TITLE: Pramipexole in Bipolar Disorder: Targeting Cognition (PRAM-BD)

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INTRODUCTION, BACKGROUND MATERIAL, SIGNIFIGANCE AND PRELIMINARY DATA

PROJECT SUMMARY

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, 12-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.

BACKGROUND

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. Our collaborator, Katherine Burdick and team, recently completed one of the first controlled trials of cognition as a treatment target in BD (Burdick et al. 2012). They 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 collaborating group (Burdick et al. 2007). In a sample of 52 Caucasian BD probands and 102 Caucasian healthy controls, they 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). They 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.

SIGNFICANCE

Neurocognition in Bipolar Disorder (BD). Historically, it was believed that BD patients achieve complete inter-episode recovery, particularly with regard to cognition (Kraeplin, 1913), contributing to the notion that the cognitive deficits in BD are transient and merely a consequence of acute symptoms. While some of the impairment seen during acute episodes may be ameliorated by effective treatment, *remitted* BD patients demonstrate deficits in attention, verbal learning, and executive function (Arts et al. 2008; Bora et al. 2009; Robinson et al. 2006; Torres et al., 2007) at around -1 standard deviation vs. healthy controls. As has been repeatedly shown in SZ (Green, 1996, Green et al. 2000; McClure et al. 2007; McGurk & Mueser, 2006; Novick et al. 2009; Perlick et al. 2008; Shamsi et al. 2011; Ventura et al. 2009), these deficits contribute significantly to functional disability in BD (Martinez-Aran et al. 2007; Jaeger et al. 2007; Brissos et al. 2008; Bowie et al. 2010; Burdick et al. 2010; Harvey et al. 2010) making them a critical treatment target (Burdick et al. 2007).

Functional Disability in BD. Although BD has been characterized as an illness with an episodic course and resultant functional recovery (Murray & Lopez, 1997); data clearly document that neither complete symptomatic nor functional recovery are the norm. Even early in the illness, patients have strikingly high levels of *subthreshold* symptomatology despite standard treatment (Tohen et al. 2003). Real-world functioning is significantly impaired. Only 19-23%of patients are married vs. 60% of the general population (Abood et al. 2002). Unemployment rates in BD are 57-65% (Dion et al. 1988) and only ½ of those who were employed had returned to their premorbid work-level, suggesting that ~80% of BD patients are at least partially vocationally disabled. Finally, 19-58% of patients do not live independently, requiring family support (Kupfer et al. 2002).

Early data suggest that, as in SZ, 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.

Rationale for Targeting Dopamine (DA). 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).

DA also plays an important role in other BD-relevant symptom domains that will be the focus of our exploratory aim in this revised submission. Namely, mood regulation, affective processing, and reward-based decision-making are all influenced by DA and will be carefully assessed in this project.

Pramipexole. 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. Our collaborator previously reported on the safety and efficacy of pramipexole in a 6-week controlled trial in BD patients with treatment resistant depression (Goldberg et al. 2004). They administered a brief battery of psychomotor and attention tests pre- and post-treatment. Results from that study indicated that pramipexole significantly improved attention (Burdick et al. 2007); however, due to the improvement in depressive symptom severity, they were unable to disentangle the effects on cognition from the antidepressant effect. We designed a follow-up study to test for its potential pro-cognitive effects in *affectively-stable* patients with BD, which was funded by the Stanley Medical Research Institute (PIs Burdick & Malhotra). This was the first controlled trial of a DA agonist with cognition as the primary outcome measure in patients with BD. We hypothesized that pramipexole would significantly improve attention and working memory due to their link with PFC function.

Data from this 8-week, randomized, controlled cognitive enhancement trial (Burdick et al. 2012) are detailed below. Our findings suggest that pramipexole is effective in improving cognition in a *subgroup* of patients with BD. ***These results warrant follow-up, with an eye toward optimizing study design***. Specifically, our results highlight several methodological challenges in designing cognitive trials in patients with BD.

1) The episodic nature of the illness requires careful consideration of baseline symptom severity, particularly in light of data suggesting a significant influence of affective symptoms on cognitive performance (Martinez-Aran et al. 2000; Basso et al. 2002). In the case that symptomatic patients are included and cognitive improvement is reported, it may be difficult to rule out pseudospecificity. As noted above, preliminary data from our first trial (Goldberg et al. 2004) provided evidence of a potential role for pramipexole as a cognitive enhancement agent; however, the patients in that trial also improved with regard to depression, making it impossible to determine the extent to which the cognitive improvement was related to the amelioration of depressive symptoms. *This trial is specifically designed to address this issue, by stratifying randomization based upon presence/absence of depressive symptoms at baseline. This will increase recruitment feasibility given the prevalence of persistent low-grade depression in BD and will provide direct data on the influence of baseline mood on cognitive outcome.*

2) A second methodological issue concerns the considerable cognitive heterogeneity that is seen in BD, with about 40% displaying 'normal' cognition (Martino et al. 2008; Reichenberg et al. 2009; Bora et al. 2010). We did not impose a minimal impairment for inclusion; however, the potential utility of doing so is reflected in that lower baseline performance correlates with greater improvement due to pramipexole (Burdick et al. 2012). Moreover, ceiling effects in BD are of real concern. The current proposal is designed to address this issue by pre-screening subjects for objective evidence of *global* cognitive dysfunction and including only these patients.

3) Another limitation, as in most studies of BD patients, is the use of concomitant psychotropic medications. Although it is impractical/unethical to require a washout of medications in a stable patient, our data indicate that certain restrictions may optimize benefits. Given the limited sample size, we were only able to superficially determine the effects of concomitant medications by dividing groups based on the presence/absence of specific drug classes (e.g. antipsychotics, lithium). In using a DA agonist to target cognition, the use of antipsychotics was of particular concern due to their action at the D2 receptor; however, given their widespread use in BD, it was not feasible to exclude all subjects taking these agents. Our data suggest that antipsychotics may indeed limit the degree of improvement attributed to pramipexole (see preliminary data); thus, this proposal will address this issue more conclusively by recruiting a large enough sample to allow for stratification by concomitant antipsychotic status at the time of randomization.

4) In our previous study, we utilized a fixed-dose design with a highly conservative maximum daily dose (1.5 mg/day) in an effort to reduce the chances of mania or psychosis induction, which may have limited the potential for cognitive benefit. There were no concerning side-effects or clinical worsening; 100% of subjects reached the maximum dosage by week 4. In pramipexole trials in BD depression, efficacious and tolerable doses ranged from 1.0 to 5.0 mg/day suggesting that a higher dose would be well-tolerated and may have greater beneficial effects. There is some indication of a dose-response relationship in BD depression (Aiken, 2007). The current study will test this potential by using the recommended slow titration (Boehringer Ingelheim International, 2007) but allowing for flexible dosing up to a *maximum of 4.5 mg/day (the maximum FDA-approved dosage in PD)*.

5) Finally, as the previous trial included an 8-week treatment phase, our ability to measure the long-term safety and efficacy of pramipexole was limited. Moreover, improving quality of life and day-to-day functioning is an important goal in any study targeting cognition. The measurement of social and occupational capacities in the context of an 8-week trial is inadequate, as it is very unlikely that a person's occupational status would change that rapidly even if the study drug was highly effective. Therefore, in an effort to extend our safety and efficacy data and to allow for the assessment of changes in community functioning, we will lengthen the treatment and follow-up phase of the current trial to 12-weeks and include detailed co-primary measures of functional capacity.

Pramipexole: Safety Data. In our published reports (Goldberg et al. 2004; Burdick et al. 2012), pramipexole was a safe adjunctive in the treatment of depression and cognitive dysfunction in BD. In studies of pramipexole in affective patients, the most common side effects included nausea, headache, and somnolence (Aiken, 2007). In Burdick et al. (2012), only a single adverse event (restlessness) was reported more frequently in the active vs the placebo group. Importantly, there is no evidence to suggest a high risk for medication-induced manic switching, with combined data indicating a switch rate of ~5% for hypomania and ~1% for mania over an average of 14 weeks. These rates are lower than those reported with other antidepressants (~11% hypomania; ~8% mania; Aiken, 2007). Although in Parkinson's trials, psychosis has been reported, most commonly in the form of visual hallucinations, the rates of psychosis in mood disordered patients is less than 1% (Aiken, 2007) and in our own work, we have not experienced any psychosis-related adverse events (Goldberg et al. 2004; Burdick et al. 2012).

DA is not only implicated in normal cognition but is also known to play a critical role in reward-based learning (Schultz, 2006; Balleine et al., 2007). While several studies have demonstrated beneficial cognitive effects of pro-dopaminergic agents on attention and working memory (Costa et al., 2009; Granon et al., 2000; Mehta et al., 2000; Mattay et al., 2000), pramipexole and other DA agonists have also been implicated in the emergence of risk-seeking behaviors such as pathological gambling in Parkinson disease (PD) patients (Dodd et al., 2005; Voon et al., 2006; Potenza, Voon, & Weintraub, 2007; Lader, 2008; Bodi et al., 2009; Weintraub et al., 2010; Weintraub et al., 2006; Voon et al., 2006a; Voon et al., 2006b; Pontone et al., 2006). A purported mechanism for this effect is related to pramipexole's high selective affinity for D3 receptors, which are primarily expressed in the mesocorticolimbic DA pathway – a circuitry active during impulsive decision-making (Madden et al., 2010). Although there is a paucity of data on the potential for pramipexole to cause DA disinhibition syndrome in BD, given the data in other clinical samples and the predisposition toward impulsive behaviors in BD (Adida et al. 2008; Adida et al., 2011, Jollant et al., 2007, Malloy-Diniz et al., 2009, Malloy-Diniz et al., 2009; Martino et al., 2011; Yechiam et al., 2008), it would be reasonable to predict heightened susceptibility to the development of behaviors associated with poor decision-making when taking a DA agonist. We measured emotional decision-making, using the Iowa Gambling Task (IGT), before and after drug administration and found an increase in high-risk/high-reward choices after active treatment. There were no reports of disinhibited behaviors (e.g. gambling, hypersexuality), nor any increase in mania (*Burdick et al. 2013*). Currently the clinical significance of this change is unknown; however, follow-up is warranted over a longer duration. The current proposal will include *several* sophisticated cognitive-neuroscience-based measures of reward processing to carefully assess potential changes associated with pramipexole in BD patients who might be especially vulnerable to these deleterious effects.

INNOVATION

The current proposal will represent the first long-term, controlled treatment trial of pramipexole as a pro-cognitive agent in stable BD patients. In this 2-site study, we will randomize 100 *stable* BD patients with objective evidence of *global* cognitive impairment to 12-weeks of pramipexole vs. placebo. *Randomization will be 1:1 and stratified for concomitant antipsychotic status and presence/absence of subthreshold baseline depressive symptoms.*

Target: The first innovative aspect of this study is its primary focus on targeting the RDoC relevant phenotype of neurocognition in BD, as opposed to the affective symptoms of the illness. While there are many ongoing trials in SZ, there are very few cognitive enhancement studies in BD. There have been a handful of case reports/series described in the literature that have included an assessment of cognition as part of a treatment trial in BD patients; however most have utilized subjective (patient-rated) reports of cognitive improvement (Jacobsen et al. 1999; Schrauwen et al. 2006; Teng et al. 2006) and no objective cognitive tests were administered. Given the lack of correlation between subjective ratings of cognition and neuropsychological test results in BD

patients (Burdick et al. 2005; Martinez-Aran et al. 2005) the extent to which previously reported cognitive improvement represented cognitive enhancement as opposed to an effect on mood or general well-being is unknown. Limited data derived from studies of the cholinesterase inhibitor, galantamine, in BD are promising (Ghaemi et al. 2009; Iosifescu et al. 2009) and are ongoing in work being conducted by a Co-I on this proposal (R01 MH079157; PI: Iosifescu). *Intervention:* In considering intervention strategies that might be efficacious, we chose to focus on enhancing DA neurotransmission using an already marketed agent. Although by definition, this agent is not novel, the 're-purposing' of already approved medications is highlighted as an important component of continuing drug discovery by Tom Insel (NIH Director; Insel, 2012). Pramipexole is a partial/full D2/D3 agonist with an 8-fold greater affinity for D3 over the D2 receptor (Mierau et al. 1995; Gerlach et al. 2003). Its relative specificity allows for a unique opportunity to enhance DA in phylogenetically older brain regions associated with emotion regulation, reward, and cognitive function (Camacho-Ochoa et al. 1995). Consistent with this mechanism of action, pramipexole has a direct antidepressant effect in PD patients (Leentjens et al. 2009) above its efficacy for motor symptoms (Barone et al. 2010). This antidepressant effect has also been noted in affective disordered patients (Aiken, 2007; Goldberg et al. 2004; Zarate et al. 2004) and preclinical data suggest a neurotrophic effect of pramipexole in neurodegenerative models (Lauterbach et al. 2010) mediated by the anti-apoptotic protein bcl-2 (Takata et al. 2000), supporting its use in cognitive remediation strategies (Lauterbach & Mendez, 2011).

PRELIMINARY DATA

Data from our previous work provided below support: 1) the feasibility of completing the proposed study by including the original investigators and staff involved in the prior successful trial; 2) the efficacy of adjunctive pramipexole in targeting cognition in BD patients; 3) the safety of adjunctive pramipexole in BD; and 4) the importance of addressing several confounds to optimize cognitive enhancement strategies in BD.

1) Feasibility: To address potential concerns related to the feasibility of completing a 12-week clinical trial in stable BD patients, we note our successful completion of a trial very similar in scope to the proposed project (led by both of the site PIs Burdick and Malhotra). We randomized 50 stable BD patients to pramipexole vs. placebo in an 8-week trial with 90% completion rate. Recruitment and retention efforts will parallel those used. Safety and efficacy measures will be collected by experienced staff members trained by the PIs most of whom participated in the prior trial. *Although the sample was more heterogeneous in our earlier work, we have optimized our recruitment strategies based upon prior experience. We will now allow subthreshold depression, which will also increase feasibility. At both sites, our study physicians carry large case-loads of BD patients and are responsible for their ongoing clinical care. This will be critical in capturing those patients who are not taking antipsychotic medications or who can be safely discontinued (e.g. those subjects who are taking very low doses for sleep or other indications). We have evaluated our own databases to determine the feasibility of recruiting sufficient numbers of patients with global impairment (based on MCCB composite scores of at least -1 SD) and find that while approximately 35% of healthy controls meet this threshold (as might be expected based on normal curves), approximately 72% of our euthymic BD patients meet this criterion. While this may present as an increased challenge, it is critically important to ensure that the subjects being enrolled are the subjects that are best suited for intervention. We believe that this is a wholly feasible recruitment goal.*

2) Cognitive efficacy of pramipexole in BD: **Study 1**(Goldberg et al. 2004) -We conducted a 6-week, controlled study demonstrating the safety and efficacy of pramipexole, in treatment resistant BD depression (Goldberg et al. 2004). We included a brief assessment of psychomotor functioning

and attention. In a small sample (n=7), pramipexole had significant effects on concentration and visual search efficiency. Cognitive enhancement was evidenced by a significant change in performance on an index of concentration (t=-2.9, df=6, p=0.03; Burdick et al. 2007). These data provided the motivation for the subsequent study directly targeting cognition in BD.

Study 2 (Burdick et al. 2012) – In an effort to disentangle the antidepressant effects and the pro-cognitive effects of pramipexole in BD subjects, we designed our second study to include only patients who were not experiencing significant depression or mania (HamD <12; CARS-M <8) and we utilized cognition as the primary outcome. Results indicated a slight but statistically non-significant improvement in the pramipexole arm vs. placebo in the full sample of completers (n=45). Post hoc analyses revealed a significant effect of pramipexole in the *euthymic* subset of the sample (n=34; Fig. 1; F=2.62; df=1,33; p=0.030). We found significantly greater improvement in the patients taking pramipexole vs. placebo for WAIS Digits Backward (F=4.98; df=1,33; p=0.033) and Stroop Color (F=10.37; df=1,33; p=0.003), with a generalized pattern of greater improvement in the pramipexole group.

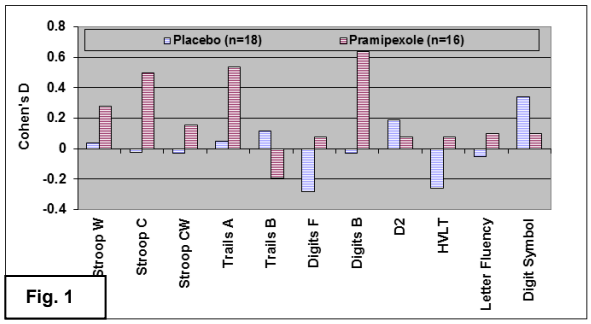

Fig. 1

3) Safety of pramipexole in BD: In Study 1 (Goldberg et al. 2004), BD depressed subjects reported higher rates of nausea in the active arm (58%) vs. the placebo (20%) and 1 subject developed mania at week 6 while on pramipexole. In Study 2 (Burdick et al. 2012), affectively-stable BD subjects reported higher rates of restlessness in the active arm (25%) vs the placebo arm (0%);(χ^2=5.4; p=0.02) and there were no exacerbations of mania, depression, or psychosis. No subject discontinued due to side effects in either study. Overall, pramipexole appears safe when used as an adjunctive in depressed and affectively-stable BD patients.

As described above, DA agonists, as a class, increase the risk of developing impulse-control disorders, such as pathological gambling, in PD patients, albeit at a very low rate (Aiken, 2007). For additional safety data collection in Burdick et al. (2012), we evaluated performance on the IGT in a subset of the sample (measure added part way through trial) at baseline and again after 8-weeks of treatment. Healthy individuals learn over 5 blocks to choose cards from the more conservative decks and to avoid the high-risk/high-reward decks, as they result in a net loss – represented in Figure 2 (dotted blue line). RM ANCOVA revealed a significant main effect of Time (F=6.03; df=1; p=0.02) and a significant three-way interaction for Time x Block x Group (F=2.54; df=4; p=0.04) indicating that after 8-weeks of treatment, the BD subjects in the placebo group show evidence of learning (practice effects/improvement) – approaching a normal learning curve, while the patients pramipexole develop an abnormal pattern of learning (reverse learning curve; red arrow). This pattern is indicative of a preference for high risk/high reward card choices that was not present at baseline *and these results are now published (Burdick et al. 2013).*

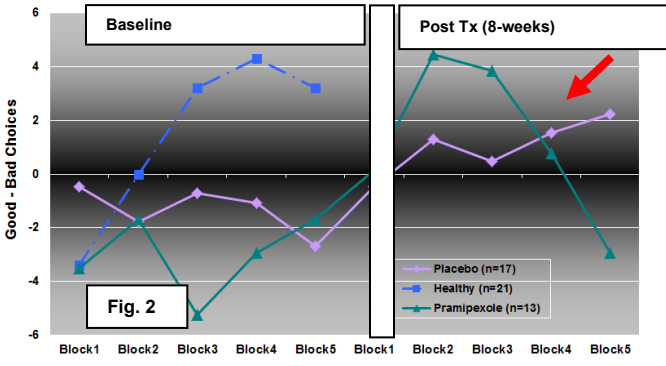

Fig. 2

This abnormal pattern of performance did not correlate with risky or impulsive behaviors, or with manic symptoms so this change is of unknown clinical relevance but will be a focus of the proposed application. We will administer this task as we did previously and extend the time of follow-up to ensure that these data do not indicate impending affective instability that may not have been adequately captured in the 8-week trial. We will use changes in IGT performance at week 8

as a potential predictor of changes in mood state at all subsequent visits to address whether it signals the very early stages of manic switch. Our prior data did not allow for this analysis, as the IGT testing was done at the end of the trial and clinical follow up did not continue beyond that time.

4) Confounds to prior design: As described in Burdick et al. (2012), several design issues limited the efficacy signal of the initial trial. The proposed 2-site collaborative effort will allow for enhanced recruitment and increased selectivity of subjects to address the following issues: **a)** BD subjects with subsyndromal levels of depression did not fare as well as euthymic patients. A considerably larger effect size improvement was noted in the subgroup of *euthymic* subjects who received pramipexole in comparison with the full (unselected) sample in the active arm. *These data alongside evidence from our group and others that indicate pramipexole as an effective anti-depressant in BD are somewhat counterintuitive, making the decision to include or exclude subjects with subthreshold depression less obvious one. In the first application we suggested that it was prudent to limit enrollment to euthymic BD patients; however, we modify this strategy in the revision to enhance feasibility and generalizability and to provide more data on the potential interactions between baseline mood state and cognitive outcome. We will now allow subthreshold depressive symptoms at baseline and stratify randomization based upon this factor*; **b)** Subjects with greater baseline impairment improved more. We carried out correlations with the hypothesis that baseline performance on a given measure would have a significant relationship with the change score calculated for the same measure (week 8 performance – baseline performance). In the placebo group, baseline performance on WAIS Digits Backward was *not* correlated with the Digits Backward change score (**r=0.23; p=0.28**) nor the Stroop change score (**r=-0.28; p=0.18**); however, correlations between these variables in the pramipexole group were strong and statistically significance (Digits **r=-0.61; p=0.003**); (Stroop r=**-0.42; p=0.05**). These results suggest that higher levels of baseline cognitive impairment (lower scores) is associated with greater cognitive improvement post-pramipexole treatment. This does not reflect a general tendency or regression toward the mean, as it is not noted in the placebo sample. Taken together with evidence suggesting that there is significant cognitive heterogeneity in BD (Reichenberg et al. 2009), we will address this by prescreening and excluding those subjects who are least likely to benefit from cognitive enhancement due to a lack of sufficient baseline impairment; and **c)** Concomitant antipsychotic medications appeared to diminish the beneficial effect of pramipexole. Specifically the improvements noted on WAIS Digits Backward were considerably stronger in the subjects who were not taking antipsychotic medications (**Eta^2=0.32**) than in those taking antipsychotics (**Eta^2=0.12**). Likewise, improvement on Stroop Color was greater in subjects not taking antipsychotics (**Eta^2=0.33**) vs. subjects on antipsychotics (**Eta^2=0.16**). While this suggests a potential interaction, the data are not definitive. In the current proposal, we will stratify randomization by concomitant antipsychotics and allow only half of the total sample to be on antipsychotics and we will directly test for effects of this factor.

OBJECTIVE(S)/SPECIFIC AIMS AND HYPOTHESES

COLLABORATIVE PLAN

The overall organization of this project is provided by the PIs, Drs. Burdick and Malhotra. Each site [Icahn School of Medicine at Mount Sinai (ISMMS) and the Zucker Hillside Hospital (ZHH)] will be responsible for managing the activities of their site. Overall organization and management of sites will be provided by ISMMS. All PIs and Co-Is will participate in monthly conference calls over the first 3.5 years of the study. During the data analytic phase, the frequency of conference calls will be increased to weekly.

Mount Sinai will serve as the coordinating site for this trial; therefore, Dr. Burdick will be the contact PI and responsible for all interactions between sites and with NIH. All procedures specific to the clinical trial will be identical at the two sites. Rater training will be initiated with an in-person, on-site meeting to ensure adequate reliability for clinical and neurocognitive assessments. We are uniquely situated to ensure reliability, as Dr. Burdick was formerly the Director of the Neurocognitive Assessment Unit at the second site (ZHH) and she conducted training with staff at both sites. All statistical analyses will be led by the statistician (Co-I) Michael Parides from ISMMS. This will include intermittent safety data analyses for the Data Safety and Monitoring Committee (DSMB) review and all analyses at the conclusion of the trial.

The PIs will work together to discuss any changes in the research project and reprogramming of funds, if necessary. This study team has a long track record of collaborating successfully do not anticipate problems. All co-investigators will first identify primary publications and then negotiate the order of authorship using a principle of fairness. PIs will coordinate publication efforts so that: manuscripts can be submitted and published in a timely fashion; authorship can be apportioned consistently and fairly among the investigators; disputes about authorship can be resolved through respectful negotiations; and junior investigators at each site can write manuscripts. All manuscripts/abstracts shall have author representation from each site. No author will be listed who has not made a material contribution to the scientific content. If a conflict develops, the PIs shall meet to resolve the dispute. If they fail, the disagreement will be referred to a multiple PI arbitration committee composed of faculty of ISMMS and ZHH. The PIs agree that any decisions made will be final and binding.

OBJECTIVE

The current proposal will represent the first long-term, controlled treatment trial of pramipexole as a pro-cognitive agent in stable BD patients. In this 2-site study, we will randomize 100 *stable* BD patients with objective evidence of *global* cognitive impairment to 12-weeks of pramipexole vs. placebo. *Randomization will be 1:1 and stratified for concomitant antipsychotic status and presence/absence of subthreshold baseline depressive symptoms.*

SPECIFIC AIMS

Specific aims are:

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.

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.

3. ***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.

EXPERIMENTAL DESIGN

METHODS

Subjects: Subjects will be recruited primarily from The Zucker Hillside Hospital, a very large acute care psychiatric facility serving a very diverse patient population from the greater New York City area, and its affiliated programs and outpatient clinics. Recruitment will include word of mouth and posting of IRB approved advertisements throughout The Zucker Hillside Hospital, on internet webpages (e.g.craigslist) and in local newsletters (e.g. NAMI). Krasnoff Quality Management Institute (KQMI) will be used to provide lists of potentially eligible patients within the health system that meet study criteria. A letter will be mailed to these potential participants that include an explanation of why they are being contacted, a basic description of the study and how to contact the study team if interested. If necessary, we will recruit through community advertisements. Up to 50 affectively stable patients with Bipolar Disorder will be randomized. Additional subjects will be screened, with an assumption of some not meeting eligibility; therefore, we estimate 90 patients to be consented for 50 to be randomized.

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 4 or more concomitant psychotropic medications. 1st generation antipsychotics 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.

PROCEDURES

Subjects will be recruited from the Zucker Hillside Hospital and its affiliates as described above. Community advertisements will be placed if needed (none currently attached for review). Potentially eligible patients are identified by the patient's clinical care taker (nurse practitioner and/or physician), who would then grant permission for our research team to approach and explain the protocol. A research member will approach that individual and explain the study objectives, procedures, risks and benefits, and begin the informed consent process if the patient wishes.

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). 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 $\geq$ 8). Study drug will be blinded and matched to placebo. 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/day and increased every week to a target of 4.5 mg/day. 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). Dosing will be flexible based on side effects; however, if 1.5 mg/day cannot be tolerated, the subject will be discontinued. Ideally, 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). Measures are described in detail below.

Clinical Assessments and their frequency: Research study visits will occur at baseline, weeks 1 2, 3, 4, 6, 8, and 12. Patients who will be terminating early will be asked to also complete week 12 assessments at their end-of-study visit.

Safety Outcome Measures
PRISE Side Effects Checklist (physician administered) – (all visits)
Vital signs including blood pressure (standing/supine) – (all visits)
Electrocardiogram (ECG) – (screening, week 6 and week 12)
Liver function tests; chemistry panel; CBC; urinalysis – (screening, week 12)
Medication log of current medications and all medications administered during previous week – (all visits)
Pregnancy test for women of childbearing age – (screening, week 12)
Urine toxicology – (screening, week 12)

Clinical/Symptom Measures
Structured Clinical Interview for the DSM-IV (SCID–IV) – (screening)
Symptom rating scales: Young Mania Rating Scale (YMRS); Hamilton Rating Scale for Depression (HRSD); Brief Psychiatric Rating Scale (BPRS) – (all visits)
Columbia Suicide Severity Rating Scale – (all visits, except screening)
Smoking Questionnaire – (baseline, week 6, week 12)

Neurocognitive/Functional Measures
Screening cognitive battery (see inclusion criteria 4 and 6.) – (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)
Iowa Gambing Task – (baseline, week 6, week 12)
UCSD Performance Skills Assessment (UPSA) – (baseline, week 12)
World Health Organization Disability Assessment Schedule – self-administered version (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

STUDY TIMELINE

There will be a 2-month start-up, 40 months of recruitment and 6 months of follow-up. The last patient randomized will be mid-way through Year 3 to ensure study completion by end of Year 4. Analyses and manuscript preparation will be completed immediately thereafter. We will screen ~3 patients per month (~1 patient randomized/month), totaling 70 patients screened and 50 patients randomized.

STUDY ENDPOINTS

The primary endpoints related to the safety and efficacy on neurocognitive functioning of pramipexole will be measured. Neurocognitive performance on the MATRICS Consensus Cognitive Battery will be measured at baseline, week 6, and 12 (or end of study). Safety measures will be assessed at each visit throughout the study. Co-primary measures of everyday functioning will be assessed at baseline, week 6 and 12.

SPECIMEN BANKING

Blood samples collected through this project for the purposes of genetic analyses will be stored in the laboratory of the Division of Psychiatric Genomics within the Department of Psychiatry at ISMMS. Any and all identifying information connected to these blood samples will be removed before the samples are sent to this lab. 32 ml (2 tbsp) of blood will be collected for these purposes if the participant chooses to partake in this optional component.

INCLUSION AND EXCLUSION CRITERIA Subject Selection

Human Subject Involvement, Characteristics and Design

Involvement: The study will involve human subjects as their participation is required to obtain information about pramipexole in patients with bipolar disorder.

Subject Characteristics: Fifty subjects will be randomized for this clinical trial comparing the effects of pramipexole treatment on cognition in patients with bipolar disorder versus placebo capsules.

Inclusion Criteria will be: (1) Age 18-65. (2) DSM-IV 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 (CVLT). Clinically-significant impairment will be defined as scoring ≥ 1 SD below normative means on any one of these measures. This will be done by standardizing each score and computing a mean z-score. (5) Clinically-acceptable, stably-dosed, mood stabilizing medication regimen for ≥ 1 month prior to enrollment, with no medication changes planned over the 12-week study period. (6) Wide Range Achievement Test (WRAT-3) score of >70.

Exclusion Criteria will be*:* (1) History of CNS trauma, neurological disorder, ADHD, MR, and/or learning disability. (2) Positive urine toxicology inconsistent with participant report or DSM-IV 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) 4 or more concomitant psychotropic meds. (6). Any disallowed medications per Concomitant Medications section of protocol, such as 1st generation antipsyhotics or drugs known to interact with pramipexole. (7) Abnormal lab or ECG result at screen. (8) Any significant cardiovascular risk factors as determined by the study physician. (9) Significant suicidal risk (HRSD item 3 > 2 or by clinical judgment). (10) Pregnancy, breastfeeding, not using contraception. (11) Participation in any other investigational cognitive enhancement study within 30 days. (12) ECT in the past 12 months.

Participants are free to refuse to answer any of the questions that are being asked of them in the study. If the withheld information is critical to study eligibility the participant may not be enrolled.

Rationale for inclusion criteria: The diagnostic, age and medical exclusions are derived from requirements specific to the proposed study (e.g. safety requirements specific to pramipexole treatment). Evidence of current symptoms is required to allow assessment of treatment effects.

Inclusion of Women and Minorities: There are no restrictions related to gender, race or ethnicity to study participation.

RECRUITMENT PROCEDURES

Recruitment will follow procedures that are IRB approved. Referrals for the study will come from clinicians or self-referral by patients. Patients may find out about the study through IRB-

approved recruitment flyers and other approved advertisements. If a clinician referral, the clinician will first seek permission from the patient for referral. The consent process begins with an assessment of the patient's ability to give informed consent. Patients who on initial evaluation by the study investigator are deemed not to be capable of giving informed consent will not be evaluated further. Patients who are deemed capable of giving informed consent will then be provided with a full and complete description of the study.

We will review a list of participants from a prior study (05-069) which corresponded to Aim #1 of this protocol. Those subjects that are likely to be eligible will be contacted via phone or email and given the option to participate in this study. The consent form for study 05-069 did not provide an option to decline future contact.

INFORMED CONSENT

Consent will follow IRB approved procedures. A potential participant 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 the questions the potential participant may have. Participants are advised that they can withdraw from the study at any time. Participants 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 the Institutional Review Board.

DISCOMFORTS AND RISKS

Potential Risks

During the informed consent process, participants will be informed of the potential risks associated with the study. At each weekly visit the study physician will meet with participants and conduct a thorough review of symptoms including mood, and suicidal 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 participant receives emergency care or hospitalization. Participation in the study will be discontinued in any case of clear symptom worsening. Between weekly visits, the participants 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 main risks to subjects are: 1) risks directly associated with study treatment, 2) risks of blood collection, 4) risks of other study procedures, 5) risks of loss of confidentiality. These are presented below followed by a discussion in the next section on procedures to minimize risks.

Risks directly associated with study treatment:

Risks associated with pramipexole treatment: The most common side effects of pramipexole are nausea, headache, dizziness, insomnia, constipation, muscle weakness, abnormal dreams, confusion, memory problems, urinary frequency. Participants will be educated about the potential for these side effects. Rare side effects have also been reported including sedating effects, impulse control symptoms, restlessness, hallucinations, and orthostatic hypotension.

Risks associated with abrupt cessation of pramipexole treatment:

If pramipexole is stopped too quickly, withdrawal symptoms including fever, confusion, and severe muscle stiffness may occur. Participants will also be advised that there is a risk of side effects associated with the abrupt discontinuation of medication. They will be educated on how to taper-off the medication at the completion of the study and be provided with a subject specific titration schedule (see also Discontinuation of Study; Drug Information). The informed consent process will alert participants to these potential risks and close monitoring will ensure prompt response to any adverse effects with appropriate treatment and/or study discontinuation, as indicated.

Risks associated with blood collection include bruising at the blood collection site and the possibility of infection.

Risks of other study procedures include the possibility that subjects will become annoyed or upset with the assessment questions.

Risks of loss of confidentiality include the possibility that subject information may become known to unauthorized individuals.

Protections to Minimize Specific Risks

Medication treatments: Careful monitoring of subjects is a key aspect of the study. Subjects progress will be monitored by research psychiatrists and side effects assessed by standardized instruments.

Phlebotomy risks: Experienced and certified personnel will be used for all blood collections.

Distress from assessments: As part of the consent process, subjects will have been informed that they can stop study procedures at any time that they wish. Interviewers will be experienced conducting assessments and will be trained to be sensitive to subject concerns. If a subject becomes distressed, study procedures will be stopped.

Loss of Confidentiality: All information collected will be maintained in accordance with the standards mandated by the IRB. We will apply for a Certificate of Confidentiality at study onset. Any information gained from this research will be kept confidential. Reports from patients' clinical records concerning research observations will not be made available to outside medical facilities without written consent of the patient. Each subject will be assigned a unique identification number and data will be coded using this number. The coded link to subjects' identities will be kept separate from the database in a locked file cabinet accessible only to the study staff. All research staff are required to demonstrate their understanding of human subjects protection issues, including confidentiality issues, by means of passing examinations mandated by the IRB. PHI will need to be collected for subjects to insure that subjects receive the proper treatment for them (e.g. preventing medication errors) and from all subjects to schedule assessments. The study data files will not have nor need PHI included as the unique identification number will suffice. Information that carries personally identifying material and links to subject identities will be kept in locked files and will be accessible only by the PI and his designees (e.g., research coordinator). All computer entries will be identified by code only and kept confidential. Patients' identities will not be revealed in any description or publication of this research. The Northwell Health, its members and healthcare providers conform to the Health Insurance Portability and Accountability Act (HIPAA). This act includes rules that protect the privacy of health information about subjects that will either be created or used in connection with

this research study. We will ask all subjects to grant authorization to use their health information in the informed consent.

POTENTIAL BENEFITS

Potential Benefits of the Proposed Research to Human Subjects and Others

There may be no immediate potential benefit to the participant 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 BD.

All subjects will receive compensation for their time performing research procedures at rates approved by the IRB. Participants will be informed during the consent process of the study compensation. Participants will be paid $100 for the screening visit; $50 for baseline and week 6; $20 for weeks 1, 2, 3, 4, and 8; $100 for week 12. In the consent there is an optional DNA blood draw. If the participant chooses to consent to this they will receive an extra $10 at the time of the blood draw. Total possible payment is $410 for study completion and DNA blood draw. Screen failures will receive the screening rate ($100) provided they undergo study procedures at that visit.

DISCONTINUATION OF STUDY/ SUBJECT WITHDRAWAL

The study may be discontinued at any time. Prior to the study being discontinued, all subjects will have been informed of their treatment allocation during the study. Study data in the case of early study termination will be retained to allow for future study analyses.

Subjects may be prematurely terminated from the study if the investigators assess that the subject's clinical condition requires treatment(s) not available within the study context.

Participants with an exacerbation of mania/depression (YMRS $\geq$ 15 or HRSD $\geq$ 18) will be discontinued and treated by the study physician. Suicidal ideation will be assessed at each visit with 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 for potential need for hospitalization). Participants at risk for suicidal behavior will be discontinued. Side effects will be rated by a study physician at each visit. Any side effect deemed to be a serious adverse event or an unanticipated follow up will be reported to the PI, and the ISSMS Institutional Review Board (IRB) and appropriate follow up will be conducted. In addition, participants who exhibit an inability to follow the protocol will be discontinued and withdrawn from the study.

Participants may withdraw from the study for any reason at any time by contacting the principle 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 principle 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.

To ensure orderly termination from the study, the study physician would meet with the participant to discuss termination and discontinuation of medication at their last study visit (whether this occurs at study completion at week 12 or at an earlier study visit, if the participant chooses to withdraw or is withdrawn by staff). Safety measures will be collected and a follow-up visit by phone will be scheduled to further ensure safe discontinuation. Pramipexole will then be tapered-off at a rate of .75 mg/day over the course of ten (10) days. A subject-specific day-to-day titration schedule (based on the maximum dose of study medication at the end of study completion) will be provided to the subject. A member of the study team will follow-up with the subject via phone at the end of the 10 day titration to assure compliance and check on any reported symptoms. If there are any remaining concerns by the participant, we will schedule an in-person follow-up visit.

THE DATA AND SAFETY MONITORING PLAN

Monitoring of the study will follow the guidelines of the respective study IRBs. In addition, 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 Hillside Hospital (ZHH). The DSMB monitors all clinical trials conducted under the aegis of the Center. Meetings are held via teleconference. 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; ISMMS Co-I), the DSMB will be asked to review data on this trial (both sites) at any time that there is a serious adverse event, reportable to the Institutional Review Board (IRB) and every 6 months.As the DSMB has a set meeting schedule and cannot meet on demand, the study will be reviewed at the first meeting following the enrollment of the first subject (0-6 months from time of enrollment). The study will be on the schedule for review every 6 months thereafter. The DSMB will have access to all relevant clinical data on all subjects necessary to assess the adequacy of human subjects protection provided throughout the study. The complete protocol and consent form are provided to the DSMB. In addition to the DSMB, the PI at each site will review safety data in real time to address any concerning adverse events.

The trial will be registered in Clinical Trials.gov.

CRITERIA FOR EVALUATING RESPONSE/STATISTICAL ANALYSIS

Statistical Analyses

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 4, 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.

Power and sample size considerations: A total of one hundred patients will be randomized 1:1(50 from ISMMS, 50 from ZHH). 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.

SCHEDULE OF EVENTS:

Measure	Screen	Baseline	Wk1	Wk2	Wk3	Wk4	Wk6	Wk8	Wk12
SCID	xx								
Ncog-Sc	xx								
YMRS	xx	xx	xx	xx	xx	xx	xx	xx	xx
HRSD	xx	xx	xx	xx	xx	xx	xx	xx	xx
CSSRS		xx	xx	xx	xx	xx	xx	xx	xx
MCCB		xx					xx		xx
PSST		*xx*					*xx*		*xx*
UPSA		xx							xx
WHODAS		xx							xx
AEs	xx	xx	xx	xx	xx	xx	xx	xx	xx
IGT		xx					xx		xx
BPRS	xx	xx	xx	xx	xx	xx	xx	xx	xx
Smoking		xx					xx		xx
ECG	xx						xx		xx
Labs	xx								xx
Vitals	xx	xx	xx	xx	xx	xx	xx	xx	xx

TABLE KEY: Safety Outcome Measures: Adverse Events (AEs) measured by the PRISE side effects checklist (physician administered); Vital signs/blood pressure (standing/supine); Electrocardiogram (ECG); liver function tests; chemistry panel; CBC; urinalysis; Beck Scale for Suicidal Ideation (BSI) and Columbia Suicide Severity Rating Scale (CSSR); Iowa Gambling Task (IGT). Clinical/Symptom Measures: Structured Clinical Interview for the DSM-IV (SCID); Symptom rating scales including Young Mania Rating Scale (YMRS), Hamilton Rating Scale for Depression (HRSD) and Brief Psychiatric Rating Scale (BPRS). Neurocognitive/Functional Measures: MATRICS Consensus Cognitive Battery (MCCB); Probabilistic Stimulus Selection Task (PSST); UCSD Performance Skills Assessment (UPSA); World Health Organization Disability Assessment Schedule (WHODAS) (self-administered version)and Smoking Questionnaire.

CONFLICT OF INTEREST

Dr. Malhotra has no conflicts of interest to disclose.

DRUG INFORMATION

Randomization will be conducted via a computer generated program and all study staff, except pharmacy 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. The study medication blinding will be done per prescriptions by local site pharmacy.
Active drug dosing: 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 QD and increased every week to a target of *4.5 mg/day*. *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 PD) 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).* 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 5 and then efforts will be made to maintain the same dose until the completion of the trial (week 12). As previously mentioned, at the completion of the trial (week 12) the subject will be titrated off the study medication at a rate of .75 mg/day over the course of 10 days. Also, see Appendix

ADVERSE EVENTS

The study includes structured assessments of side effects at each study visit. All subjects will be seen by research psychiatrists who will provide appropriate clinical management of adverse events.

Adverse events will be reported to the IRB following the current IRB guidelines in effect at the time of the adverse event occurrence. Adverse events will also be presented to the Data Safety and Monitoring Board (DSMB) following the guidelines established by the DSMB for the study.

DRUG ACCOUNTABILITY

Pramipexole tablets that are used in this study are purchased by the pharmacy from several different manufacturers and a small research stock is maintained by the pharmacist.
The research coordinator will be responsible for getting the prescription to the pharmacist as well as communicating possible doses that would be needed.

Encapsulation Process

1. If patient is on active Pramipexole the pharmacist places Pramipexole tablet into an orange, blue or white capsule (according to dosing protocol) size 1 or 0, using gloves, and fills each capsule with lactose powder. The compounded capsules are cleaned with tissue and placed into a prescription vial with child proof cap.
2. If patient is on placebo the pharmacist places lactose powder into an orange, blue or white capsule (according to dosing protocol) size 1 or 0, using gloves. The compounded capsules are cleaned with tissue and placed into a prescription vial with child proof cap.
3. Pharmacist will log all lot numbers, manufacturer information and expiration dates of medication, capsules and lactose powder in patient specific compounding log.

4. The Pharmacist will create a patient specific compound lot number and new expiration date for compounded capsules. Expiration date is calculated as 1 year from current date or 50% of manufacturer's expiration date, whichever is less.

Drug Storage: The medication will be stored in a temperature controlled environment that is in the range of 15°C to 30°C (59° to 86° F) monitored 24 hours a day and checked by regular temperature checks. The pharmacy uses a daily room temperature log and when temperatures are out of range the following procedure will be followed. Temperatures rechecked after 1 hour and if temperatures remain out of range then pharmacy supervisor & engineering department will be notified. The medications will be removed and placed in another temperature monitored location. When the temperature is in an acceptable range the medications will be returned to their original location.

INSTITUTIONAL REVIEW BOARD (IRB)

The Northwell Health IRB will be the IRB for the study. Also study procedures will follow the guidelines of the IRB. Specifically, prior approval of the protocol and the informed consent form will be required prior to any study subject procedures being performed.

CONFIDENTIALITY

All information collected will be maintained in accordance with the standards mandated by the IRB. We will apply for a Certificate of Confidentiality at study onset. Any information gained from this research will be kept confidential. Reports from patients' clinical records concerning research observations will not be made available to outside medical facilities without written consent of the patient. Each subject will be assigned a unique identification number and data will be coded using this number. The coded link to subjects' identities will be kept separate from the database in a locked file cabinet accessible only to the study staff. All research staff are required to demonstrate their understanding of human subjects protection issues, including confidentiality issues, by means of passing examinations mandated by the IRB. PHI will need to be collected for subjects to insure that subjects receive the proper treatment for them (e.g. preventing medication errors) and from all subjects to schedule assessments. The study data files will not have nor need PHI included as the unique identification number will suffice. Information that carries personally identifying material and links to subject identities will be kept in locked files and will be accessible only by the PI and his designees (e.g., research coordinator). All computer entries will be identified by code only and kept confidential. Patients' identities will not be revealed in any description or publication of this research. The Northwell Health, its members and healthcare providers conform to the Health Insurance Portability and Accountability Act (HIPAA). This act includes rules that protect the privacy of health information about subjects that will either be created or used in connection with this research study. We will ask all subjects to grant authorization to use their health information in the informed consent.

Contacting Via Texting/ Email

We have found that it is often easier to reach participants for the purposes of scheduling and confirming activities via text message or email. Text messages or emails will only be sent to remind participants of upcoming appointments and/or to request that the

participant contact the coordinator for additional information. No PHI will be transmitted via text message or email. Any cell phone number or email address that specifically identifies the participant will not be used to report information about the project and will be stored separately from other data in order to protect the identity of the participant to the maximum extent.

DATA DISCLOSURE/PUBLICATION/CONFIDENTIALITY

All study publications will report only de-identified data. Only de-identified data sets are eligible for data sharing. Any data sharing must confirm with the IRB guidelines in effect at the time for the proposed data sharing.

APPENDICES

Data on the pramipexole formulation to be used is included in the Appendix. **Literature Cited**

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