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A Placebo-Controlled Adjunctive Trial of Pramipexole in Patients with Bipolar Disorder: Targeting Cognitive Dysfunction

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Abstract

Objective—Patients with bipolar disorder suffer from significant cognitive impairment which contributes directly to functional disability in bipolar patients, yet few studies have targeted these symptoms for treatment and the optimal study design remains unclear. We evaluated the effects of the dopamine D₂/D₃ receptor agonist, pramipexole, on cognition in bipolar disorder.

Methods—50 DSM-IV stable bipolar I outpatients enrolled in an 8-week, double-blind, randomized, placebo-controlled cognitive enhancement trial. Patients completed neurocognitive testing at baseline and at week 8. Symptoms and side effects were monitored weekly.

Results—Forty-five patients completed the study [Placebo (n=24); Pramipexole (n=21)] and groups were well-matched on demographic and clinical features. Primary cognitive analyses were negative; however, secondary analyses revealed some interesting results which serve to highlight several important methodological issues. Subsyndromal mood symptoms at baseline had a significant influence on the degree of improvement due to active drug, with strictly euthymic patients faring best. In addition, the degree of baseline cognitive impairment was also an important factor in treatment response.

Conclusions—Although largely interpreted as a negative cognitive enhancement trial, our data suggest a potentially beneficial effect of pramipexole on some aspects of cognition in a *subgroup* patients with bipolar disorder. These data highlight the importance of rigorous subject selection

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for cognitive trials in bipolar illness. Future studies will be necessary to determine the possible clinical and functional implications of these results.

This trial was registered at <http://www.clinicaltrials.gov/> with the identifier: NCT00597896.

Introduction

Neurocognitive impairment is common in bipolar disorder. Deficits in attention, verbal learning, and executive function can be observed across multiple phases of bipolar disorder, with severity during acute phases of the illness comparable to that reported in schizophrenia (Daban et al., 2006; Martinez-Aran et al., 2000; Martinez-Aran et al., 2004). Several meta-analyses indicate that the deficits during affective remission are less severe than in schizophrenia; however, performance still falls $\frac{3}{4}$ to 1 standard deviation below that of healthy comparison samples (Arts et al., 2008; Bora et al., 2009; Robinson et al., 2006; Torres et al., 2007). These persistent deficits contribute significantly to functional disability in bipolar disorder (Bowie et al., 2010; Brissos et al., 2008; Burdick et al., 2010; Jaeger et al., 2007; Malhi et al., 2007; Martinez-Aran et al., 2007), making them an important target for treatment (Burdick et al., 2007a). Although several cognitive enhancement studies have been conducted in schizophrenia, there have been very few controlled trials with cognition as a primary outcome in patients with bipolar disorder.

Specific methodological challenges arise in designing a cognitive trial in patients with bipolar disorder that have not yet been formally addressed in a systematic study. The episodic nature of the illness requires consideration of the inclusion of patients with active symptomatology at baseline, particularly in light of convergent data suggesting a significant influence of affective symptoms on neurocognitive performance (REF). In the case that symptomatic patients are included and cognitive improvement is reported, it becomes difficult to rule out pseudospecificity. Ideally, only patients who are euthymic at the time of treatment initiation would be included; however, many patients with bipolar disorder maintain significant levels of subsyndromal symptoms even when considered to be in remission (Judd et al. xxxx; REFS). Thus, including only strictly euthymic subjects, although scientifically justified, would limit the generalizability of the findings. A second issue is related to the considerable cognitive heterogeneity that is seen in bipolar patients, with a significant proportion of patients displaying 'normal' neuropsychological functioning (Rechenberg et al. xxxx; Bora et al. xxxx; Martino et al. xxxx). This raises the potential need to assess subjects for a minimal level of neurocognitive impairment prior to inclusion in the treatment study to ensure that there is room for improvement with treatment. Finally, the clinical presentation of bipolar disorder is typically marked by multiple common comorbidities including high rates of substance use disorders and anxiety disorders (REF) and polypharmacy is the norm. Again, without limiting the generalizability of the trial, these issue should be addressed as rigorously as possible in considering the optimal cognitive enhancement trial design in bipolar patients.

The neurobiological basis of persistent cognitive impairment in bipolar disorder is not well-understood, yet convergent evidence suggests that the enhancement of dopaminergic activity may be a useful strategy towards improving cognition in bipolar disorder. Neuroimaging

studies highlight structural brain abnormalities in bipolar patients in regions with high dopamine receptor density including several areas of the prefrontal cortex (anterior cingulate, dorsolateral, orbital, and subgenual) (Drevets et al., 1998; Lopez-Larson et al., 2002) and the basal ganglia (Baumann and Bogerts, 2001). Abnormal activation in these same brain regions has been reported in bipolar patients performing cognitive tasks during a functional magnetic resonance imaging (fMRI) (Blumberg et al., 2000; Gruber et al., 2004). In addition, data derived from cognitive studies of healthy individuals suggest that enhancing dopamine via the administration of dopamine agonists such as pergolide, a D1 agonist (Kimberg and D'Esposito, 2003) or bromocriptine, a D2 agonist (Kimberg et al., 1997; Luciana et al., 1998), improves cognition, particularly in cognitive domains linked to prefrontal cortical functions. Finally, molecular genetic studies support the importance of dopamine in normal cognitive functions. Several cognitive studies have focused on the gene that codes for catechol-o-methyl transferase (COMT), an enzyme responsible for the degradation of catecholamines, including dopamine, in the prefrontal cortex (Dickinson and Elvevag, 2009). Convergent results demonstrate an association between genetic variation within *COMT* and neurocognitive function in schizophrenia (Bilder et al., 2002; Egan et al., 2001) unaffected relatives of schizophrenia patients (Rosa et al., 2004), and healthy volunteers (Malhotra et al., 2002; Tsai et al., 2003). *COMT* has also been implicated in the susceptibility for bipolar disorder (Kirov et al., 1998; Mynett-Johnson et al., 1998; Papolos et al., 1998; Shifman et al., 2004). We reported a significant association between a risk allele in *COMT* and poorer verbal memory performance in bipolar patients and in healthy controls, particularly with regard to prefrontal strategies for learning (Burdick et al., 2007b).

We previously reported on the safety and efficacy of pramipexole, a D₂/D₃ agonist, in the context of a 6-week, randomized, double-blind, placebo-controlled trial in patients with treatment resistant bipolar depression (Goldberg et al., 2004). In addition to the primary efficacy measures, a brief battery of psychomotor and attention measures was administered pre- and post-treatment in that trial. In the subset of the sample with complete data, preliminary results indicated that pramipexole significantly improved attention and processing speed, as measured by the d2 Test of Attention (Burdick et al., 2007a). Given the prior evidence that increased availability of dopamine may have positive effects on neurocognition in bipolar disorder, alongside the promising preliminary data, we conducted the first controlled trial of a dopamine agonist with cognition as the primary outcome measure in patients with bipolar disorder. We hypothesized that pramipexole would significantly improve cognitive function, particularly on attention and working memory tasks related to prefrontal cortical function. We also attempted to begin to address some of the methodological challenges that complicate study design and analyses.

Methods

This study was an 8-week, double-blind, placebo-controlled trial of pramipexole versus placebo in 50 stable outpatients with bipolar disorder. Patients screened were 18–65 years of age and carried a clinical diagnosis of bipolar I disorder. After a complete description of the study to the subjects, written informed consent was obtained. All consenting subjects underwent a structured diagnostic interview (Structured Clinical Interview for DSM-IV, Patient edition (SCID) (First et al., 1998). SCID interviews, augmented by medical records,

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were presented and discussed weekly in a meeting comprised of senior researchers, psychiatric residents, and research staff. After diagnosis was confirmed, current affective symptoms were evaluated by formal psychometric assessments conducted by trained raters (inter-rater reliability >0.80) both at initial contact and again at least 4 weeks later.

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At the outset of the study, we adopted a very strict inclusion/exclusion policy, keeping in mind the challenges noted above. First, an initial inclusion criterion was euthymic mood state that was strictly defined by adapting criteria described by Frank and colleagues (Frank et al., 1991); total score ≤ 6 on the Clinician Administered Rating Scale for Mania (CARS-M) (Altman et al., 1994) and ≤ 6 on the Hamilton Rating Scale for Depression (Ham-D) (Hamilton, 1967). In addition, the duration of euthymia was to be *at least* four weeks prior to the date of randomization, as confirmed by consecutive ratings. Second, due to the action of the study agent (pramipexole) on D2 receptors, we disallowed subjects who were taking any antipsychotic medications, including second generation antipsychotics. All subjects were required to be taking another FDA-approved medication for the treatment of bipolar disorder at a stable therapeutic dose, with no record of medication change within the 4-weeks prior to randomization.

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For practical purposes, we modified the inclusion exclusion criteria significantly approximately one-year into the trial, with only three subjects having randomized. Due to the difficulty in recruiting patients who fell within the strict definition of euthymic, we amended the inclusion criteria to allow patients who demonstrated “affective remission” to enter the study. Specifically, due to potential concerns related to mania-induction, we maintained a cutoff of ≤ 6 on the CARS-M but changed our entry criteria for depression to include subjects with subthreshold levels of depression, allowing Ham-D scores ≤ 12 at the time of randomization. No subjects meeting criteria for an acute episode of either polarity were included in the trial. Baseline ratings of depression and mania were accounted for as covariates in analyses as described below. In addition, as the use of antipsychotic agents had become very common as a method of mood stabilization, to ensure adequate enrollment, we chose to allow patients taking antipsychotic medications to enroll in the trial. We have attempted to address this statistically below.

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Additional exclusion criteria were: a documented history of CNS trauma, neurological disorder, Attention Deficit Hyperactivity Disorder (ADHD), or learning disability. Subjects with current or recent substance abuse or dependence (within 1 month) were also excluded; however, a more remote history of substance use disorders was not an exclusion criterion. Further, to help control for medication effects on cognition, the use of benzodiazepines, sedatives, or sleeping pills within 6 hours of neurocognitive testing was disallowed. In addition, patients taking topiramate, tricyclic antidepressants, or anticholinergic medications were excluded from participation due to known effects on cognition. Subjects taking any medications known to interact with pramipexole (e.g. cimetidine) were also excluded. No drugs that potentially enhance cognition were allowed (e.g. other dopamine agonists, modafinil). While recognizing the potential for lithium, anticonvulsants, antidepressants, and antipsychotic medications to influence cognitive performance, it was not feasible to disallow these medications given their widespread use in mood stabilization. We did require a stable regimen for at least four weeks prior to randomization with no medication/dosage changes

during the 8-week study period. We have evaluated the effects of concomitant medications in our statistical approach described below.

Study Medication

Adapting from previous work in treatment resistant bipolar depression (Goldberg et al., 2004), the dosage titration schedule was slow and flexible. Dosing was initiated at 0.125 mg BID, and was increased weekly to a target dose of 1.5 mg/day. The maximum dose of 1.5 mg/day was chosen based on the mean daily dose in our prior work (Goldberg et al., 2004). A maximum of 4.5 mg/day was allowed in our previous study in bipolar depression; however, a more cautious dosing strategy was prudent in the current study because patients were affectively stable at the time of randomization. Side effects were monitored and recorded weekly by the study physicians and vital signs were taken at each visit (blood pressure, pulse, temperature, weight). Clinic visits occurred weekly over the 8-week trial and mood assessments (Ham-D and CARS-M) were conducted at each visit.

At baseline and again at week 8, neurocognitive assessment was conducted by highly-trained psychometricians. The battery was designed to tap into all basic cognitive domains, while focusing more heavily on measures of attention and processing speed. Tasks were also chosen with the Measurement and Treatment of Cognition in Schizophrenia (MATRICS) initiative in mind. The MATRICS Consensus Cognitive Battery (MCCB) (Green and Nuechterlein, 2004) was not finalized at the commencement of this trial; therefore, included tasks were derived from both the beta version of the MCCB and our preliminary report (Burdick et al., 2007a). The battery was administered in a uniform order and lasted 1.5 hours. It consisted of: Wechsler Adult Intelligence Scale-Third Edition (WAIS-III) Digit span subtest (Digits forward and backward); WAIS-III Digit Symbol subtest; Stroop Color-Word Test; Trailmaking Test Part A and B (Trails A and B); d2 Test of Attention (d2 TOA); Hopkins Verbal Learning Test (HVLN); and Controlled Oral Word Association Test (COWAT) letter fluency. Alternate forms for the HVLN and the COWAT were utilized at time 2 testing to reduce the potential for practice effects. The Wide Range Achievement Test-Third edition (WRAT-3) Reading subtest was used as an estimate of premorbid intellectual function at baseline. A single measure from each task was utilized in analyses for a total set of eleven primary outcome measures.

This study was approved by the North Shore Long Island Jewish Health System (NSLIJHS) Institutional Review Board (IRB) and was registered on clinicaltrials.gov (NCT00597896).

Statistics

For primary analyses to assess for a treatment effect of pramipexole on neurocognitive performance, we first calculated change scores by subtracting performance at baseline from performance at week 8 on each of the eleven primary outcome measures. Change scores were then entered as dependent variables in a multivariate analysis of variance (MANOVA) with treatment group as a fixed factor.

Secondary analyses addressed several points including: 1) the effect of baseline mood symptoms on outcome; 2) the effect of concomitant medications on outcome; and 3) the degree to which baseline impairment contributed to cognitive improvement. These were

evaluated using several steps. First, we repeated the multivariate analysis in the subgroup of patients who were strictly defined as euthymic at baseline and included baseline Ham-D and CARS-M scores to determine to what extent mood state at the time of treatment influenced the results. Effect sizes for change (Cohen's *d*) were calculated in the total sample and again in the euthymic group to determine the degree to which the treatment effect was related to baseline symptom status. Next, we included antipsychotic status as a fixed factor in the MANCOVA to evaluate the influence of concomitant D2 blockade on treatment effect. Finally, we incorporated baseline cognitive performance on measures of interest in univariate MANCOVAs in an effort to understand the impact of impairment level on cognitive outcome after treatment.

Results

Subjects

Subject screening and enrollment details are provided in Figure 1. Fifty subjects were randomized (twenty-six to placebo and twenty-four to pramipexole); four did not complete the study and were missing cognitive data at Time 2 (not included in analyses). One patient was excluded from analysis due to not meeting diagnostic criteria after he/she was presented in consensus conference (did not meet DSM-IV criteria for Bipolar I or Bipolar II). Seventeen patients were characterized by *subthreshold* symptoms at baseline (Ham-D > 6 but < 12). All subjects who completed both cognitive assessments were included in the primary analyses; however, in line with our original study design, we also conducted secondary analyses excluding the 17 subjects who demonstrated subthreshold levels of depression. Other than the severity of baseline mood symptoms the seventeen patients excluded from these analyses did not differ from the euthymic sample of 28 on demographic features such as age ($t=1.8$; $p=0.08$), sex ($\chi^2=0.07$; $p=0.79$), race ($\chi^2=1.19$; $p=0.28$), or premorbid IQ ($t=0.09$; $p=0.93$).

Results in the Full Completers Sample (n=45)—Of the forty-five individuals who completed two testing sessions, twenty-four subjects were randomized to placebo and twenty-one subjects received pramipexole. Groups were well-matched by clinical and demographic features (Table 1). We found no significant effects of treatment group on measures of depression or mania over the eight-week trial (Table 1) and there were no reports of psychosis or mania induction in either of the treatment groups. All patients completing the trial reached and maintained the maximum dosage (1.5 mg/day) by week 6; therefore at week 8 the average daily dosage of pramipexole was 1.5 mg/day. The frequency of concomitant medications, by class, in the full sample of forty-six was as follows: 65% antipsychotics; 46% antidepressants; 57% anticonvulsants; and 39% lithium. On average, patients were taking 2.32 ± 0.9 psychotropic medications. Concomitant medication load, as calculated based on number, type and dosage of medications (Hassel et al. 2008) did not significantly differ by treatment group (Table 1).

The only side effect reported more frequently by participants in the active treatment group (25%) than those taking placebo (0%) was restlessness ($\chi^2=5.4$; $p=0.02$). Side effects were recorded by the study physician thereby maintaining a blinded status for the individuals

conducting the neurocognitive testing and the mood ratings. The frequencies of all common side effects (> 5% frequency) at week 8 are presented in Table 2.

Cognitive Outcome in the Full Completers Sample

Results from the primary multivariate analysis of covariance revealed a non-significant treatment group effect ($F=0.81$; $df=1,45$; $p=0.62$). Only one individual measure reached *uncorrected* statistical significance; Stroop Color ($F=5.03$; $df=1,45$; $p=0.031$), with a greater improvement in performance noted in the pramipexole group versus the individuals assigned to placebo. Effect size changes were calculated for both treatment groups (depicted in Figure 2) and although not statistically significant, it is worth noting that greater improvement was seen in the pramipexole group than in the placebo group on 8/11 measures—a pattern indicative of a generalized but very modest advantage over placebo.

Results in the Euthymic Subgroup (n=35)—The initial study design was to allow only strictly defined euthymic subjects into the trial. Therefore, we carried out secondary analyses in the 35 subjects who were euthymic at baseline (see below). Nineteen patients received placebo and sixteen received pramipexole; demographic and clinical features were comparable in each group (Table 3). Again, only very subtle fluctuations in mood ratings were noted and they were similar in the placebo group as in the pramipexole group (Table 3). The frequency of concomitant medications, by class, in the subsample of thirty-five was as follows: 63% antipsychotics; 46% antidepressants; 54% anticonvulsants; and 40% lithium. On average, patients were taking 2.26 ± 1.0 psychotropic medications. Concomitant medication load, as calculated based on number, type and dosage of medications (Hassel et al. 2008) did not significantly differ by treatment group (Table 3).

Cognitive Outcome in the Euthymic Subgroup

After covarying for baseline Ham-D and CARS-M scores, and concomitant antipsychotic medication status, MANCOVA revealed a significant overall effect of treatment group ($F=2.38$; $df=1,34$; $p=0.047$) on neurocognitive functioning in the euthymic subgroup of patients. The overall MANCOVA significance suggests a generalized improvement in cognition due to pramipexole treatment. Specifically, we found significantly greater improvement on two neurocognitive tasks in the patients taking pramipexole versus those taking placebo: WAIS Digits Backward ($F=6.60$; $df=1,34$; $p=0.016$), and Stroop ColorWord ($F=7.69$; $df=1,34$; $p=0.010$; Figure 3). Effect size calculations indicate a notably enhanced benefit of pramipexole in this subgroup of euthymic patients as compared with the full completers sample (Fig 4), highlighting the importance of baseline mood state in cognitive enhancement trials in bipolar disorder.

Discussion

Results from this 8-week, randomized, placebo-controlled trial provide preliminary evidence to suggest that the D₂/D₃ agonist, pramipexole, may be effective in treating cognitive impairment in *euthymic* patients with bipolar disorder when added to a stable mood stabilizing regimen. Although primary analyses including patients with subthreshold depression at baseline were not significant for most measures, we found significantly greater

improvements on measures of processing speed and working memory in the euthymic subgroup of patients assigned to pramipexole versus those taking placebo. Effect sizes range from small to large, with the most prominent improvement noted on a working memory task (WAIS Digits Backward).

To our knowledge, this study is the first placebo-controlled cognitive enhancement trial in euthymic bipolar patients using a pro-dopaminergic agent. There have been a handful of case reports or case series described in the literature that have included an assessment of cognition as part of a treatment trial in bipolar patients; however most have utilized subjective (patient-rated) reports of cognitive improvement (Jacobsen and Comas-Diaz, 1999; Schrauwen and Ghaemi, 2006; Teng and Demetrio, 2006) and no objective neurocognitive tests were administered. Given the lack of correlation between subjective ratings of cognition and neuropsychological test results in bipolar 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.

Our positive results are consistent with the two previously published studies which have included objective neurocognitive performance as an outcome measure in bipolar disorder. The first was focused on the treatment of residual depressive symptoms in 20 bipolar patients using mifepristone (RU-486), a progesterone receptor antagonist (Young et al., 2004). This study was a double-blind, placebo-controlled cross-over design specifically targeting depression; however, neurocognitive function was also assessed at baseline and 3 weeks after the start of each medication. Mifepristone treatment was associated with enhanced performance on measures of verbal fluency, spatial working memory, and recognition memory as compared with placebo but these improvements were in the context of a significant reduction in depressive symptoms; thus, pseudospecificity cannot be ruled out. Iosifescu et al. (Iosifescu et al., 2009) conducted an open-label study, administering galantamine to 19 remitted bipolar patients (HamD = 10) over a four month period. Only 11 patients completed the study; however, subjectively-rated cognition improved significantly over the course of the trial. Moreover, structured cognitive testing was completed at baseline and again at 16 weeks and the design included a yoked healthy control sample also tested at both time points. The authors report a significant improvement in the bipolar group on a measure of sustained attention and on a measure of verbal memory based on calculated change scores from baseline to end of study.

Pramipexole is a partial/full D₂/D₃ agonist with highest affinity for the D₃ receptor (Mierau et al., 1995; Gerlach et al., 2003) and it is FDA-approved for the treatment of Parkinson's disease (Boehringer Ingelheim International). Its relative specificity allows for a unique opportunity to enhance dopamine in phylogenetically older regions of the brain that are associated with emotion regulation and cognitive function (Camacho-Ochoa et al., 1995). Consistent with this mechanism of action, pramipexole has a direct antidepressant effect in patients with Parkinson's disease (Leentjens et al., 2009) above and beyond its efficacy for motor symptoms associated with the illness (Bxarone et al., 2010). Moreover, several additional studies suggest that pramipexole's antidepressant effect may be extended to psychiatric samples (Aiken, 2007) including bipolar disorder (Goldberg et al., 2004; Zarate

et al., 2004). Preliminary data from our earlier work in treatment-resistant bipolar depression (Goldberg et al. 2004) provided evidence of a potential role for pramipexole as a cognitive enhancement agent (Burdick et al., 2007a). As patients in our prior study (Goldberg et al., 2004) improved with regard to depressive symptoms, we were unable to rule out pseudospecificity as an explanation for cognitive improvement; therefore, the current study was specifically designed to directly assess the potentially beneficial cognitive effects of pramipexole by utilizing strictly-defined euthymic bipolar patients. Unfortunately, the decision to allow patients with subthreshold depression into the trial was made for practical reasons related to recruitment challenges; results indicate that this may be an important distinction in designing future studies.

Our study has several limitations. First, the change in study design with regard to the inclusion of subthreshold depressive symptoms necessitated a two-level analytic approach and the subsample of euthymic patients included in the secondary analysis was limited in size. Given the known effects of mood state on cognition in bipolar disorder (Basso et al., 2002; Martinez-Aran et al., 2000), we felt that the separate analysis limiting the sample to those patients who were euthymic at baseline was critical. This approach involved a reduction in power due to the exclusion of eleven subjects who were enrolled with subthreshold depressive symptoms at baseline (HDRS > 8 but < 12); however, we chose to adopt this approach to better address our primary aim, which was to evaluate the effects of pramipexole on cognition *without* the confounding effects of depressive symptom improvement. Moreover, the functional implications of cognitive impairment in bipolar disorder are of particular importance during periods of euthymia when patients might otherwise be expected to return to normal occupational and social functioning (Bowie et al., 2010; Brissos et al., 2008; Burdick et al., 2010; Jaeger et al., 2007; Malhi et al., 2007; Martinez-Aran et al., 2007). Second, psychotropic medication represents a potential confound in nearly all studies of cognition; however, it is impractical and potentially unethical to require a washout of medications when a patient is psychiatrically stable. Thus, we attempted to determine the effects of concomitant medications by including drug classes as fixed factors in our analyses and by using statistical methods previously described (Hassel et al., 2008). Third, although our positive results would not survive a strict Bonferroni correction for multiple testing; neurocognitive measures are not independent of one another and importantly, effect size calculations indicate clinically meaningful improvements on several measures. Fourth, we opted to utilize a fixed-dose design with a relatively low maximum dose which may have limited the potential for cognitive benefit, particularly in light of the possibility of reduced binding in the presence of antipsychotic medications. Future studies should evaluate the possibility of dose-related effects and further assess the effects of concomitant medications. Finally, the duration of the current trial was only 8-weeks, limiting our ability to measure functional changes such as work and social functioning.

In summary, we provided preliminary evidence of a cognitively beneficial effect of the D₂/D₃ agonist, pramipexole, in euthymic patients with bipolar disorder. This study is among the first placebo-controlled trials using cognition as a primary outcome measure in bipolar disorder and serves as a proof of concept. It also emphasizes some of the challenges that

might be specific to the episodic course of bipolar disorder (e.g. heterogeneous baseline mood state) when designing cognitive enhancement studies in this population. It is our hope that these promising results lead to an increased effort to target cognitive dysfunction in bipolar disorder with the goal of improving patients' quality of life (Harvey et al., 2010).

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Figure 1.
Subject Flow Diagram indicating subject enrollment and inclusion.

Figure 2. Effect Size of Neurocognitive Change by Treatment Group (All Completers)

All 46 completers are included in the primary analysis with results shown in this figure. The x-axis labels the individual neurocognitive measures included in the analyses. The Y-axis represents the effect size of the change from baseline to week 8 on each of these measures. Effect size is depicted as Cohen's D. The pattern of change indicates some benefit of pramipexole over placebo but only one measure reaches modest statistical significance (Stroop Color; $p=0.03$).

Figure 3. Effect Size of Neurocognitive Change by Treatment Group (Euthymic Subgroup)
 Only the euthymic subgroup is included in these results. Again the x-axis indicates specific cognitive tasks and the y-axis scale is Cohen's D, estimating effect size changes in each treatment group. Here the overall MANCOVA achieves statistical significance ($p=0.03$), as do two specific neurocognitive measures (Stroop Color; $p=0.02$; and WAIS Digits Backward; $p=0.01$).

Figure 4. Enhanced Effect Size Change in the Euthymic Subgroup Treated with Pramipexole
 The X-axis indicates individual neurocognitive measures and the Y-axis again depicts effect size in Cohen's D. The solid red bars represent all patients who were assigned to pramipexole (n=21) and the striped red bars represent the euthymic subgroup who received pramipexole (n=16). The results indicate enhanced effect of pramipexole in the context of euthymia on 8/11 measures.

Table 1

Subject Characteristics by Treatment Group (All Completers)

Feature	Placebo (n=25)	Pramipexole (n=21)	Statistic	p-value
Mean Age (SD)	45.1 (12.4)	43.81 (9.4)	F=0.16	0.69
Sex	10male/15female	7male/14female	$\chi^2=0.22$	0.64
Race	10white/15non-white	7white/14non-white	$\chi^2=0.22$	0.64
Mean HamD Baseline (SD)	5.4 (3.6)	5.9 (3.4)	F=0.28	0.60
Mean CARS-M Baseline (SD)	2.4 (2.1)	3.1 (2.4)	F=1.25	0.27
Change in HamD (Week 8-Baseline)	+0.6 (3.0)	-0.5 (5.5)	F=0.59	0.45
Change in CARS-M (Week 8-Baseline)	-0.1 (2.6)	-0.2 (3.2)	F=0.01	0.93
Mean Premorbid IQ (WRAT Reading)	95.9 (13.0)	96.5 (12.7)	F=0.03	0.87
<i>Medications</i>	<i>Placebo (n=25)</i>	<i>Pramipexole (n=21)</i>	<i>Statistic</i>	<i>p-value</i>
Lithium (%)	32.0	52.0	$\chi^2=1.17$	0.28
Anticonvulsants (%)	64.0	47.6	$\chi^2=1.25$	0.26
Antipsychotics (%)	64.0	66.7	$\chi^2=0.04$	0.85
Antidepressants (%)	52.0	38.1	$\chi^2=0.89$	0.35
Mean Total # meds	2.4 (0.9)	2.2 (1.0)	F=0.33	0.57
Mean Medication Load	4.5 (2.1)	4.1 (2.3)	F=0.30	0.59

Total # meds=total number of psychotropic medications taken currently excluding prn; Medication Load=calculated using dosage and drug class information (as per Hassel et al. 2008).

Table 2

Side Effects by Treatment Group (All Completers)

Side effects at week 8 (n)	Placebo (n=25)	Pramipexole (n=21)	χ^2	p-value
Restlessness	0	4	5.2	0.02*
Dry Mouth	5	4	0.01	0.94
Increased Appetite	4	5	0.4	0.51
Drowsiness	2	4	1.2	0.27
Headache	1	2	0.6	0.45
Increased Motor Activity	2	1	0.2	0.66
Decreased Motor Activity	1	3	1.5	0.22
Tremor	4	2	0.4	0.52
Urinary Retention	3	0	2.7	0.10
Nocturnal Enuresis	2	2	0.03	0.86
Hypersomnia	2	2	0.03	0.86
Insomnia	2	1	0.2	0.66
Paresthesia	1	0	0.9	0.35
Agitation	1	0	0.9	0.35
Decreased Appetite	2	0	1.8	0.19
Cramps	1	1	0.02	0.90
Decreased Libido	1	0	0.9	0.35
Hypertension	0	1	1.2	0.27
Dizziness	0	1	1.2	0.27
Edema	1	0	0.9	0.35
Nasal Congestion	2	1	0.2	0.66
Fever	0	1	1.2	0.27
Nausea	1	2	0.6	0.45
Vomiting	1	0	0.9	0.35
Diarrhea	1	2	0.6	0.45
Menstrual Disturbance	1	4	2.7	0.10
Decreased Libido	3	2	0.10	0.79
Impaired Sexual Perform	1	1	0.02	0.90
Rash	1	0	0.9	0.35
Joint Pain	1	0	0.9	0.35
Muscle Pain	2	1	0.2	0.66

Table 3

Subject Characteristics (Euthymic Subgroup)

Feature	Placebo (n=19)	Pramipexole (n=16)	Statistic	p-value
Mean Age (SD)	43.7 (13.4)	41.6 (9.3)	t=0.53	0.60
Sex	7male/12female	5male/11female	$\chi^2=0.12$	0.73
Race	8white/11non-white	6white/10non-white	$\chi^2=0.08$	0.78
Mean HamD Baseline (SD)	3.8 (2.4)	4.5 (2.5)	t=0.85	0.40
Mean CARS-M Baseline (SD)	1.8 (1.8)	2.5 (2.1)	t=1.08	0.29
Change in HamD (Week 8-Baseline)	+1.1 (3.0)	+0.3 (5.2)	F=0.46	0.50
Change in CARS-M (Week 8-Baseline)	+ 0.8 (3.0)	-0.5 (4.0)	F=1.6	0.21
Mean Premorbid IQ (WRAT Reading)	97.8 (12.5)	94.9 (13.3)	t=0.67	0.51
<i>Medications</i>	<i>Placebo (n=19)</i>	<i>Pramipexole (n=16)</i>	<i>Statistic</i>	<i>p-value</i>
Lithium	26.3	56.3	$\chi^2=3.24$	0.07
Anticonvulsants	68.4	37.5	$\chi^2=3.35$	0.07
Antipsychotics	57.8%	68.8%	$\chi^2=0.44$	0.51
Antidepressants	52.6	37.5	$\chi^2=0.80$	0.37
Total # meds	2.26	2.25	t=0.04	0.97
Medication Load	4.27 (2.1)	3.77 (2.0)	t=0.64	0.53

Total # meds=total number of psychotropic medications taken currently excluding prn; Medication Load=calculated using dosage and drug class information (as per Hassel et al. 2008).