will be conducted for MCCB domain scores and measure of reward processing. The use of two post baseline evaluations (weeks 6 and 12) and the ability of the model to incorporate all available data, also improves efficiency (i.e., power). This approach will also be employed in subsequent comparisons of specific domains and for measures of reward processing. These additional analyses will be conducted at a nominal 0.05 level and will focus on enhancing interpretation of the primary analysis by highlighting the specific domains most affected by pramipexole. Since randomization is stratified by concomitant antipsychotic use and baseline depression status, indicators of stratification will be included in the model as fixed effects.

Missing data: Although the mixed effects modeling approach allows patients with evaluations at week 4 but missing at week 8 to be included, bias may be introduced if missing data are related to patient response. For example, it may be that patients responding poorly are less likely to have a week 8 evaluation than those patients with better response. The mixed effects analysis would weigh the results of these poorly performing patients less (as they provide fewer data) and in the presence of a positive effect of pramipexole, decrease power. To assess the extent that any bias has been introduced by missing data, we will impute missing week 8 values. Note that if no bias is produced by the missing data, analyses with and without imputation should provide virtually identical results. If the analyses produce different results, we will work to identify the causes by comparing patients with and without missing data. Based on our prior trial experience we expect relatively few patients (< 10) to be missing the week-8 visit due to attrition. Patients with missing data will have their 8 week MCCB score imputed via multiple imputation assuming that the data are MAR, i.e., the missing nature of the variable is independent of the value of the variable given the observed data. The specific imputation model to be used will be determined prior to examination of any outcome data, but will include MCCB score at baseline and at 4 weeks. Separate imputations will be done for each randomization group.

Due to the 12 week course of the study, mixed models will still be utilized for variables collected with sufficient frequency; however, when incorporating missing data, we will only be able to do so when at least two time points are included. Subjects with only baseline data will be included in descriptive analyses but will be dropped for analyses where necessary.

***Sample size/Power*:** A total of one hundred patients will be randomized 1:1(15 from BWH, 35 from Icahn School of Medicine at Mount Sinai, 50 from Zucker Hillside Hospital). The adequacy of this sample size is based on the ability to reject the null hypotheses of no difference between treatment groups with respect to the MCCB composite score with sufficient power (80%). Ideally, sample size would be determined

to ensure adequate power to detect the minimal clinically important difference. No specific guidelines exist to establish such a threshold in this setting but cognitive change of at least a moderate effect would likely be necessary to allow for clinical meaningfulness. Our sample size provides approximately 80% power to detect a standardized difference (e.g., Cohen's d) of approximately 0.55 with a two-tailed 0.05 level test. For the pre-specified subgroup analysis based on concomitant use at baseline, the detectable standardized difference is about 0.80.

VII. RISKS AND DISCOMFORTS

Primary risks in this study include the exacerbation of clinical symptoms (psychosis, depression, cognitive symptoms); 2) suicidal ideation or homicidal ideation; and 3) adverse events or side effects associated with pramipexole.

Risk Associated with Pramipexole: As pramipexole may have the potential to induce manic-like or psychotic symptoms, each participant will be monitored closely for an exacerbation and all subjects will be required to be taking a mood stabilizing medication in addition to the study drug. We will very closely monitor psychotic and affective symptoms on a weekly basis throughout the study period using standardized rating scales described above. In addition, at each scheduled visit a physician-level psychiatrist 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 (as outlined in the research plan) and the blind will be broken if warranted. Between weekly visits, the patients will have emergency contact information.

Any signs of suicidal ideation will result in a full risk assessment by trained/licensed study staff. Dependent on the determined risk, discontinuation of the trial and/or hospitalization will follow as per BWH treatment guidelines.

Side effects/Adverse events: The most common side effects noted for pramipexole are nausea, headache, and insomnia. Rarely more severe side effects can occur including hallucinations, narcolepsy, restlessness, and problems with impulse control. Therefore, side effects will be monitored and recorded at each visit to ensure patient safety and the study drug will be discontinued if side effects are intolerable. For changes in sleep specifically, at each visit standardized rating scales will be administered. These scales inquire about insomnia, hypersomnia, and lack of need for sleep. Changes on these ratings are closely tracked and if changes occur, they are discussed with the patient and if significant enough, the patient will be discontinued. A baseline ECG and chemistry profile including renal function testing will be carried out prior to exposure to pramipexole and again at week 8 and at the end of study (6 months or early termination). The following ECG parameters will be recorded: heart rate, PR, QRS, QT, and QTc. All ECG results will be interpreted by a MD Investigator as *Normal, Abnormal; not clinically significant (NCS), or Abnormal; clinically significant (CS)*. The MD Investigator will

refer a subject with an abnormal result to a cardiologist when deemed appropriate to do so. In addition, pramipexole can interact with some medications commonly used to treat gastrointestinal symptoms (e.g. cimetidine); therefore, subjects taking these medications will not be permitted to enroll in this trial. Any significant findings will result in study exclusion and/or referral for appropriate medical care. 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.

In September 2012, the FDA issued the following warning regarding pramipexole, "*FDA notified healthcare professionals about a possible increased risk of heart failure with Mirapex (pramipexole). Results of recent studies suggest a potential risk of heart failure that needs further review of available data. Because of the study limitations, FDA is not able to determine whether Mirapex increases the risk of heart failure. FDA is continuing to work with the manufacturer to clarify further the risk of heart failure with Mirapex and will update the public when more information is available. FDA evaluated a pooled analysis of randomized clinical trials and found that heart failure was more frequent with Mirapex than with placebo; however, these results were not statistically significant. FDA also evaluated two epidemiologic studies that suggested an increased risk of new onset of heart failure with Mirapex use. However, study limitations make it difficult to determine whether excess heart failure was related to Mirapex use or other influencing factors (see FDA Drug Safety Communication Data Summary for a detailed discussion of the studies).*" This potentially serious side effect of the study medication will be addressed in our protocol primarily by the exclusion of patients with any prior cardiac disease or at high risk for cardiac events (see exclusion criteria). Further, we will monitor for any updates to this warning, which in its current form does not suggest any changes to dosing or normal clinical usage of this agent. There have been no updates to this warning as of early 2017.

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 each 9 mL blood draw; however, a trained phlebotomist will perform the procedure to avoid any additional discomfort.

Confidentiality: All subject data will be secured on an MS SQL server with Windows integrated security. Only research staff with specific permissions will have access to the data. Subjects will only be identified with a numerical code in compliance with HIPPA regulations. Moreover, subjects will be apprised of their ensured confidentiality and told that clinical data collected from them will be included in a data base for research distribution only after all information that can reasonably identify them has been removed.

VIII. POTENTIAL BENEFITS

There may be no immediate potential benefit to the subject from participation in this research study; however, the investigational use of the medication for treating neurocognitive functioning may result in an improvement in these symptoms in some of the subjects. In addition, data from this study may lead to subsequent larger scale studies aimed at treating cognitive impairment in patients with bipolar disorder.

IX. MONITORING AND QUALITY ASSURANCE

A formal Data Safety and Monitoring Board (DSMB) will be utilized. The DSMB is already established and is operating through the NIH-funded ACISR center grant at Zucker Hillsides Hospital (ZHH). The membership includes 2 physician researchers who are not involved with the current trial but have experience in clinical trials in psychiatric samples, as well as other senior faculty in the Division of Psychiatry Research at ZHH. In collaboration with the primary statistician for this trial (Michael Parides; Sinai Co-I), the DSMB will be asked to review data on this trial at any time that there is a serious adverse event, reportable to the Institutional Review Board (IRB) *and* after the completion of each set of 10 randomized subjects (regardless of site).

In addition to the DSMB, the PI will review safety data in real time to address any concerning adverse events. Dr. Burdick has served as an active member of three IRBs over the past 15 years and will ensure that all AEs are appropriately reported and followed up.

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