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

Katherine E. Burdick, PhD; Raphael J. Braga, MD; Charles U. Nnadi, MD; Yaniv Shaya, MA; Walter H. Stearns, MD; and Anil K. Malhotra, MD

ABSTRACT

Objective: Patients with bipolar disorder suffer from significant cognitive impairment that contributes directly to functional disability, yet few studies have targeted these symptoms for treatment, and the optimal study design remains unclear. We evaluated the effects of the dopamine D_2/D_3 receptor agonist pramipexole on cognition in bipolar disorder.

Method: Fifty stable outpatients with *DSM-IV*–diagnosed bipolar I or bipolar II disorder enrolled in an 8-week, double-blind, randomized, placebo-controlled cognitive enhancement trial between July 2006 and April 2010. Patients completed neurocognitive testing at baseline and at week 8, and the primary outcome measures were change scores calculated for each of the 11 tasks. 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 indicated no compelling cognitive benefit of pramipexole versus placebo; however, secondary analyses highlight several important methodological issues for future trials and identify a subgroup of patients who might benefit more readily from cognitive enhancement strategies. This outcome suggests that the study design played a very important role in the results—implying a failed rather than altogether negative trial. Specifically, we found that even very subtle, subsyndromal mood symptoms at baseline had a significant influence on the degree of improvement due to active drug, with strictly euthymic patients faring best (multivariate analysis of variance, $P = .03$ in euthymic subgroup). In addition, the extent of baseline cognitive impairment also contributed to the likelihood of treatment response. Finally, concomitant medications may weaken, or in some cases enhance, response to cognitive treatment and should be accounted for in study design.

Conclusions: Although our results point toward a lack of clear effect of pramipexole on cognition in bipolar patients, our data revealed a potentially beneficial effect of pramipexole in a *subgroup*, providing some enthusiasm for pursuing this line of research in the future. Moreover, this study emphasizes the importance of rigorous subject selection for cognitive trials in bipolar illness. Future studies will be necessary to determine the possible clinical and functional implications of these results.

Trial Registration: clinicaltrials.gov Identifier: NCT00597896

J Clin Psychiatry 2012;73(1):103–112

Submitted: *July 29, 2011; accepted October 4, 2011.*
Online ahead of print: *November 29, 2011 (doi:10.4088/JCP.11m07299).*
Corresponding author: *Katherine E. Burdick, PhD, Mount Sinai School of Medicine, One Gustave L. Levy Pl, Box 1230, New York, NY 10029 (katherine.burdick@mssm.edu).*

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.[1–3] Several meta-analyses indicate that the deficits during affective remission are less severe than in schizophrenia[4–7]; however, performance still falls three-quarters to 1 standard deviation below that of healthy comparison samples.[8] These persistent deficits contribute significantly to functional disability in bipolar disorder,[9–14] making them an important target for treatment.[15] 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.

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 toward 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)[16,17] and the basal ganglia.[18] Abnormal activation in these same brain regions has been reported in bipolar patients performing cognitive tasks during functional magnetic resonance imaging.[19,20] In addition, data derived from cognitive studies of healthy individuals suggest that enhancing dopamine via the administration of dopamine agonists such as pergolide, a D_1 agonist,[21] or bromocriptine, a D_2 agonist,[22,23] 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*-methyltransferase (COMT), an enzyme responsible for the degradation of catecholamines, including dopamine, in the prefrontal cortex.[24] Convergent results demonstrate an association between genetic variation within *COMT* and neurocognitive function in schizophrenia,[25,26] unaffected relatives of schizophrenia patients,[27] and healthy volunteers.[28,29] *COMT* has also been implicated in the susceptibility for bipolar disorder.[30–33] 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.[34]

We previously reported on the safety and efficacy of pramipexole, a D_2/D_3 agonist, in the context of a 6-week, randomized, double-blind, placebo-controlled trial in patients with treatment-resistant bipolar depression.[35] In addition to the primary efficacy measures, a brief battery of psychomotor and attention measures was administered pretreatment and posttreatment 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.[15] Given the prior evidence that increased availability of dopamine may have positive effects on neurocognition in bipolar disorder, together with 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.

- Many patients with bipolar disorder suffer from disabling neurocognitive impairment, yet this symptom domain has not been a common target for treatment.
- Formal neurocognitive assessment and thorough clinical evaluation will be important in determining which patients with bipolar disorder might optimally benefit from cognitive intervention.
- Although preliminary, our data are promising and suggest that improving neurocognitive functioning in patients with bipolar illness is a feasible ambition. Future studies of pramipexole and other agents will be important in continuing efforts to enhance treatment outcome and quality of life.

Clinical Points

METHOD

This study was an 8-week, double-blind, placebo-controlled trial of pramipexole versus placebo in 50 stable outpatients with bipolar disorder. Patients were enrolled between July 2006 and April 2010. Patients screened were 18–65 years of age and carried a clinical diagnosis of bipolar I or II disorder. After a complete description of the study to the subjects, written informed consent was obtained. All consenting subjects underwent the Structured Clinical Interview for *DSM-IV*, Patient Edition (SCID).[36] SCID interviews, augmented by medical records, were presented and discussed weekly in a meeting composed 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 (interrater reliability > 0.80) both at initial contact and again at least 4 weeks later.

At the outset of the study, as per our clinical trial application submitted (and funded) by the Stanley Medical Research Institute, we adopted a very strict inclusion/exclusion policy. First, an initial inclusion criterion was euthymic mood state that was strictly defined by adapting criteria described by Frank and colleagues[37]: total score ≤ 8 on the Clinician-Administered Rating Scale for Mania (CARS-M)[38] and ≤ 8 on the Hamilton Depression Rating Scale (HDRS).[39] In addition, the duration of euthymia was to be at least 4 weeks prior to the date of randomization, as confirmed by consecutive ratings. Second, due to the action of the study agent (pramipexole) on D_2 receptors, we disallowed subjects who were taking any antipsychotic medications, including second-generation antipsychotics. All subjects were required to be taking another US Food and Drug Administration (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. The original goal for randomization was n = 50, and this was the a priori design on which the analytic plan was based.

For practical purposes, we modified the inclusion/exclusion criteria significantly approximately 1 year into the trial, with only 3 subjects having been randomized. Due to the difficulty in recruiting patients who fell within the strict definition of euthymia, 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 ≤ 8 on the CARS-M but changed our entry criteria for depression to include subjects with subthreshold levels of depression, allowing HDRS 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 in the Statistics section. 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 enter the trial. We have included in this article subanalyses related to antipsychotic status.

Additional exclusion criteria were a documented history of central nervous system trauma, neurologic disorder, attention-deficit/hyperactivity disorder, 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 (eg, cimetidine) were also excluded. No drugs that potentially enhance cognition were allowed (eg, other dopamine agonists, modafinil). While the potential for lithium, anticonvulsants, antidepressants, and antipsychotic medications to influence cognitive performance was recognized, it was not feasible to disallow these medications given their widespread use in mood stabilization. We did require a stable regimen for at least 4 weeks prior to randomization with no medication or dosage changes during the 8-week study period. We have evaluated the effects of concomitant medications in our statistical approach.

Study Medication

Adapted from previous work in treatment-resistant bipolar depression,[35] 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/d. The maximum dose of 1.5 mg/d was chosen on the basis of a mean daily dose of 1.7 mg/d in our prior work.[35] A maximum of 4.5 mg/d 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 and the data on mania induction using pramipexole were very limited at the commencement of this study. Side effects were monitored and recorded weekly by the study physicians, and vital signs were measured at each visit (blood pressure, pulse, temperature, weight). Clinic visits occurred weekly over the 8-week trial, and mood assessments (HDRS 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[40] was not finalized at the commencement of this trial; therefore, included tasks were derived from both the beta version of the instrument and our preliminary report.[15] The battery was administered in a uniform order and lasted 1.5 hours. It consisted of the Wechsler Adult Intelligence Scale–Third Edition (WAIS-III) Digit Span subtest (Digits Forward and Backward); WAIS-III digit symbol subtest; Stroop Color-Word Test; Trail Making Test Parts A and B; d2 Test of Attention; Hopkins Verbal Learning Test; and Controlled Oral Word Association Test letter fluency. Alternate forms for the Hopkins Verbal Learning Test and the Controlled Oral Word Association Test were utilized at time 2 testing to reduce the potential for practice effects. The Wide Range Achievement Test–Third Edition reading subtest was used as an estimate of premorbid intellectual function at baseline (all test citations in Spreen and Strauss[41]). A single measure from each task was utilized in analyses for a total set of 11 primary outcome measures.

This study was approved by the North Shore Long Island Jewish Health System Institutional Review Board 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 11 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 MANOVA including only the subgroup of patients who were strictly defined as euthymic at baseline and entered baseline HDRS and CARS-M scores to evaluate the main effects of even very low-level baseline symptoms in the euthymic sample. Effect sizes for change (Cohen *d*) were calculated in the total sample and again in the euthymic group to allow for direct comparisons. Next, for measures of interest, we carried out univariate analyses of variance splitting groups based on concomitant medication status (yes/no) to evaluate the influence of concomitant lithium, antipsychotic, antidepressant, and anticonvulsant use on treatment effect. Finally, in an effort to understand the impact of initial impairment level on cognitive outcome after treatment, we tested for correlations between baseline performance and cognitive change scores.

RESULTS

Subjects

Subject screening and enrollment details are provided in Figure 1. Fifty subjects were randomly assigned to treatment (26 to placebo and 24 to pramipexole); 4 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 being presented in consensus conference (did not meet *DSM-IV* bipolar I or bipolar II criteria). Eleven patients were characterized by subthreshold symptoms at baseline (HDRS score > 8 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 11 subjects who demonstrated subthreshold levels of depression. The 11 patients excluded from these analyses did not differ from the euthymic sample of 34 on demographic features such as sex ($\chi^2 = 0.37$; $P = .55$), race ($\chi^2 = 0.68$; $P = .41$), or premorbid IQ ($F = 0.09$; $P = .76$); however, they were older than the subgroup of euthymic patients ($F = 5.08$; $P = .03$).

Results in the Full Completers Sample

Of the 45 individuals who completed 2 testing sessions, 24 subjects were randomly assigned to receive placebo and 21 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 8-week trial (Table 1), and there were no reports of psychosis or mania induction in either treatment group. All patients completing the trial reached and maintained the maximum dosage (1.5 mg/d) by week 6; therefore, at week 8 the mean daily dosage of pramipexole was 1.5 mg/d. The frequency of concomitant medications, by class, in the full sample of 45 was as follows: 40% (n = 18), lithium; 64% (n = 29), antipsychotics; 44% (n = 20), antidepressants; and 56% (n = 25), anticonvulsants. Patients were taking a

© Copyright 2011 Physicians Postgraduate Press, Inc.

Figure 1. Flow Diagram Indicating Subject Enrollment and Inclusion

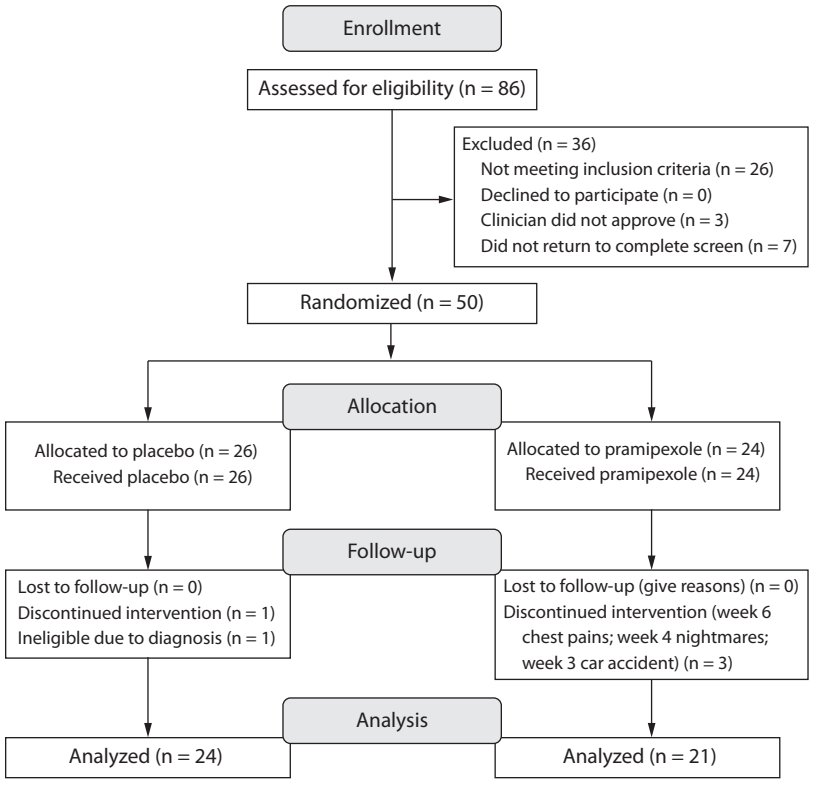


Table 1. Subject Characteristics by Treatment Group (all completers)

Characteristic	Placebo (n = 24)	Pramipexole (n = 21)	Statistic	*P* Value
Age, mean (SD), y	44.42 (12.2)	43.81 (9.4)	$F = 0.03$	.85
Sex, male/female, n	10/14	7/14	$\chi^2 = 0.33$	.57
Race, white/nonwhite, n	10/14	7/14	$\chi^2 = 0.33$	.57
HDRS score at baseline, mean (SD)	5.5 (3.5)	5.9 (3.4)	$F = 0.12$	.73
CARS-M score at baseline, mean (SD)	2.5 (2.1)	3.1 (2.4)	$F = 0.92$	.34
Change in HDRS (week 8 – baseline), mean (SD)	−1.5 (3.2)	−0.9 (5.5)	$F = 0.23$	.63
Change in CARS-M (week 8 – baseline), mean (SD)	−0.9 (3.0)	0.5 (4.0)	$F = 1.62$	.21
Premorbid IQ (WRAT-3 reading), mean (SD)	96.1 (13.3)	96.5 (12.7)	$F = 0.01$	.92
History of psychosis, % (n)	70.8 (17)	42.9 (9)	$\chi^2 = 3.59$	.06
History of substance use disorder, % (n)	45.8 (11)	47.6 (10)	$\chi^2 = 0.01$	.91
Comorbid anxiety disorder, % (n)	41.7 (10)	33.3 (7)	$\chi^2 = 0.33$	.57
Bipolar type I, % (n)	83.3 (20)	66.7 (14)	$\chi^2 = 1.68$	.19
Medication use				
Lithium, % (n)	33.3 (8)	47.6 (10)	$\chi^2 = 0.95$	.33
Anticonvulsants, % (n)	62.5 (15)	47.6 (10)	$\chi^2 = 1.00$	.32
Antipsychotics, % (n)	62.5 (15)	66.7 (14)	$\chi^2 = 0.09$	.77
Antidepressants, % (n)	50.0 (12)	38.1 (8)	$\chi^2 = 0.64$	.42
Total no. of medications, mean (SD)[a]	2.4 (0.9)	2.2 (1.0)	$F = 0.23$	.64
Medication load, mean (SD)[b]	4.3 (2.1)	4.1 (2.3)	$F = 0.13$	.72

[a]Psychotropic medications taken currently, excluding prn.
[b]Calculated using dosage and drug class information (as per Hassel et al[42]).
Abbreviations: CARS-M = Clinician Administered Rating Scale for Mania, HDRS = Hamilton Depression Rating Scale, WRAT-3 = Wide Range Achievement Test–Third Edition.

mean (± SD) of 2.31 ± 0.9 psychotropic medications. Concomitant medication load, as calculated based on number, type, and dosage of medications,[42] did not significantly differ by treatment group (Table 1). In addition, 76% (n = 34) of the sample had bipolar I disorder, and 58% (n = 26) had a history of psychosis during acute episodes. The remaining 24% (n = 11) of the sample was diagnosed with bipolar II disorder. A prior history (not currently active as per SCID) of substance use disorders was present in 47% (n = 21) of the subjects, and comorbid anxiety disorders were diagnosed in 38% (n = 17) of the subjects. Treatment groups did not differ with regard to the distribution of bipolar subtype, history of psychosis, or comorbid anxiety (Table 1).

The only side effect reported more frequently by participants in the active treatment group (19%; 4/21) than those taking placebo (0%) was restlessness ($\chi^2 = 5.2$; $P = .02$). 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. Results from the primary MANOVA revealed a nonsignificant treatment group effect ($F_{1,44} = 0.54$; $P = .86$). No individual measure reached statistical significance (all P values > .05). Effect size changes were calculated for both treatment groups and are depicted in Figure 2.

Results in the Euthymic Subgroup

As noted above, the initial study was designed to allow only strictly defined euthymic subjects into the trial. Therefore, we carried out secondary analyses in the 34 subjects who were euthymic at baseline and covaried for baseline HDRS and CARS-M scores to better elucidate the effects of baseline mood symptoms on cognitive change in response to treatment. Eighteen patients received placebo, and 16 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 and the pramipexole group (Table 3). The frequency of concomitant medications, by class, in the subsample of 34 was as follows: 62% (n = 21), antipsychotics; 44% (n = 15), antidepressants; 53% (n = 18), anticonvulsants; and 41% (n = 14), lithium. Patients were taking a mean (± SD) of 2.24 ± 1.0 psychotropic medications. Concomitant medication load, as calculated based on number, type, and dosage of medications,[42] did not significantly differ by treatment group (Table 3). Seventy-seven percent (n = 26) of the euthymic subgroup had bipolar I disorder,

Table 2. Side Effects at Week 8 by Treatment Group (all completers)

Side Effect	Placebo (n = 24), n	Pramipexole (n = 21), n	χ^2	*P* Value
Restlessness	0	4	5.2	.02*
Dry mouth	4	4	0.04	.83
Increased appetite	4	5	0.4	.51
Drowsiness	2	4	1.2	.27
Headache	1	2	0.6	.45
Increased motor activity	2	1	0.2	.66
Decreased motor activity	1	3	1.5	.22
Tremor	4	2	0.4	.52
Urinary retention	3	0	2.7	.10
Nocturnal enuresis	2	2	0.03	.86
Hypersomnia	2	2	0.03	.86
Insomnia	2	1	0.2	.66
Paresthesia	1	0	0.9	.35
Agitation	1	0	0.9	.35
Decreased appetite	2	0	1.8	.19
Cramps	1	1	0.02	.90
Decreased libido	1	0	0.9	.35
Hypertension	0	1	1.2	.27
Dizziness	0	1	1.2	.27
Edema	1	0	0.9	.35
Nasal congestion	2	1	0.2	.66
Fever	0	1	1.2	.27
Nausea	1	2	0.6	.45
Vomiting	1	0	0.9	.35
Diarrhea	1	2	0.6	.45
Decreased libido	2	2	0.03	.86
Impaired sexual performance	1	1	0.02	.90
Rash	1	0	0.9	.35
Joint pain	1	0	0.9	.35
Muscle pain	1	1	0.02	.90

*$P < .05$.

and 59% (n = 20) had a history of psychosis during acute episodes. A history of substance use disorders was noted in 44% (n = 15) of the subsample, and comorbid anxiety disorders were present in 38% (n = 13) of the euthymic subjects. Treatment groups did not differ with regard to the distribution of bipolar subtype, history of psychosis, or comorbid anxiety in this subgroup (Table 3).

Effects of baseline affective symptoms. After covarying for baseline HDRS and CARS-M scores, multivariate analysis of covariance (MANCOVA) revealed a significant overall effect of treatment group ($F_{1,33} = 2.62$; $P = .030$) 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 2 neurocognitive tasks in the patients taking pramipexole versus those taking placebo: WAIS Digits Backward ($F_{1,33} = 4.98$; $P = .033$) and Stroop Color ($F_{1,33} = 10.37$; $P = .003$; Figure 3). A generalized pattern of greater improvement in the pramipexole group versus placebo is noted. Effect size calculations indicate a notably enhanced benefit of pramipexole in this subgroup of euthymic patients as compared with the full completers sample (Figure 4), highlighting the importance of baseline mood state in cognitive enhancement trials in bipolar disorder.

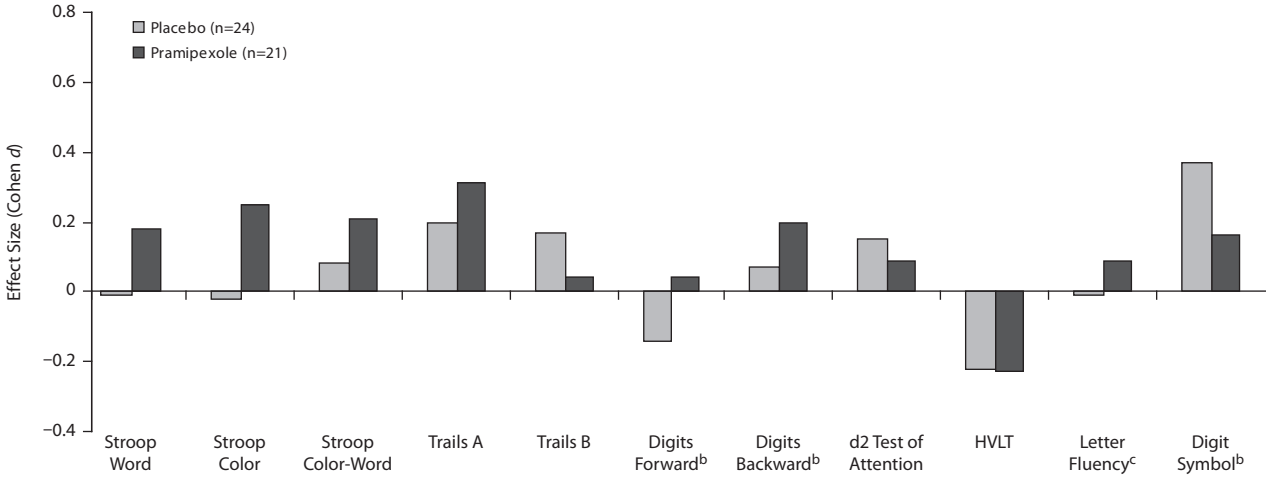
Effects of concomitant medications. In an effort to evaluate the effects of concomitant medications on cognitive improvement with pramipexole, we performed post hoc univariate ANOVAs splitting the euthymic subgroup on the basis of the presence or absence of the 4 main categories of concomitant drugs: lithium, antipsychotics, antidepressants, and anticonvulsants. The beneficial effect of pramipexole on WAIS Digits Backward was considerably stronger in the subjects who were not taking lithium ($\eta^2 = 0.36$) versus those who were taking lithium ($\eta^2 = 0.03$) and stronger in subjects who were not taking antipsychotic medications ($\eta^2 = 0.32$) than in those taking antipsychotics ($\eta^2 = 0.12$). In contrast, positive effects of pramipexole on Digits Backward were greater in subjects who were taking antidepressants ($\eta^2 = 0.32$) than in those who were not taking antidepressants ($\eta^2 = 0.07$) and much larger in the subgroup who were taking anticonvulsants ($\eta^2 = 0.67$) versus those subjects not taking anticonvulsants ($\eta^2 = 0.001$). Concomitant medication analyses for Stroop Color improvement revealed no clear differences in effect size changes in the subjects who were taking lithium ($\eta^2 = 0.25$) versus those who were not ($\eta^2 = 0.21$); however, the effect of pramipexole was weakened in those taking concomitant antipsychotics ($\eta^2 = 0.16$) versus those who were not ($\eta^2 = 0.33$). Subjects taking antidepressants fared much better ($\eta^2 = 0.50$) than those not taking them ($\eta^2 = 0.12$), as did subjects prescribed anticonvulsants ($\eta^2 = 0.29$) compared to those not taking anticonvulsants ($\eta^2 = 0.18$). Although the medication regimens were more complex than these analyses were able to address, these data suggest that concomitant medications should be taken into account when designing cognitive enhancement trials in bipolar disorder.

Effects of baseline cognitive impairment. Finally, we were interested in understanding the extent to which the degree of cognitive impairment at baseline contributes to the amount of change seen in a cognitive trial in patients with bipolar disorder. To begin to address this question, 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 ($r = 0.23$; $P = .28$); however, correlations between these variables in the pramipexole group reached statistical significance ($r = -0.61$; $P = .003$). Likewise, baseline performance on Stroop Color was not significantly correlated with Stroop change scores in the placebo group ($r = -0.28$; $P = .18$), but there was a significant relationship in the pramipexole group ($r = -0.42$; $P < .05$). These results suggest that higher levels of baseline cognitive impairment (lower scores) are associated with greater cognitive improvement after pramipexole treatment.

DISCUSSION

Results from this 8-week, randomized, placebo-controlled cognitive enhancement trial suggest that the D_2/D_3 agonist pramipexole may be effective in a subgroup of euthymic patients with bipolar disorder. Although primary analyses including patients with subthreshold depression

Figure 2. Effect Size of Neurocognitive Change by Treatment Group (all completers)[a]



[a]All 45 completers are included in this depiction of the primary analysis, which shows the effect size of the change from baseline to week 8 on each measure. The pattern of change indicates no clear pattern of benefit for pramipexole over placebo.
[b]From the Wechsler Adult Intelligence Scale–Third Edition.
[c]From the Controlled Oral Word Association Test.
Abbreviation: HVLT = Hopkins Verbal Learning Test.

Table 3. Subject Characteristics (euthymic subgroup)

Feature	Placebo (n = 18)	Pramipexole (n = 16)	Statistic	*P* Value
Age, mean (SD), y	42.7 (13.1)	41.6 (9.3)	$F = 0.08$	.78
Sex, male/female, n	7/11	5/11	$\chi^2 = 0.22$	.64
Race, white/nonwhite, n	8/10	6/10	$\chi^2 = 0.17$	.68
HDRS score at baseline, mean (SD)	3.9 (2.4)	4.5 (2.5)	$F = 0.43$	.52
CARS-M score at baseline, mean (SD)	1.9 (1.7)	2.5 (2.1)	$F = 0.85$	.37
Change in HDRS (week 8 – baseline), mean (SD)	−0.9 (3.2)	+0.1 (5.7)	$F = 0.42$	.52
Change in CARS-M (week 8 – baseline), mean (SD)	+0.1 (2.7)	+0.2 (3.2)	$F = 0.01$	.94
Premorbid IQ (WRAT-3 reading), mean (SD)	98.2 (12.7)	94.9 (13.3)	$F = 0.56$	.46
History of psychosis, %	66.7 (12)	50.0 (8)	$\chi^2 = 0.97$	.32
History of substance use disorder, %	44.4 (8)	43.8 (7)	$\chi^2 = 0.01$	.97
Comorbid anxiety disorder, %	44.4 (8)	31.3 (5)	$\chi^2 = 0.62$	.43
Bipolar type I, %	83.3 (15)	68.8 (11)	$\chi^2 = 1.00$	.32
Medication use				
Lithium, %	27.8 (5)	56.3 (9)	$\chi^2 = 2.84$	.09
Anticonvulsants, %	66.7 (12)	37.5 (6)	$\chi^2 = 2.89$	.09
Antipsychotics, %	50.0 (9)	75.0 (12)	$\chi^2 = 2.24$	.13
Antidepressants, %	50.0 (9)	37.5 (6)	$\chi^2 = 0.54$	.46
Total no. of medications, mean (SD)[a]	2.26	2.25	$t = 0.04$	.97
Medication load, mean (SD)[b]	4.27 (2.1)	3.77 (2.0)	$t = 0.64$	.53

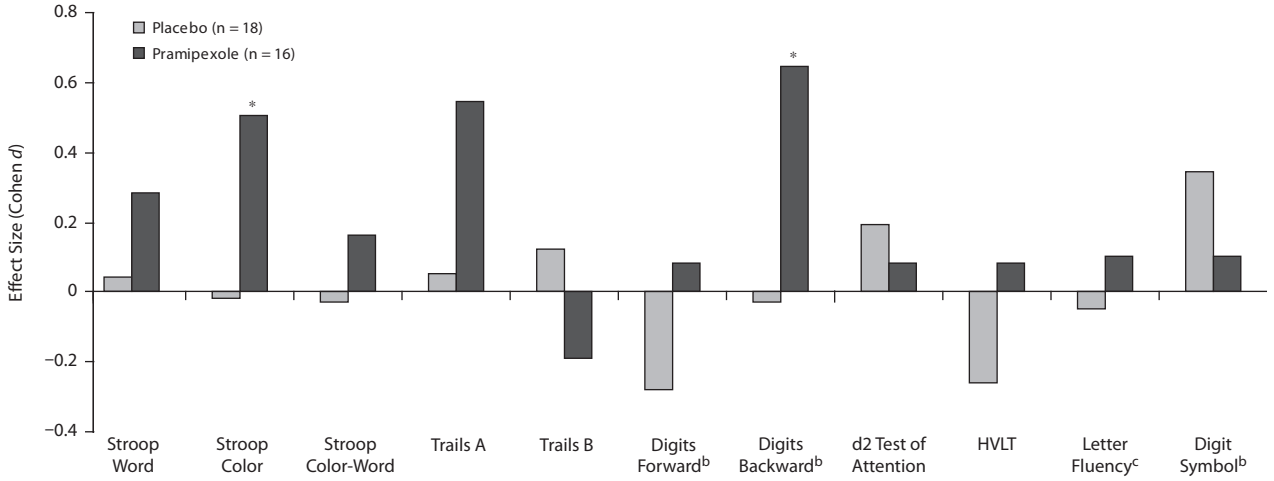
[a]Psychotropic medications taken currently, excluding prn.
[b]Calculated using dosage and drug class information (as per Hassel et al[42]).
Abbreviations: CARS-M = Clinician Administered Rating Scale for Mania, HDRS = Hamilton Depression Rating Scale, WRAT-3 = Wide Range Achievement Test–Third Edition.

at baseline were not significant, 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. These results warrant follow-up, despite the post hoc nature of the analyses, as the functional implications of cognitive impairment in bipolar disorder may be of particular importance during periods of euthymia when patients might otherwise be expected to return to normal occupational and social functioning.[9–14]

To our knowledge, this study is the first placebo-controlled cognitive enhancement trial in affectively stable bipolar patients. A handful of case reports and case series have been 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,[43–45] and no objective neurocognitive tests were administered. Given the lack of correlation between subjective ratings of cognition and neuropsychological test results in bipolar patients,[46,47] the extent to which previously reported cognitive improvement represented cognitive enhancement as opposed to an effect on mood or general well-being is unknown. In an open-label design, Iosifescu et al[48] administered galantamine to 19 remitted bipolar patients (HDRS score ≤ 10) over a 4-month period. Only 11 patients completed the study; however, structured cognitive testing was completed at baseline and again at 16 weeks. Results were promising, with a significant improvement in the bipolar group on a measure of sustained attention and on a measure of verbal memory, but larger, controlled trials will be needed to determine the cognitive efficacy of galantamine in bipolar disorder. Although the cognitive effects of pramipexole have never been evaluated in bipolar patients, it is interesting to note that at least 1 study[49] in patients with Parkinson's disease reported a deleterious effect of pramipexole on cognition, inconsistent with our findings.

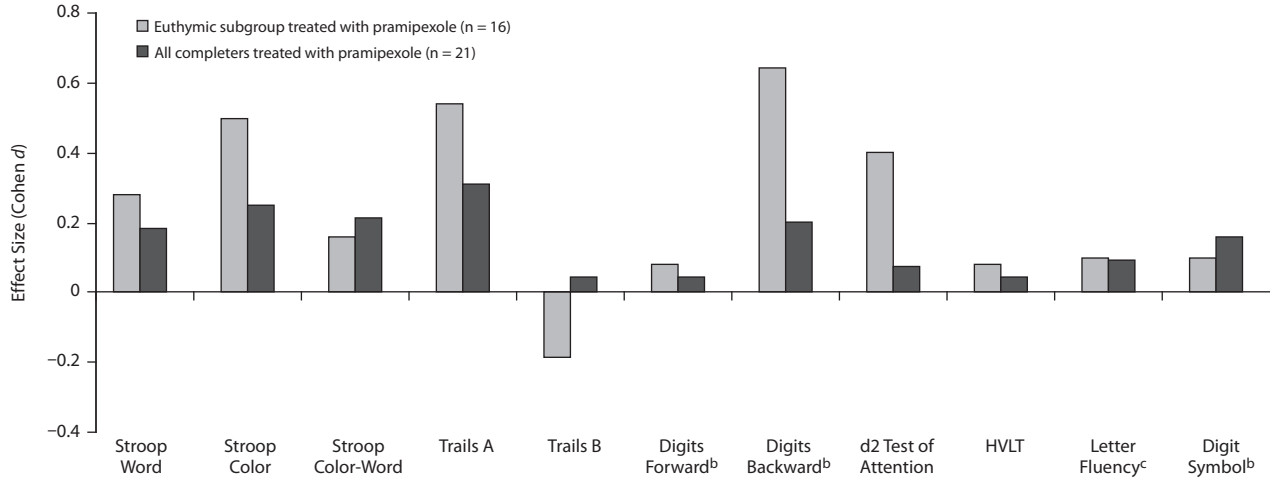
Our results highlight specific methodological challenges in designing cognitive trials in patients with bipolar disorder. The episodic nature of the illness requires the careful consideration of active symptomatology at baseline, particularly

Figure 3. Effect Size of Neurocognitive Change by Treatment Group (euthymic subgroup)[a]



[a]Only the euthymic subgroup is included in these results, and subthreshold symptom ratings are included as covariates. The overall multivariate analysis of covariance achieved statistical significance ($P = .03$), as did 2 specific neurocognitive measures (indicated in the figure by asterisks; Stroop color, $P = .003$; and Digits Backward, $P = .03$).
[b]From the Wechsler Adult Intelligence Scale–Third Edition.
[c]From the Controlled Oral Word Association Test.
Abbreviation: HVLT = Hopkins Verbal Learning Test.

Figure 4. Enhanced Effect Size of Neurocognitive Change in the Euthymic Subgroup Treated With Pramipexole[a]



[a]This analysis includes all patients who were assigned to pramipexole and the euthymic subgroup who received pramipexole. It indicates enhanced effect of pramipexole in the context of euthymia on 8 of 11 measures.
[b]From the Wechsler Adult Intelligence Scale–Third Edition.
[c]From the Controlled Oral Word Association Test.
Abbreviation: HVLT = Hopkins Verbal Learning Test.

in light of convergent data suggesting a significant influence of affective symptoms on neurocognitive performance.[2,50] In the case that symptomatic patients are included and cognitive improvement is reported, it may be difficult to rule out pseudospecificity. For example, preliminary data from our earlier work in treatment-resistant bipolar depression provided evidence of a potential role for pramipexole as a cognitive enhancement agent[35]; however, the patients in that trial also improved with regard to depressive symptoms, making it impossible to determine the extent to which the improvement in cognitive functioning was related to the amelioration of depressive symptoms. The current trial was specifically designed to address this issue by initially restricting inclusion to patients who were strictly euthymic at the time of treatment initiation; however, many patients with bipolar disorder maintain significant levels of subsyndromal symptoms even when considered to be in remission.[51] Thus, this strict inclusion criterion, although scientifically justified, not only reduces the feasibility of completing the trial but also inherently limits the generalizability of the findings.

A second methodological issue concerns the considerable cognitive heterogeneity that is seen in bipolar patients,

with a substantial proportion of patients displaying "normal" neuropsychological functioning.[52–54] This raises the need to consider prescreening subjects for a minimal level of neurocognitive impairment to ensure that there is reasonable room for improvement with treatment. Although the current study did not impose a minimal level of cognitive impairment for inclusion, the potential utility of doing so is reflected in our findings that lower baseline cognitive performance correlates with greater change over time. Moreover, the potential for ceiling effects in some patients with bipolar illness is of real concern in optimizing study designs.

Pramipexole is a partial/full D_2/D_3 agonist with highest affinity for the D_3 receptor,[55,56] and it is FDA-approved for the treatment of Parkinson's disease.[57] 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.[58] Consistent with this mechanism of action, pramipexole has a direct antidepressant effect in patients with Parkinson's disease[59] above and beyond its efficacy for motor symptoms associated with the illness.[60] Moreover, several additional studies suggest that pramipexole's antidepressant effect may be extended to psychiatric samples[61] including those with bipolar disorder.[35,62] The current study was not designed to assess antidepressant effects of pramipexole, and we did not note any significant improvement in the low-grade depressive symptoms that were present in our cohort even when we evaluated this in the symptomatic group alone. This lack of effect may be due to the subthreshold nature of the symptoms, concomitant medications including antipsychotic medications, or the relatively conservative dose of pramipexole utilized in this trial.

Our study has several limitations. First, the change in study design with regard to the inclusion of subthreshold depressive symptoms necessitated a 2-level analytic approach, and the subsample of euthymic patients included in the secondary analysis was limited in size. This approach involved a reduction in power due to the exclusion of 11 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 initial aim, which was to evaluate the effects of pramipexole on cognition *without* the confounding effects of depressive symptom improvement. The initial power analysis for the trial was based on the large effect size noted in our preliminary data,[34] and the subsample of euthymic patients is not adequately powered to detect a small or medium effect size. A sample size of 34 is only powered to detect an effect equivalent to a Cohen *d* approaching 1.0. Thus, the negative findings in this study should be interpreted with caution, and follow-up studies will be critical.

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 dividing groups based on medication classes. The inclusion of patients receiving antipsychotics may be of particular concern in this study due to the action of pramipexole on the D_2 receptor.

Third, 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 other medications. There were no concerning side effects and no indication of affective or psychotic exacerbation; therefore, it is likely that a higher dose would be well tolerated and could possibly have greater beneficial effects. Future studies should evaluate dose-related effects and further assess the effects of concomitant medications on treatment response.

Fourth, although our positive results in the euthymic subgroup 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. 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 provide preliminary evidence of a modest, cognitively beneficial effect of the D_2/D_3 agonist pramipexole in a subgroup of strictly defined 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. We believe that these preliminary data are very encouraging. The study also emphasizes some of the challenges that might be specific to the episodic course of bipolar disorder (eg, 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.[63]

Drug names: bromocriptine (Parlodel, Cycloset, and others), cimetidine (Tagamet and others), galantamine (Razadyne), lithium (Lithobid and others), modafinil (Provigil), pramipexole (Mirapex and others), topiramate (Topamax and others).

Author affiliations: Mount Sinai School of Medicine, New York (Dr Burdick); Zucker Hillside Hospital-North Shore Long Island Jewish Health System, Glen Oaks (Drs Braga, Stearns, and Malhotra and Mr Shaya); Hofstra North Shore-LIJ School of Medicine at Hofstra University, Hempstead (Drs Braga and Malhotra); Harlem Hospital, Columbia University College of Physicians and Surgeons, New York (Dr Nnadi); and Feinstein Institute for Medical Research, Manhasset (Dr Malhotra), New York.

Potential conflicts of interest: **Dr Burdick** has served on the speakers bureau for Schering Plough/Merck. **Dr Malhotra** has received grant support from Eli Lilly; served as a consultant to Wyeth, PGx Health, and Eli Lilly; and been on the speakers bureaus of Schering Plough/Merck and Arbor Scientia (Sepracor). **Drs Braga, Nnadi**, and **Stearns** and **Mr Shaya** report no conflict of interest.

Funding/support: Funding was received from the Stanley Medical Research Institute (SMRI #05T-670 to Drs Burdick and Malhotra). Work was also supported by National Institute of Mental Health grant K23MH077807 (to Dr Burdick).

Previous presentation: This work was presented, in part, at the 49th Annual Meeting of the American College of Neuropsychopharmacology; December 8–12, 2010; Miami, Florida.

Acknowledgment: The authors thank the patients who participated in the study.

© Copyright 2011 Physicians Postgraduate Press, Inc.

REFERENCES

1. Daban C, Martinez-Aran A, Torrent C, et al. Specificity of cognitive deficits in bipolar disorder versus schizophrenia: a systematic review. *Psychother Psychosom*. 2006;75(2):72–84.
2. Martínez-Arán A, Vieta E, Colom F, et al. Cognitive dysfunctions in bipolar disorder: evidence of neuropsychological disturbances. *Psychother Psychosom*. 2000;69(1):2–18.
3. Martínez-Arán A, Vieta E, Reinares M, et al. Cognitive function across manic or hypomanic, depressed, and euthymic states in bipolar disorder. *Am J Psychiatry*. 2004;161(2):262–270.
4. Arts B, Jabben N, Krabbendam L, et al. Meta-analyses of cognitive functioning in euthymic bipolar patients and their first-degree relatives. *Psychol Med*. 2008;38(6):771–785.
5. Bora E, Yucel M, Pantelis C. Cognitive endophenotypes of bipolar disorder: a meta-analysis of neuropsychological deficits in euthymic patients and their first-degree relatives. *J Affect Disord*. 2009;113(1–2):1–20.
6. Robinson LJ, Thompson JM, Gallagher P, et al. A meta-analysis of cognitive deficits in euthymic patients with bipolar disorder. *J Affect Disord*. 2006;93(1–3):105–115.
7. Torres IJ, Boudreau VG, Yatham LN. Neuropsychological functioning in euthymic bipolar disorder: a meta-analysis. *Acta Psychiatr Scand Suppl*. 2007;116(434):17–26.
8. Burdick KE, Goldberg TE, Cornblatt BA, et al. The MATRICS Consensus Cognitive Battery in patients with bipolar I disorder. *Neuropsychopharmacology*. 2011;36(8):1587–1592.
9. Bowie CR, Depp C, McGrath JA, et al. Prediction of real-world functional disability in chronic mental disorders: a comparison of schizophrenia and bipolar disorder. *Am J Psychiatry*. 2010;167(9):1116–1124.
10. Brissos S, Dias VV, Carita AI, et al. Quality of life in bipolar type I disorder and schizophrenia in remission: clinical and neurocognitive correlates. *Psychiatry Res*. 2008;160(1):55–62.
11. Burdick KE, Goldberg JF, Harrow M. Neurocognitive dysfunction and psychosocial outcome in patients with bipolar I disorder at 15-year follow-up. *Acta Psychiatr Scand*. 2010;122(6):499-506.
12. Jaeger J, Berns S, Loftus S, et al. Neurocognitive test performance predicts functional recovery from acute exacerbation leading to hospitalization in bipolar disorder. *Bipolar Disord*. 2007;9(1–2):93–102.
13. Malhi GS, Ivanovski B, Hadzi-Pavlovic D, et al. Neuropsychological deficits and functional impairment in bipolar depression, hypomania and euthymia. *Bipolar Disord*. 2007;9(1–2):114–125.
14. Martinez-Aran A, Vieta E, Torrent C, et al. Functional outcome in bipolar disorder: the role of clinical and cognitive factors. *Bipolar Disord*. 2007;9(1–2):103–113.
15. Burdick KE, Braga RJ, Goldberg JF, et al. Cognitive dysfunction in bipolar disorder: future place of pharmacotherapy. *CNS Drugs*. 2007;21(12):971–981.
16. Drevets WC, Ongür D, Price JL. Neuroimaging abnormalities in the subgenual prefrontal cortex: implications for the pathophysiology of familial mood disorders. *Mol Psychiatry*. 1998;3(3):220–226, 190–191.
17. López-Larson MP, DelBello MP, Zimmerman ME, et al. Regional prefrontal gray and white matter abnormalities in bipolar disorder. *Biol Psychiatry*. 2002;52(2):93–100.
18. Baumann B, Bogerts B. Neuroanatomical studies on bipolar disorder. *Br J Psychiatry suppl*. 2001;41:s142–s147.
19. Blumberg HP, Stern E, Martinez D, et al. Increased anterior cingulate and caudate activity in bipolar mania. *Biol Psychiatry*. 2000; 48(11):1045–1052.
20. Gruber SA, Rogowska J, Yurgelun-Todd DA. Decreased activation of the anterior cingulate in bipolar patients: an fMRI study. *J Affect Disord*. 2004;82(2):191–201.
21. Kimberg DY, D'Esposito M. Cognitive effects of the dopamine receptor agonist pergolide. *Neuropsychologia*. 2003;41(8):1020–1027.
22. Kimberg DY, D'Esposito M, Farah MJ. Effects of bromocriptine on human subjects depend on working memory capacity. *Neuroreport*. 1997;8(16):3581–3585.
23. Luciana M, Collins PF, Depue RA. Opposing roles for dopamine and serotonin in the modulation of human spatial working memory functions. *Cereb Cortex*. 1998;8(3):218–226.
24. Dickinson D, Elvevåg B. Genes, cognition and brain through a COMT lens. *Neuroscience*. 2009;164(1):72–87.
25. Bilder RM, Volavka J, Czobor P, et al. Neurocognitive correlates of the COMT Val(158)Met polymorphism in chronic schizophrenia. *Biol Psychiatry*. 2002;52(7):701–707.
26. Egan MF, Goldberg TE, Kolachana BS, et al. Effect of COMT Val108/158 Met genotype on frontal lobe function and risk for schizophrenia. *Proc Natl Acad Sci U S A*. 2001;98(12):6917–6922.
27. Rosa A, Peralta V, Cuesta MJ, et al. New evidence of association between COMT gene and prefrontal neurocognitive function in healthy individuals from sibling pairs discordant for psychosis. *Am J Psychiatry*. 2004;161(6):1110–1112.
28. Malhotra AK, Kestler LJ, Mazzanti C, et al. A functional polymorphism in the *COMT* gene and performance on a test of prefrontal cognition. *Am J Psychiatry*. 2002;159(4):652–654.
29. Tsai SJ, Yu YW, Chen TJ, et al. Association study of a functional catechol-*O*-methyltransferase-gene polymorphism and cognitive function in healthy females. *Neurosci Lett*. 2003;338(2):123–126.
30. Kirov G, Murphy KC, Arranz MJ, et al. Low activity allele of catechol-*O*-methyltransferase gene associated with rapid cycling bipolar disorder. *Mol Psychiatry*. 1998;3(4):342–345.
31. Mynett-Johnson LA, Murphy VE, Claffey E, et al. Preliminary evidence of an association between bipolar disorder in females and the catechol-*O*-methyltransferase gene. *Psychiatr Genet*. 1998;8(4):221–225.
32. Papolos DF, Veit S, Faedda GL, et al. Ultra-ultra rapid cycling bipolar disorder is associated with the low activity catecholamine-*O*-methyltransferase allele. *Mol Psychiatry*. 1998;3(4):346–349.
33. Shifman S, Bronstein M, Sternfeld M, et al. *COMT*: a common susceptibility gene in bipolar disorder and schizophrenia. *Am J Med Genet B Neuropsychiatr Genet*. 2004;128B(1):61–64.
34. Burdick KE, Funke B, Goldberg JF, et al. COMT genotype increases risk for bipolar I disorder and influences neurocognitive performance. *Bipolar Disord*. 2007;9(4):370–376.
35. Goldberg JF, Burdick KE, Endick CJ. Preliminary randomized, double-blind, placebo-controlled trial of pramipexole added to mood stabilizers for treatment-resistant bipolar depression. *Am J Psychiatry*. 2004;161(3):564–566.
36. First MB, Spitzer R, Williams JBW, et al. *Structured Clinical Interview for Axis I DSM IV Disorders-Patient Edition (SCIDI/P, Version 2.0)*. New York, NY: Biometric Research Department; 1998.
37. Frank E, Prien RF, Jarrett RB, et al. Conceptualization and rationale for consensus definitions of terms in major depressive disorder: remission, recovery, relapse, and recurrence. *Arch Gen Psychiatry*. 1991;48(9):851–855.
38. Altman EG, Hedeker DR, Janicak PG, et al. The Clinician-Administered Rating Scale for Mania (CARS-M): development, reliability, and validity. *Biol Psychiatry*. 1994;36(2):124–134.
39. Hamilton M. Development of a rating scale for primary depressive illness. *Br J Soc Clin Psychol*. 1967;6(4):278–296.
40. Green MF, Nuechterlein KH. The MATRICS initiative: developing a consensus cognitive battery for clinical trials. *Schizophr Res*. 2004;72(1):1–3.
41. Spreen O, Strauss E. *A Compendium of Neuropsychological Tests: Administration, Norms, and Commentary*. 2nd ed. New York, NY: Oxford University Press; 1998.
42. Hassel S, Almeida JR, Kerr N, et al. Elevated striatal and decreased dorsolateral prefrontal cortical activity in response to emotional stimuli in euthymic bipolar disorder: no associations with psychotropic medication load. *Bipolar Disord*. 2008;10(8):916–927.
43. Jacobsen FM, Comas-Díaz L. Donepezil for psychotropic-induced memory loss. *J Clin Psychiatry*. 1999;60(10):698–704.
44. Schrauwen E, Ghaemi SN. Galantamine treatment of cognitive impairment in bipolar disorder: four cases. *Bipolar Disord*. 2006;8(2):196–199.
45. Teng CT, Demetrio FN. Memantine may acutely improve cognition and have a mood stabilizing effect in treatment-resistant bipolar disorder. *Rev Bras Psiquiatr*. 2006;28(3):252–254.
46. Burdick KE, Endick CJ, Goldberg JF. Assessing cognitive deficits in bipolar disorder: are self-reports valid? *Psychiatry Res*. 2005;136(1):43–50.
47. Martínez-Arán A, Vieta E, Colom F, et al. Do cognitive complaints in euthymic bipolar patients reflect objective cognitive impairment? *Psychother Psychosom*. 2005;74(5):295–302.
48. Iosifescu DV, Moore CM, Deckersbach T, et al. Galantamine-ER for cognitive dysfunction in bipolar disorder and correlation with hippocampal neuronal viability: a proof-of-concept study. *CNS Neurosci Ther*. 2009; 15(4):309–319.
49. Brusa L, Bassi A, Stefani A, et al. Pramipexole in comparison to L-dopa: a neuropsychological study. *J Neural Transm*. 2003;110(4):373–380.
50. Basso MR, Lowery N, Neel J, et al. Neuropsychological impairment among manic, depressed, and mixed-episode inpatients with bipolar disorder. *Neuropsychology*. 2002;16(1):84–91.
51. Judd LL, Akiskal HS, Schettler PJ, et al. The long-term natural history of the weekly symptomatic status of bipolar I disorder. *Arch Gen Psychiatry*. 2002;59(6):530–537.
52. Bora E, Yücel M, Pantelis C. Cognitive impairment in affective psychoses:

a meta-analysis. *Schizophr Bull*. 2010;36(1):112–125.
53. Martino DJ, Strejilevich SA, Scápola M, et al. Heterogeneity in cognitive functioning among patients with bipolar disorder. *J Affect Disord*. 2008;109(1–2):149–156.
54. Reichenberg A, Harvey PD, Bowie CR, et al. Neuropsychological function and dysfunction in schizophrenia and psychotic affective disorders. *Schizophr Bull*. 2009;35(5):1022–1029.
55. Mierau J, Schneider FJ, Ensinger HA, et al. Pramipexole binding and activation of cloned and expressed dopamine D_2, D_3 and D_4 receptors. *Eur J Pharmacol*. 1995;290(1):29–36.
56. Gerlach M, Double K, Arzberger T, et al. Dopamine receptor agonists in current clinical use: comparative dopamine receptor binding profiles defined in the human striatum. *J Neural Transm*. 2003;110(10):1119–1127.
57. Mirapex (pramipexole dihydrochloride) [package insert]. Ridgefield, CT: Boehringer Ingelheim; 2009.
58. Camacho-Ochoa M, Walker EL, Evans DL, et al. Rat brain binding sites for pramipexole, a clinically useful D_3-preferring dopamine agonist. *Neurosci Lett*. 1995;196(1–2):97–100.
59. Leentjens AF, Koester J, Fruh B, et al. The effect of pramipexole on mood and motivational symptoms in Parkinson's disease: a meta-analysis of placebo-controlled studies. *Clin Ther*. 2009;31(1):89–98.
60. Barone P, Poewe W, Albrecht S, et al. Pramipexole for the treatment of depressive symptoms in patients with Parkinson's disease: a randomised, double-blind, placebo-controlled trial. *Lancet Neurol*. 2010;9(6):573–580.
61. Aiken CB. Pramipexole in psychiatry: a systematic review of the literature. *J Clin Psychiatry*. 2007;68(8):1230–1236.
62. Zarate CA Jr, Payne JL, Singh J, et al. Pramipexole for bipolar II depression: a placebo-controlled proof of concept study. *Biol Psychiatry*. 2004;56(1):54–60.
63. Harvey PD, Wingo AP, Burdick KE, et al. Cognition and disability in bipolar disorder: lessons from schizophrenia research. *Bipolar Disord*. 2010;12(4):364–375.