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Pramipexole to Improve Cognition in Bipolar Disorder

A Randomized Controlled Trial

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Abstract:

Background: Adults with bipolar disorder (BD) often experience neurocognitive impairment that negatively impacts functioning and quality of life. Previous trials have found that dopamine agonist agents improve cognition in healthy volunteers and that adults with BD who have stable mood and mild cognitive deficits may also benefit. We hypothesized that pramipexole, a dopamine agonist, would improve neurocognitive function in patients with BD.

Methods: We recruited 60 adults (aged 18–65 years) with a diagnosis of BD I or II for an 8-week, double-blind, placebo-controlled trial (NCT02397837). All had stable mood and clinically significant neurocognitive impairment at baseline. Participants were randomized to receive pramipexole (n = 31) or a placebo (n = 29), dose was initiated at 0.125 mg 2 times a day and increased to a target of 4.5 mg/d.

Results: At trial end, the primary outcome, MATRICS Consensus Cognitive Battery composite score, had not improved more in the pramipexole group (mean [SD] = 1.15 [5.4]) than in the placebo group (mean [SD] = 4.12 [5.2], Cohen's $d = 0.56$, $P = 0.049$), and mixed models, controlling for symptoms, showed no association between treatment group and MATRICS Consensus Cognitive Battery scores. No serious adverse events were reported.

Conclusions: These results suggest that pramipexole is not an efficacious cognitive enhancement agent in BD, even in a sample enriched for characteristics that were associated with a beneficial response in prior work. There are distinct cognitive subgroups among adults with BD and may be related differences in neurobiology that affect response to pramipexole. Additional research to better understand the onset and nature of the cognitive deficits in people with BD will be an important step toward a more personalized approach to treatment.

Key Words: bipolar disorder, pramipexole, cognition, randomized controlled trial

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Adults with bipolar disorder (BD) often experience poor quality of life, and BD is a leading cause of disability worldwide.[1] Although BD is often perceived as an episodic illness in which patients experience periods of wellness between mood episodes, most patients never recover full premorbid functioning after a major mood episode.[2] This may be due to persistent subthreshold mood symptoms, efforts to reduce stress to minimize risk of relapse, and medical comorbidities, among other factors. Neurocognitive impairment also contributes to dysregulated mood and poor functioning, even during euthymic mood.[3]

Most patients with BD experience cognitive deficits.[4] However, relative to other serious mental illnesses (eg, schizophrenia) for which cognitive deficits are seen as a primary characteristic, the cognitive profile of BD has received less attention. Consequently, fewer resources have been invested in ameliorating the consequences of these deficits, which significantly affect functioning[3,4]; most adults with BD are either unemployed or underemployed, and many experience a decline in work status and performance over time.[5] Finally, a significant proportion of people with BD do not live independently, requiring significant support from family and/or social services.[6]

Multiple large clinical trials to reduce cognitive impairment in people with schizophrenia have been conducted,[7] whereas relatively little work has focused on cognitive impairment in people with BD. In one of the first investigations of cognition as a treatment target in BD,[8] we reported that enhancing dopaminergic function may improve neurocognition in BD, at least in a subset of patients. Results from other investigations offer support for this hypothesis; neuroimaging studies have shown that areas in which dopamine plays a significant role (eg, anterior cingulate, dorsolateral, orbital, and subgenual cortex) often shown abnormalities in people with BD during cognitive tasks.[9,10] Of note, dopamine plays a critical role in reward-based learning and dopamine agonists can induce risk-seeking behaviors and impulsive decision-making in individuals without a history of these behaviors.[11]

Dopamine receptor agonists improve cognition in healthy volunteers.[12] Pramipexole (Mirapex), a novel D_2/D_3 agonist, has been used as an adjunctive antidepressant in BD and is Food and Drug Administration (FDA)–approved for Parkinson disease and restless leg syndrome. In a 6-week controlled trial to address treatment-resistant depression in adults with BD,[13] preliminary data indicated that pramipexole improved both depression and attention.[14] This led to a trial, designed specifically to measure the cognitive effects of pramipexole in affectively stable BD patients.[8] Although the overall results of this trial were not significant, there

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was a subset of participants who showed improved cognition at trial end. On average, the patients who benefitted most had fewer subthreshold mood symptoms and greater cognitive impairment at baseline.[8]

The goal of the present study was to optimize the study design to evaluate the effect of pramipexole treatment on cognitive function among participants with BD who were most likely to benefit (ie, those experiencing clinically significant cognitive impairment despite affective stability) based on our previous trial. We also increased our target pramipexole dose from 1.5 to 4.5 mg/d and extended the follow-up period to maximize the potential impact, particularly on measures of everyday functioning. In addition, because medications commonly prescribed to people with BD may affect cognition (eg, anticonvulsants, mood stabilizers, lithium)[15] or may counteract the effects of pramipexole (eg, antipsychotics),[16] we required participants to be on a stable medication regimen, with no changes permitted during the trial and we stratified randomization based on antipsychotic use. We hypothesized that pramipexole would be associated with cognitive improvement in this optimized design.

Methods

Participants

Participants were recruited from 2 psychiatry departments in the New York metro area. Inclusion criteria included being between the ages of 18 to 65 years, diagnosis of BD I or II, mood stability (Young Mania Rating Scale [YMRS] score <8, Hamilton Depression Rating Scale [HAMD] score <16) over a 4-week period (between screening and baseline), and clinically significant neurocognitive impairment (defined as >1 SD below average on a global composite *z* score derived from a set of standard cognitive assessments that differed from the tests used as primary outcomes, see hereinafter). Exclusion criteria included any history of traumatic brain injury, neurological disorder, learning disability, or attention-deficit/hyperactivity disorder; positive toxicology screen or recent (past 3 months) history of a substance use disorder; medical condition likely to affect cognition and/or contribute to cardiovascular risk (pramipexole carries an FDA warning related to heart failure); and significant suicide risk based on clinician judgment and Columbia Suicide Severity Rating Scale.[17] Certain concomitant treatments were also considered exclusionary, including those medications with known cognitive effects (ie, topiramate, anticholinergics, amphetamine, other dopamine agonists), benzodiazepines (within 6 hours of testing), electroconvulsive therapy in the past 12 months, any drug known to interact with pramipexole, or older generation neuroleptics and/or risperidone because these have a high binding potential at the D_2 receptor and may interfere with pramipexole's activity.

Procedure

The study received approval from the institutional review boards at the 2 participating institutions, and all participants completed informed consent before any procedures were conducted. Screening began with a clinical interview using the Structured Clinical Interview for the *Diagnostic and Statistical Manual of Mental Disorders*, *Fourth Edition* (SCID)[18] to confirm diagnosis of BD I or II, as well as the YMRS,[19] and the HAMD[20] to assess symptoms of mania and depression, respectively. Interviews were conducted by highly trained PhD- or master-level study staff. In addition, at screen, participants completed a series of neuropsychological tests to ensure that there was sufficient impairment to warrant treatment. The tests were Trails B,[21] Wechsler Adult Intelligence Scale[22] Digit Symbol, Wechsler Adult Intelligence Scale Digit Span Forward and Backward, Wisconsin Card Sorting Test,[23] and the California Verbal Learning Test.[24] Scores from these assessments were standardized and combined into a *z* score. Patients with scores of 1 standard deviation (SD) or more below the mean (M) were deemed eligible for randomization. Participants also underwent a physical examination that included assessment of vital signs, blood laboratories, and an electrocardiogram.

At the baseline appointment, approximately 4 weeks after screening, participants were again assessed with the YMRS and HAMD to ensure that the affective stability criteria were still met. Eligible participants then completed the MATRICS Consensus Cognitive Battery (MCCB),[25] the primary outcome assessment of neurocognitive function. In addition, participants completed the Iowa Gambling Task (IGT),[26] which measures an individual's ability to learn to select cards from certain decks to minimize monetary losses and is often used to evaluate impulsive and/or risky decision making. As was seen in our prior work, pramipexole treatment is associated with an increase in high-risk/high-reward choices on the IGT; therefore, the IGT was included to assess the potential adverse effects of pramipexole. In addition, participants were asked to report on whether they experienced any adverse effect or other adverse event at each study appointment.

Eligible participants were randomized to receive pramipexole or a placebo using a computer algorithm, which stratified the sample based on antipsychotic medication use (yes/no) as well as depression status (strictly euthymic vs subthreshold depression) to ensure an equal distribution of these traits across treatment groups. Study staff and participants were blinded to group assignment. Pramipexole was initiated at 0.125 mg 2 times a day and increased every 3 days to a target of 4.5 mg/d. The target dose was based on the maximum FDA-approved dose, as well as previous work in which a maximum dose of 1.5 mg/d was used.[8] Dosing was flexible to facilitate appropriate management of adverse effects. Participants who could not tolerate at least 1.5 mg/d were discontinued. Titration occurred up to week 6, after which the dose was continued through the end of the trial, other than the case of adverse events.

After the baseline appointment, participants' symptoms were assessed on a weekly basis for 4 weeks and then again at weeks 6 and 12. Mood symptoms and vital signs were evaluated at each office visit. The MCCB and the IGT were repeated at weeks 6 and 12.

Multilevel models, with a random intercept to account for participant differences in baseline MCCB scores, controlling for subthreshold manic (YMRS scores) and depressive (Hamilton Depression Rating Scale scores) symptoms, were used to test for significant effects of treatment group on cognition (MCCB scores). In addition, we tested whether antipsychotic status influenced cognitive outcomes[8] and whether outcomes varied depending on whether patients had a history of psychosis. Intention to treat analyses were conducted, including all enrolled participants, with the exception of the analyses that used *t* tests to compare change scores that we calculated for the MCCB, HAMD, and YMRS—these analyses included only participants with data from at least 2 visits. All analyses were conducted using the nlme and lme4 packages in R.

Results

Sixty participants were enrolled and randomized in the study (NCT02397837) from October 2014 to July 2018, 31 in the pramipexole group (Fig. 1). The average age was 39.4 ± 13.3 years, and 58% were female. Depressive and manic symptom severity, MCCB performance, and IGT scores were largely equivalent across the 2 sites and between the pramipexole and placebo groups at baseline; see Tables 1 and S1, http://links.lww.com/JCP/A760. Fifty patients remained in the trial through week 12 when final outcomes

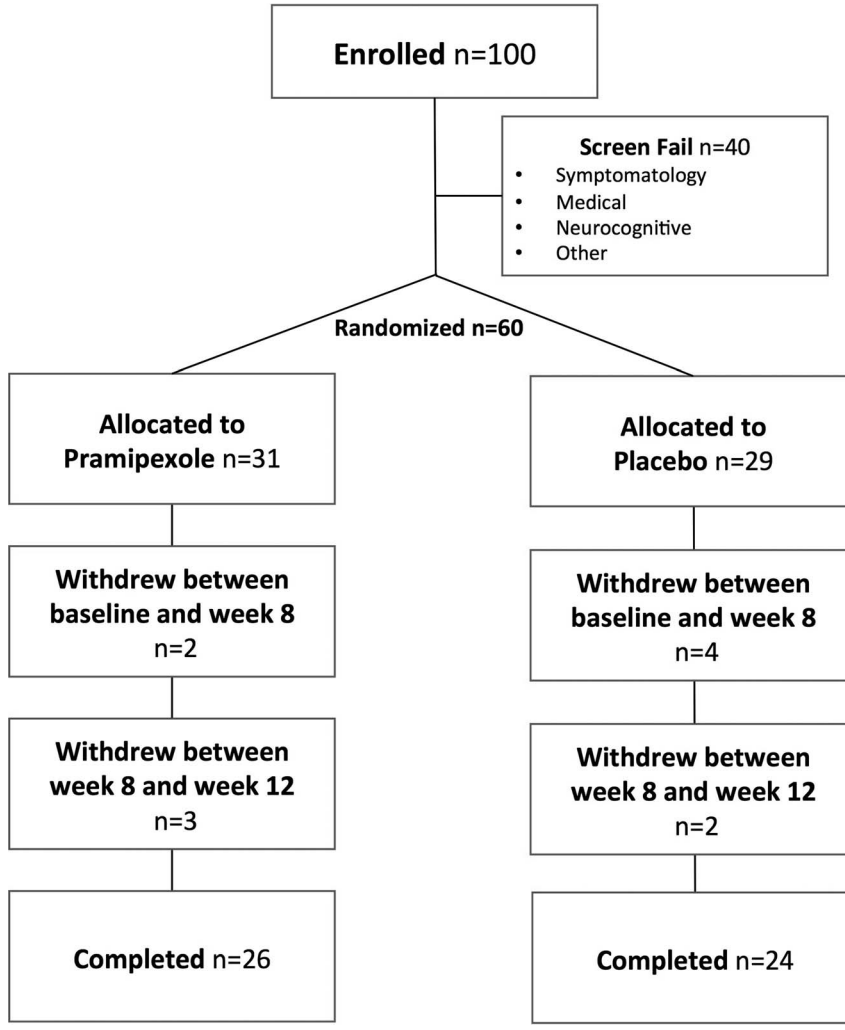

FIGURE 1. Consort diagram.

TABLE 1. Baseline Characteristics by Treatment Group

		Pramipexole	Placebo
		M (SD)	
	Age	40.98 (14.3)	37.83 (12.1)
	HAMD	4.83 (3.9)	6.4 (3.9)
	YMRS	2.65 (2.4)	2.62 (2.5)
	IGT Total Money *	−648.50 (1350.9)	−736.90 (1413.8)
MATRICS Cognitive Consensus Battery	Composite T-Score	35.58 (12.4)	38.07 (10.5)
	Speed Processing T-Score	41.48 (11.7)	41.93 (9.8)
	Attention Vigilance T-Score	35.03 (10.6)	37.90 (13.8)
	Working Memory T-Score	41.77 (11.3)	40.14 (8.4)
	Verbal Learning T-Score	40.42 (12.0)	42.83 (10.6)
	Visual Learning T-Score	44.55 (12.6)	39.52 (11.0)
	Reason Problem-Solving T-Score	40.87 (7.6)	44.97 (8.9)
	Social Cognition T-Score*	44.10 (13.8)	51.00 (11.8)

*Group scores significantly different ($P = 0.042$).

TABLE 2. Change Scores for Symptoms and Cognitive Outcomes Among Pramipexole and Placebo Groups

		Pramipexole	Placebo	
		M (SD)		Cohen's *d*
	Hamilton Depression Rating Scale	0.04 (4.4)	0.11 (3.83)	0.02
	YMRS	−1.00 (2.3)	−0.12 (2.6)	0.36
	IGT Total Money	220.08 (1530.9)	307.92 (1861.4)	0.05
MATRICS Cognitive Consensus Battery	Composite T-Score	1.15 (5.4)	4.12 (5.2)	0.56
	Speed Processing T-Score	1.32 (8.4)	4.31 (5.1)	0.43
	Attention Vigilance T-Score	−0.35 (10.7)	3.23 (6.7)	0.40
	Working Memory T-Score	−1.14 (7.1)	1.19 (6.7)	0.34
	Verbal Learning T-Score	−2.46 (8.4)	−1.27 (8.1)	0.14
	Visual Learning T-Score	0.23 (10.6)	3.19 (9.9)	0.29
	Reason Problem Solving T-Score	3.40 (8.4)	4.85 (10.6)	0.15
	Social Cognition T-Score	−0.33 (10.2)	1.81 (11.2)	0.20

were assessed, 26 in the pramipexole group and 24 in the placebo group. Those who completed the trial were older on average than those who left the trial early (t = −2.40, P = 0.019; 41.23 vs 30.60 years). Other clinical and neurocognitive measures were statistically equivalent between completers and noncompleters at baseline.

At week 12, changes in depressive (M [SD] = 0.07 [4.1]) and manic (M [SD] = −1.92 [2.2]) symptoms were minimal and equivalent across the pramipexole and placebo groups (depression t = 1.35, P = 0.183; mania t = 0.62, P = 0.538). The MCCB composite change scores did not improve more in the pramipexole group (M [SD] = 1.15 [5.4]) relative to the placebo group (M [SD] = 4.12 [5.2]; t = 2.02, P = 0.049). Change scores for the individual MCCB domain scores were all equivalent between treatment groups. Overall, effect sizes were small to medium and not statistically significant. In all cases, the placebo group had better outcomes than did the pramipexole group (Table 2).

A significant majority of patients had a history of psychosis (n = 38), and an additional seven reported a history of subclinical symptoms. The proportion of patients with history of psychosis did not vary between the treatment groups (χ^2 = 0.20, P = 0.654). Change in MCCB Composite T-Scores was the same regardless of history of psychosis (t = 0.35, P = 0.731).

We evaluated the effects of concomitant medications on cognitive change (MCCB Composite T-Scores). As was noted in our prior work, among those participants assigned to the pramipexole group, those who were taking an antipsychotic medication had a smaller change in cognition than those not on an antipsychotic, but this was only significant at a trend level (t = 1.99, Cohen's d = 0.84, P = 0.058). Prescriptions of antidepressant, lithium, or anticonvulsant medication had no significant effect. Finally, we also tested whether pramipexole dose was related to cognitive outcome; patients prescribed the maximum dose (4.5 mg/d) did not improve more than other patients (t = 0.48, Cohen's d = 0.19, P = 0.637), nor was dose associated with MCCB outcome in a mixed model controlling for symptoms and baseline differences in cognition (B = −1.45, P = 0.247).

We also tested for main effects of treatment group on MCCB Composite T-Scores over time using mixed models. Only the fixed effect for session was a significant predictor (B = 0.53, P = 0.001), suggesting an improvement in neurocognitive function across both groups (Fig. 2). In exploratory analyses, we also evaluated the effect of treatment group on specific MCCB domains. Visual learning was the only outcome for which treatment group was a significant predictor, indicating that the pramipexole group had higher scores; however, the treatment group * session predictor was not significant (ie, the scores did not increase at a significantly higher rate in the pramipexole group; Table 3).

Adverse Effects and Adverse Events

There were no serious adverse events reported; however, most participants in both groups reported the onset of some adverse effect during the trial. The percentage of patients who reported adverse effects was equivalent between the pramipexole and placebo groups with the exception of nausea (experienced by 61% in pramipexole vs 21% in placebo, χ^2 = 8.56, P = 0.003).

We included the IGT to assess for increases in risky/impulsive decision making that could be problematic—particularly among people with BD who may already be prone to impulsivity. Both the pramipexole and placebo groups won more money as they repeated the task on subsequent visits, indicating that their overall performance improved. Change in IGT total money from baseline to week 12 did not differ between the 2 groups (t = 0.18, P = 0.859).

As noted, average change in YMRS scores was equivalent between the placebo and pramipexole groups. We further checked whether any individual patient became manic during the study. Over the entire study, only 1 patient had a score indicative of clinically

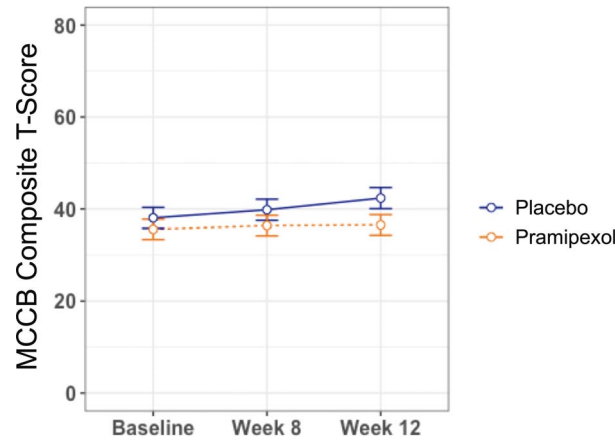

FIGURE 2. Average MCCB Composite T-Scores by treatment group.

TABLE 3. Mixed Model Results of Treatment on MCCB Scores

	Composite T-Score	Speed Processing T-Score	Attention Vigilance T-Score	Working Memory T-Score	Verbal Learning T-Score	Visual Learning T-Score	Reason Problem Solving T-Score	Social Cognition T-Score
				B (95% CI)				
Intercept	36.26 (31.21–41.31)*	37.88 (32.63 to 43.14)*	35.58 (29.44 to 41.73)*	41.19 (36.04 to 46.35)*	41.58 (36.27 to 46.89)*	35.97 (30.29 to 41.66)*	43.73 (38.62 to 48.84)*	49.76 (43.26 to 56.26)*
HAMD total	0.12 (−0.15 to 0.39)	0.25 (−0.10 to 0.59)	0.24 (−0.20 to 0.67)	−0.1 (−0.47 to 0.28)	0.31 (−0.07 to 0.69)	0.57 (0.13 to 1.01)†	−0.32 (−0.72 to 0.08)	0.33 (−0.14 to 0.81)
YMRS total	−0.15 (−0.61 to 0.30)	0.32 (−0.27 to 0.90)	−0.1 (−0.83 to 0.64)	−0.02 (−0.66 to 0.62)	−0.54 (−1.19 to 0.11)	−0.51 (−1.27 to 0.25)	0.41 (−0.28 to 1.10)	−0.04 (−0.84 to 0.76)
Session	0.53 (0.22 to 0.83)‡	0.66 (0.26 to 1.06)‡	0.44 (−0.08 to 0.95)	−0.02 (−0.47 to 0.44)	−0.15 (−0.61 to 0.31)	0.64 (0.07 to 1.20)†	0.78 (0.26 to 1.30)‡	0.04 (−0.53 to 0.61)
Treatment group	−0.79 (−7.34 to 5.77)	1.26 (−5.31 to 7.83)	−1.64 (−9.18 to 5.91)	1.29 (−4.97 to 7.55)	0.08 (−6.39 to 6.54)	8.00 (1.25 to 14.74)†	−3.3 (−9.33 to 2.74)	−6.76 (−14.65 to 1.14)
Session * treatment	−0.40 (−0.82 to 0.02)	−0.48 (−1.04 to 0.07)	−0.39 (−1.10 to 0.33)	−0.07 (−0.69 to 0.56)	−0.24 (−0.88 to 0.40)	−0.64 (−1.42 to 0.14)	−0.39 (−1.11 to 0.32)	−0.21 (−0.99 to 0.58)
				Random effects				
σ^2	12.3	21.83	36.32	28.39	29.19	44.65	37.99	44.82
$\tau_{00\ ID}$	136.16	117.11	138.81	88.78	96.91	80.17	59.98	142
Intraclass correlation	0.92	0.84	0.79	0.76	0.77	0.64	0.61	0.76
Marginal R^2/ conditional R^2	0.027/0.919	0.033/0.848	0.032/0.799	0.004/0.759	0.025/0.774	0.072/0.668	0.110/0.655	0.094/0.783

*$P < 0.0005$.
†$P < 0.05$.
‡$P < 0.005$.
CI, confidence interval.

significant manic symptoms (13 out of a possible 60) at 1 time point; this patient was in the placebo group.

DISCUSSION

The primary aim of this 2-site randomized, controlled trial was to evaluate the cognitive impact of pramipexole in adults with BD. Despite optimizing the study design to maximize the potential to detect a positive signal, on average, participants randomized to pramipexole did not experience greater improvements in cognitive function than participants randomized to placebo. These negative findings, particularly in the context of other, smaller trials that showed only mixed results,[8,13] suggest that pramipexole is likely not a strong candidate for enhancing cognitive function in BD. In our own prior work, the primary analysis, including all study completers, showed no effect of pramipexole; however, subgroup analyses revealed that a portion of BD participants (those who had fewer subthreshold symptoms and greater baseline cognitive impairment) showed significant improvement.[8] The current trial enriched the sample by prescreening for evidence of baseline cognitive impairment and stratifying based on level of depressive symptomatology, but even within this more homogeneous group, we found no significant benefit of pramipexole on cognition. We had also optimized pramipexole dose (4.5 mg/d) relative to our prior work (1.5 mg/d) to maximize potential effects; however, pramipexole dose was not significantly associated with outcome.

We also stratified our sample at randomization based on concomitant antipsychotic medication use, as dopamine antagonists may interfere with the binding of pramipexole, as was seen in our prior work.[8] As such, those participants who were taking antipsychotic medication may have less cognitive benefit from pramipexole. Although this hypothesis was supported, this did not fully account for the null results. Furthermore, given that antipsychotic medications are commonly prescribed for people with BD, augmenting interventions that are ineffective in a large proportion of BD patients would have substantially lower impact on patient outcomes. It is also possible that patients with a history of psychosis experience greater cognitive effects from their illness than those who have never been psychotic. In our sample, a significant majority had a clear history of psychosis and more than 75% had at least some past psychotic symptoms. Studying the effects of pramipexole in patients with no history of psychosis or antipsychotic use could help determine whether there is a group of patients with BD for whom pramipexole is beneficial.

If our trial revealed any clear, positive effect of pramipexole on cognition, an important next step would be to further probe target engagement, to establish the specific mechanism by which pramipexole works to influence cognition in BD. Although previous work provides evidence that pramipexole reliably binds to the D_3 receptor, even when participants are administered a single, low dose,[27] we do not have direct support for this in our trial. We did include a behavioral measure (the IGT) that quantifies the risky/impulsive decision-making characteristic of people with elevated dopamine[28] but did not find group differences in performance. This may have occurred for a variety of reasons. First, total money won on the IGT may not be psychometrically sensitive to engagement of the dopamine reward circuitry in BD and, therefore, does not serve as a valid measure of target engagement. Second, people with BD tend to perform poorly on the IGT, which may have obscured treatment group differences.[29] Positron emission tomography scanning is still the criterion standard, but tasks that probe different decision-making paradigms and computational approaches that take into account other individual and situational factors may allow for more focused assessment of target engagement in future trials.

Cognitive impairment is common among adults with BD and contributes to poor functioning and low quality of life.[3] As interest in targeting these deficits has grown, a handful of different interventions—both pharmacological and psychosocial—have been tested in small trials.[30] For this 2-site trial, we chose to evaluate pramipexole, a dopamine receptor agonist, given demonstrated cognitive enhancement effects in healthy volunteers[12] and people with BD.[8,13] Although we aimed to extend past research by recruiting a larger sample of people selected for clinical characteristics that made them more likely to benefit and by extending the follow-up to allow time for functional improvements to manifest, design modifications imposed on the trial may have reduced our ability to establish cognitive benefit. Perhaps most significantly, reductions in both sample size and follow-up duration based on funding restrictions may have played a role. Future studies of pramipexole should extend the follow-up period to provide ample time for dopamine-related improvements in cognition to manifest. In addition, although, on average, the patients in this trial were not old, given that the age of onset of BD is typically in adolescence,[31] most of the patients had likely been ill for decades. Cognition, among other domains of functioning, tends to decline with subsequent episodes.[32,33] Pramipexole has been shown to have neuroprotective effects[34] and could help protect against the cognitive decline associated with BD. Therefore, treating patients with pramipexole earlier in the course of illness might help them maintain cognitive function. Furthermore, as noted, direct assays of target engagement (eg, PET receptor occupancy measures) were not used, and we did not collect blood samples or patient self-report to assess adherence to the medication protocol. Still, this was the largest trial of pramipexole in BD to date, and the negative results suggest that only a small subset of patients who meet rigid criteria, including no concomitant antipsychotic use, are likely to show cognitive benefit from adjunctive treatment with this agent.

Further pursuit of treatments to ameliorate cognitive deficits in adults with BD is important; most individuals in this population are either unemployed or underemployed and many cannot live independently. In contrast to the resources deployed to address cognitive deficits experienced by individuals with schizophrenia (eg, the study by Sabe et al[7]), relatively few trials have been conducted in people with BD. Research suggests distinct cognitive subgroups within this population,[4] and it may be that there are related differences in neurobiology that result in differences in response to pramipexole (or, presumably, other agents). Additional research to better understand the onset and nature of the cognitive deficits in people with BD will be an important step toward a more personalized approach to treatment. For example, among those with global functioning deficits—similar to what would be expected in individuals with schizophrenia—interventions with evidence of effectiveness in people with schizophrenia may be most worthwhile, whereas individuals with more limited deficits might receive benefit from cognitive remediation targeting specific domains.

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