Pramipexole for Bipolar II Depression: A Placebo-Controlled Proof of Concept Study

Carlos A. Zarate, Jr., Jennifer L. Payne, Jaskaran Singh, Jorge A. Quiroz, David A. Luckenbaugh, Kirk D. Denicoff, Dennis S. Charney, and Husseini K. Manji

Background: *The original serotonergic and noradrenergic hypotheses do not fully account for the neurobiology of depression or mechanism of action of effective antidepressants. Research implicates a potential role of the dopaminergic system in the pathophysiology of bipolar disorder. The current study was undertaken as a proof of the concept that dopamine agonists will be effective in patients with bipolar II depression.*

Methods: *In a double-blind, placebo-controlled study, 21 patients with DSM-IV bipolar II disorder, depressive phase on therapeutic levels of lithium or valproate were randomly assigned to treatment with pramipexole (*n = *10) or placebo (*n = *11) for 6 weeks. Primary efficacy was assessed by the Montgomery-Asberg Depression Rating Scale.*

Results: *All subjects except for one in each group completed the study. The analysis of variance for total Montgomery-Asberg Depression Rating Scale scores showed a significant treatment effect. A therapeutic response (>50% decrease in Montgomery-Asberg Depression Rating Scale from baseline) occurred in 60% of patients taking pramipexole and 9% taking placebo (*p = *.02). One subject on pramipexole and two on placebo developed hypomanic symptoms.*

Conclusions: *The dopamine agonist pramipexole was found to have significant antidepressant effects in patients with bipolar II depression.*

Key Words: Antidepressant, dopaminergic, bipolar depression, pramipexole

Bipolar affective disorder is a common, severe, chronic, and often life-threatening illness. Increasingly, it is being recognized that it is the depressive phase of the illness that contributes to much of the morbidity and mortality (Calabrese et al 2003; Keck et al 2001). Compared with bipolar I depression, patients with bipolar II depression have a substantially more chronic course, with significantly more major and minor depressive episodes and shorter interepisode well intervals (Judd et al 2003). In addition, bipolar II patients compared with bipolar I patients are reportedly less likely to be prescribed a somatic treatment during and between affective episodes (Judd et al 2003) and more likely to attempt suicide (Rihmer and Pestality 1999).

Very few of the available antidepressants have been examined in randomized controlled trials in acute bipolar depression (reviewed in Keck et al 2003; Muzina and Calabrese 2003; Yatham et al 2003). This, in part, may be due to the tendency of some antidepressants to induce hypomania, mania, or rapid cycling in bipolar patients (reviewed in Keck et al 2003; Muzina and Calabrese 2003; Yatham et al 2003). Only a few uncontrolled treatment studies have been conducted specifically in the depressive phase of bipolar II disorder (Amsterdam 1998; Amsterdam and Brunswick 2003; Amsterdam and Garcia-Espana 2000; Amsterdam et al 1998; Simpson and DePaulo 1991). To our knowledge, there has never been a double-blind placebo-controlled trial specifically in bipolar II depression.

From the Laboratory of Molecular Pathophysiology (CAZ, JLP, JS, JAQ, HKM) and Experimental Therapeutics and Pathophysiology Branch (CAZ, DAL, KDD, DSC), Mood and Anxiety Disorders Program, National Institute of Mental Health, National Institutes of Health, Department of Human and Health Services, Bethesda, Maryland.

Address reprint requests to Dr. Carlos A. Zarate, Jr., 9000 Rockville Pike, Building 10, Unit 3 West, Room 3S250, Bethesda, MD 20892.

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Is Enhancing Dopamine Throughput Likely to Be Beneficial in the Treatment of Bipolar Depression?

In recent years, there has been growing appreciation that the original serotonergic and noradrenergic hypotheses do not fully account for the neurobiology of depression or the mechanisms of action of effective treatments. It is somewhat surprising that the role of the dopaminergic system in the pathophysiology and treatment of bipolar disorder has not received greater study, since it represents a prime candidate on a number of theoretical grounds. The motoric changes in bipolar disorder are perhaps the most defining characteristics of the illness, ranging from near catatonic immobility to the profound hyperactivity of manic states (Goodwin and Jamison 1990; Parker et al 1993). Similarly, loss of motivation is one of the central features of depression and anhedonia/hyperhedonic states are very prominent features of bipolar depression and mania, respectively. Several studies (Asberg et al 1984; Reddy et al 1992; Roy et al 1985) but not all studies (Koslow et al 1983; Nordin 1988; Placidi et al 2001) found lower cerebrospinal fluid (CSF) homovanillic acid (HVA) in depressed subjects than in normal control subjects. Also, direct measurement of brain monoamine metabolites from the internal jugular vein of treatment-resistant depressed patients revealed low HVA levels that were highly correlated with illness severity (Lambert et al 2000). Neuroimaging studies have been conducted in patients with major depression to directly assess the in vivo availability of dopamine D_2 receptors binding with single-photon emission computed tomography (SPECT) radiotracer [^{123}I] iodobenzamide (IBZM). The results of these studies are mixed. Two of the four studies reported higher [^{123}I] IBZM specific binding in the striatum of depressed subjects compared with control subjects (D'Haenen and Bossuyt 1994; Shah et al 1997), whereas two studies reported no changes (Ebert et al 1996; Klimke et al 1999).

Several lines of research also suggest that the dopaminergic system may be an indirect long-term target for the actions of antidepressants whose primary biochemical targets are the serotonergic and noradrenergic systems (Arnt et al 1984; D'Aquila et al 2000; Maj and Rogoz 1999a; Willner 1997). Particularly, pramipexole has been demonstrated to have antidepressant properties in animal models of depression (Maj and Rogoz 1999b).

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In toto, the data reviewed above suggest that more directly enhancing dopamine throughput in critical circuits regulating motivation, motoric function, and hedonic drive may be beneficial for the treatment of bipolar depression; however, although dopamine agents and stimulants are used for treatment-resistant depression, few of them have been subjected to systematic study (Nierenberg et al 1998). Pramipexole, a synthetic aminothiazole derivative, is a dopamine D_2/D_3 receptor agonist that currently is approved by the Food and Drug Administration for the treatment of Parkinson's disease (Bennett and Piercey 1999). Interestingly, considerable data suggest that pramipexole may have D_3 preferring effects (Piercey 1998; Piercey et al 1996); these observations are particularly noteworthy, since the D_3 receptor has an anatomic distribution that suggests it may play an important role in neuronal circuits that have been implicated in depressive states. Thus, recent primate studies have shown that pramipexole robustly decreases regional cerebral blood flow (rCBF) in the bilateral orbitofrontal cortex, thalamus, operculum, posterior and anterior (subgenual) cingulate cortex, and insula (Black et al 2002). Interestingly, these are some of the very same brain regions implicated in the pathophysiology of mood disorders (Drevets 2001; Mayberg et al 2000).

In addition to its effects at the D_2/D_3 receptor, it is now clear that pramipexole also exerts robust neurotrophic effects, many of which may be mediated via upregulation of the antiapoptotic protein Bcl-2 (Carvey et al 2001; Le and Jankovic 2001). These findings are noteworthy, since a growing body of data suggests that severe mood disorders may be associated with impairments of neuronal plasticity and cellular resilience (Manji et al 2003).

Overall, pramipexole appears to represent an intriguing agent to systematically study in bipolar depression, since it has two characteristics—enhancement of dopaminergic throughput and neurotrophic effects—which may be very relevant in the treatment of this disorder. Indeed, a series of uncontrolled studies in depression suggest that pramipexole has antidepressant properties (DeBattista et al 2000; Goldberg et al 1999; Lattanzi et al 2002; Ostow 2002; Perugi et al 2001; Sporn et al 2000), and one large controlled trial in unipolar major depression found pramipexole to be more effective than placebo and comparable to fluoxetine in the treatment of depressive symptoms (Corrigan et al 2000).

We have therefore undertaken the current study as a proof of the concept that the use of a selective dopamine agonist with neurotrophic properties will be more effective than placebo in patients with bipolar II depression. In view of the concerns that dopamine agonists may trigger manic episodes, we chose to add pramipexole to mood stabilizers (restricting ourselves to either lithium or valproate). It is now well established that lithium and valproate both exert neuroprotective effects, and that these effects may be mediated in large part by upregulation of Bcl-2 (Chen et al 1999; Manji et al 2000a, 2000b). We therefore first undertook a series of preclinical studies. We found that the addition of pramipexole to either lithium or valproate robustly further upregulated Bcl-2 levels (HK Manji, unpublished data, 2003).

Methods and Materials

Study Design

This was a 6-week single center, double-blind, randomized, placebo-controlled study that was conducted to assess the efficacy and safety of pramipexole in combination with lithium or divalproex sodium therapy in the treatment of bipolar II depression. Inpatients or outpatients with bipolar II disorder who were currently in a major depressive episode were enrolled. The study consisted of two study periods: study period I was open treatment with a mood stabilizer (either lithium or divalproex sodium) for a minimum period of 4 weeks, and study period II was double-blind treatment with either pramipexole or placebo in combination with a mood stabilizer. A 2-week, single-blind, placebo lead-in period was used to screen potential patients for inclusion in the study.

Diagnostic procedures included conducting the *Structured Clinical Interview for the Diagnostic Manual of Mental Disorders, Fourth Edition, Patient Version* (SCID-P) (First et al 2001), physical examination, psychiatric and medical history, routine laboratory analyses, and pregnancy test. Additional tests included electrocardiogram (ECG) and vital signs assessment and administration of the Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg 1979). Adequacy of antidepressant trials were determined with the Antidepressant Treatment History Form (ATHF) (Sackeim 2001).

Patients randomly assigned to pramipexole received .125 mg three times a day for the first 5 to 7 days. The dose was increased every 5 to 7 days by .125 three times a day to achieve a target range of 1.0 mg to 3.0 mg per day. The maximum dose allowable was 4.5 mg per day. Dose escalations continued until: 1) achievement of the primary endpoint (>50% reduction from baseline MADRS scores; 2) intolerable side effects; or 3) completion of the 6-week study. Treatment compliance was monitored by capsule counts.

The study was approved by the National Institute of Mental Health (NIMH) Institutional Review Board. All patients provided written informed consent before entry into the study.

Patient Selection

Subjects were recruited through advertisements placed in the local newspapers of the Washington, DC Metropolitan Area; from Howard University Hospital in Washington, DC; the Internet; and local and national referrals from physicians. All patients enrolled in the study fulfilled SCID-P criteria for bipolar II depression and scored ≥20 of the MADRS at both the screening and baseline evaluations. Final diagnosis of bipolar II depression and other axis I disorders (permitted in the study) were ascertained by general consensus of three clinicians by utilizing all available information (SCID-P, clinical interviews, and in most cases interviews of someone who knew the patient well). The total MADRS score could not have decreased by more than 20% between the screening and baseline evaluations. Eligible patients were required to have experienced at least two previous hypomanic and major depressive episodes and to have previously failed to respond to an adequate trial of at least one antidepressant based on the information collected with the ATHF. Following the psychiatric and medical screening examination, eligible patients were either continued on their mood stabilizer (lithium [$N = 2$] or divalproex sodium [$N = 3$]) or started on or switched to one of these for the purpose of the study ($n = 16$). If a patient was taking both lithium and divalproex sodium or had never been treated with a mood stabilizer at the time of the screening, preference was giving to using lithium during the study. Serum lithium (.6–1.2 mEq/L) or valproic acid (50–125 μg/mL) levels the 2 consecutive weeks before randomization was required. Serum lithium and valproic acid levels were measured on a weekly basis during the study and adjustments were not allowed unless serum levels deviated beyond the .6–1.2 mEq/L for lithium or 50–125 μg/mL for valproic acid, in which case doses were adjusted to maintain levels within the permitted range. Patients were at least 18 years old.

Patients who met DSM-IV criteria for bipolar disorder but who were not currently depressed were excluded, as were patients who had been diagnosed with DSM-IV substance abuse in the past 3 months (except nicotine or caffeine) or substance dependence in the past 12 months. A current diagnosis of comorbid anxiety disorder was permitted, as long as it was believed not to be clinically significant. Patients who had been diagnosed with another axis I disorder diagnosis in the past year were excluded. Patients who were rapid cyclers (four or more hypomanic or depressive episodes within 12 months of the baseline evaluation) were excluded. Additional exclusion criteria were any serious unstable medical disorder or condition, concomitant treatment with other psychotropic medication in the 2 weeks before randomization (5 weeks for fluoxetine), clozapine or electroconvulsive therapy in the 3 months before randomization, or judged to be a serious suicidal risk. Patients were not allowed to receive structured psychotherapy during the trial.

Assessment

During the 6-week study period, patients were assessed for both efficacy and adverse events at baseline and at weeks 1 through 6. Laboratory evaluations were performed on a weekly basis and ECG was performed at the beginning and the end of the study.

The primary efficacy measure was the total score on the MADRS and the secondary measure was the total score on the 24-item Hamilton Depression Rating Scale (HDRS) (Hamilton 1967).

Safety evaluations were based on routine adverse event monitoring, vital sign assessments, and a hypomania/mania assessment based on ≥12 on the Young Mania Rating Scale (YMRS) (Young et al 1978) or fulfilling DSM-IV criteria for a manic episode.

Raters, who trained together to establish reliability, performed patient ratings. Mood symptoms were then rated on a weekly basis using the MADRS, HDRS, and YMRS. High interrater reliability for MADRS (intraclass correlation coefficient [ICC] = .88), the HDRS (ICC = .81), and the YMRS (ICC = .91) were obtained.

Data Analysis

Data are presented from the intent-to-treat population. Repeated measures analysis of variance (ANOVA) was used to examine response with treatment as a fixed factor and time as a within-subjects factor. Mauchly's test was used to examine the sphericity assumption and Greenhouse-Geisser adjusted p values were used for within-subjects effects to deal with sphericity concerns. Significant effects were examined using Bonferroni-adjusted simple effects tests. Cohen's d effect size is shown with 95% confidence interval (CI) for treatment effects. Missing data were handled using the last observation carried forward rule. The mean and standard deviations are reported on each scale. Analyses of covariance (ANCOVAs) were run to study the effect of baseline mood and demographic factors that appeared to differ between treatment groups.

Given the sample size, additional tests were run to ensure the reliability of the findings. Thus, t tests were used to compare the proportion of change in the MADRS at the end of the trial compared with baseline for the treatment groups. Additionally, a Fisher Exact Test was used to compare the proportion of responders for each treatment. Response was defined as a 50% reduction in MADRS compared with baseline at the last week of the trial. Partial response was defined as a 25% to 49% reduction in MADRS compared with baseline at the last week of the trial. Similar reductions at intervening weeks were not counted as responses. Remission was defined as a MADRS total score of 12 or less at the last week of the trial (Tohen et al 2003).

Results

Patient Characteristics and Completion

Twenty-one patients met inclusion criteria and were randomized to treatment. Another eight subjects were not randomized because of failure to maintain mood stabilizers within therapeutic range or lack of compliance with research procedures ($n = 3$), clinical worsening of depression or of the comorbid anxiety disorder after discontinuing concomitant medications ($n = 3$), and more than a 20% improvement in MADRS scores before randomization ($n = 2$). A description of the patients randomized is included in Table 1. The mean duration of open treatment was approximately 6 weeks before randomization and was not significantly different between the groups. Completion rates (i.e., ratings obtained through week 6) were high for both groups (pramipexole: 9 of 10 [90%]; placebo: 10 of 11 [90.9%]) (Fisher Exact Test, $p = 1.00$). Noncompletion of the patient in the pramipexole group was attributed to lack of response at week 5, and noncompletion of the patient in the placebo group was attributed to worsening at week 3.

Treatment groups appeared to be similar on most demographic variables. Pramipexole patients were older with longer lifetime illness. Twelve patients were outpatients and nine patients were inpatients. The average length of stay for inpatients (includes time in study and time receiving standard treatment poststudy) was 126.9 ± 36.9 days (range: 82–186). Patients reached an average dose of 1.7 ± .90 mg/d (range: .375–4.5 mg/d) by the end of the trial.

The ANOVA for total MADRS showed a significant treatment effect [$F = 5.43$, $df = 1,19$, $p = .03$, d = 1.07 (95% CI: .104–2.27)] with a significant time effect ($F = 6.52$, $df = 3.4,64.4$, $p < .001$) but no significant interaction between treatment and time ($F = 1.96$, $df = 3.4,64.4$, $p = .12$). Pramipexole decreased depression symptoms compared with placebo. Follow-up tests seemed to show significant differences between groups after 3 ($t = 2.35$, $df = 19$, $p = .03$) and 6 ($t = 2.95$, $df = 19$, $p = .01$) weeks of treatment (Figure 1). The lack of differences at the fourth and fifth weeks of treatment seem to be from two patients in the active group who lost response after increases in dosage, one of which had moderate nausea at higher doses. This patient responded again after decreasing the dose of pramipexole.

Given the lack of group by time interaction, baseline mood was covaried out to understand whether group differences existed beyond the baseline. This did not remove the effect for treatment, suggesting that pramipexole did change mood during the trial (Treatment: $F = 4.61$, $df = 1,18$, $p = .046$; Time: $F = .41$, $df = 3.3,59.1$, $p = .76$; Interaction: $F = .68$, $df = 3.3,59.1$, $p = .58$). Further, covarying for age and length of lifetime illness did not have a significant influence on the outcome of the ANOVA (Age—Treatment: $F = 7.27$, $df = 1,18$, $p = .02$; Time: $F = 1.99$, $df = 3.5,63.4$, $p = .11$; Interaction: $F = 2.49$, $df = 3.5,63.4$, $p = .06$; Length of Illness—Treatment: $F = 3.73$, $df = 1,17$, $p = .07$; Time: $F = 1.95$, $df = 3.4,58.2$, $p = .12$; Interaction: $F = 1.99$, $df = 3.4,58.2$, $p = .12$). So, baseline and demographic covariates did not alter the size of the treatment effect.

Similar results were found with the HDRS [Treatment: $F = 6.61$, $df = 1,19$, $p = .02$, d = 1.18 (95% CI: .20–2.42); Time: $F = 4.5$, $df = 3.1,59.2$, $p = .01$; Interaction: $F = 1.14$, $df = 3.1,59.2$, $p = .33$]. Pramipexole decreased depression symptoms compared with placebo. Follow-up tests showed significant differences

Table 1. Baseline Demographic and Clinical Characteristics for 21 Patients with Bipolar II Depression Randomly Assigned to Treatment with Pramipexole or Placebo

	Pramipexole (n = 10)	Placebo (n = 11)	p
Age (years)	51.2 ± 3.3	33.3 ± 9.5	.000
Gender (Male:Female)	3:7	2:9	.635
Ethnicity (Caucasian)	6 (63%)	7 (64%)	1.000
Outpatient Status	6 (60%)	6 (55%)	.575
Length of Illness (years)	38.0 (4.4)	16.5 (6.3)	.000
Length of Current Depression (months)	6.6 ± 7.1	5.1 ± 3.1	.561
Mood Stabilizer Started for the Study			.670
Lithium	5 (50%)	7 (64%)	
Valproate	5 (50%)	4 (36%)	
Mean Length of Mood Stabilizer Treatment Prior to Randomization (days)			
Lithium	40.8 ± 3.97	40.0 ± 6.2	.806
Valproate	42.0 ± 3.7	42.8 ± 3.9	.775
Blood Serum Levels of Medications During Study			
Lithium mEq/L	.80 ± .25	.77 ± .28	.727
Valproic Acid μg/mL	72.8 ± 4.7	74.0 ± 6.5	.759
Current Comorbid Psychiatric Diagnosis	4 (40%)	6 (54%)	.670
Treatment Failures (current episode)[a]			
Lithium	6 (60%)	9 (82%)	.361
Valproate	5 (50%)	6 (55%)	1.000
SSRIs	5 (50%)	6 (55%)	1.000
Atypical antipsychotic drugs	2 (20%)	3 (27%)	1.000
Carbamazepine	2 (20%)	1 (9%)	.586
Gabapentin	1 (10%)	1 (9%)	1.000
Stimulant	1 (10%)	1 (9%)	1.000
Bupropion	2 (20%)	1 (9%)	.586
Tricyclic antidepressants	1 (10%)	1 (9%)	1.000
Thyroid augmentation	1 (10%)	3 (27%)	.586
Venlafaxine	1 (10%)	3 (27%)	.586
Lamotrigine	0	2 (18%)	.476
Mirtazapine	0	2 (18%)	.476

SSRI, selective serotonin reuptake inhibitor.
[a]Includes open trial of lithium or valproate required to enter the study.

between groups after 3 (t = 3.50, df = 19, p = .002) and 6 (t = 2.44, df = 19, p = .02) weeks of treatment.

Looking at the proportion of change from baseline to trial end on the MADRS, patients on pramipexole had greater improvement compared with those on placebo [t = 3.05, df = 15, p = .01, d = 1.40 (95% CI: .18–2.39)]. Further, more patients on pramipexole had a full response than those on placebo (Fisher Exact Test: p = .02) (Table 2).

Throughout the course of the trial, only one pramipexole patient reached a YMRS of 12 or more for 1 week. This person was a responder. On placebo, two patients reached these criteria, one for 1 week and the other for 2 nonadjacent weeks. Both of

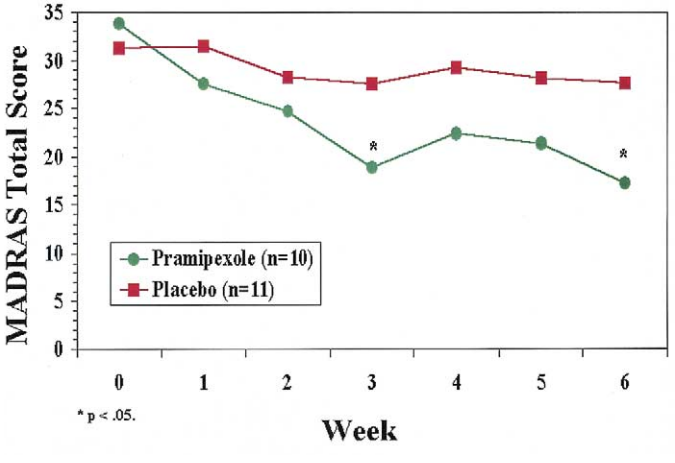

Figure 1. Mean change in MADRS total scores from baseline in patients with bipolar II depression who were treated with pramipexole or placebo for 6 weeks. MADRS, Montgomery-Asberg Depression Rating Scale.

Table 2. Outcomes for Patients with Bipolar II Depression Treated with Pramipexole or Placebo for 6 Weeks

	Pramipexole (n = 10)	Placebo (n = 11)	p
MADRS			
Baseline	33.8 ± 5.4	31.9 ± 3.4	.340
End	17.2 ± 8.4	27.6 ± 7.7	.010
% Change	47.1 ± 27.2	12.4 ± 25.0	.007
HDRS			
Baseline	26.9 ± 7.5	27.5 ± 5.2	.840
End	14.1 ± 7.1	22.6 ± 8.6	.020
Full Response	6 (60%)	1 (9%)	.020
Partial Response	8 (80%)	2 (18%)	.010
Remission	4 (40%)	1 (9%)	.149

MADRS, Montgomery-Asberg Depression Rating Scale; HDRS, 24-Item Hamilton Depression Rating Scale.

Table 3. Adverse Events of Patients with Bipolar II Depression Treated with Pramipexole or Placebo for 6 Weeks

	Pramipexole ($n = 10$)	Placebo ($n = 11$)
Insomnia	6 (60%)	5 (46%)
Nausea/Vomiting	6 (60%)	7 (64%)
Tremor	5 (50%)	2 (18%)
Agitation/Anxiety	4 (40%)	7 (64%)
Somnolence	4 (40%)	3 (27%)
Gastrointestinal Complaints	2 (20%)	2 (18%)
Weight Loss	2 (20%)	3 (27%)
Headache	1 (10%)	6 (52%)
Lassitude	1 (10%)	5 (46%)
Hypomanic/Manic Exacerbation	1 (10%)	2 (18%)

these were nonresponders. None of the ≥12 YMRS scores occurred on the last week of the trial.

Most of the side effects evaluated appeared to be similar for the treatment groups. There were no statistically significant differences in the adverse events between the groups, although tremor appeared to be more common in the active treatment group (Table 3). One patient required a dose reduction because of nausea of moderate severity. No serious adverse events were noted, and no subject discontinued the study medication because of an adverse event. No significant laboratory changes were noted. There was no relationship between dose of pramipexole and adverse events or changes in laboratory tests.

Discussion

In this double-blind, placebo-controlled proof of concept trial, the neurotrophic dopamine D_2/D_3 agonist pramipexole was associated with significant antidepressant effects in individuals with acute bipolar II depression. The efficacy was noted across several different efficacy measures obtained. Our findings of the antidepressant efficacy of pramipexole in bipolar depression are similar to those presented by Goldberg et al (2004), although in their controlled add-on study, most of the patients randomized to pramipexole had a bipolar I disorder (over 70%) diagnosis, while patients in our study exclusively had a diagnosis of bipolar II disorder.

Because there have been reports that the use of dopamine agonists may confer a greater risk of switch in bipolar I patients, we chose to study bipolar II depression, since, if a patient were to switch, it would be more likely be into hypomania, a type of episode that is more easily manageable than mania.

To the best of our knowledge, this is the first double-blind, placebo-controlled trial conducted specifically in acute bipolar II depression. Contrary to previous reports that dopamine agonists have been associated with switches into hypomania/mania in bipolar patients (Peet and Peters 1995; Silverstone 1985), we did not find this to be a problem in our study. Only one patient in the treatment group developed a rating of hypomanic exacerbation (defined as a YMRS ≥12) for 1 week compared with two patients in the placebo group, thus suggesting that this event was more likely a result of the course of illness than a drug effect. None of these patients met full DSM-IV criteria of mania. Overall, pramipexole was well tolerated.

Pramipexole is structurally distinct from the ergot-derived drugs (e.g., bromocriptine and pergolide) and pharmacologically unique in that it is a full agonist and has receptor selectivity for the D_2 subfamily of receptors (D_2, D_3, and D_4 receptor subtypes). Pramipexole has preferential affinity for the D_3 receptor subtype, which according to preclinical studies, could contribute additional efficacy for treatment of motoric and psychiatric syndromes (e.g., depression) in Parkinson's disease (Piercey 1998). These receptor-binding properties may confer advantages in terms of both efficacy and safety (receptor selectivity may reduce the risk of unwanted side effects, such as manic exacerbation), compared with other indirectly acting agonists (Bouckoms and Mangini 1993; Piercey 1998).

In addition to its dopamine D_3 effects, pramipexole was selected due to its robust neurotrophic effects (Piercey 1998). As discussed, there is a considerable body of evidence both conceptually and experimentally suggesting that impairments in neuroplasticity and cellular resilience may play an important role in the pathophysiology of recurrent mood disorders. It has been argued that for many refractory depression patients, optimal treatment may only be attained by providing both trophic and neurochemical support; the trophic support would be envisioned as enhancing and maintaining normal synaptic connectivity, thereby allowing the neurochemical signal to reinstate the optimal functioning of critical circuits necessary for normal affective functioning (Manji and Duman 2001; Manji et al 2003).

These preliminary results need to be interpreted with caution. First, the group size was small. Second, our results may not be generalized to patients with certain characteristics (e.g., rapid cycling course, presence of substance use disorders, or patients with bipolar I disorder). Third, these results may not apply beyond the acute treatment phase of bipolar depression. It is possible that if a dopamine agonist is used in patients with bipolar I disorder over long periods of time that increased rates of switching into mania may be noted. Also, long-term treatment with dopamine agonists have been associated with increased rates of psychosis, insomnia, and movement disorders in patients with Parkinson's disease (Hubble 2002). Although we did not see any of these complications in our short-term study, the efficacy and safety of using a dopamine agonist on a long-term basis in patients with bipolar disorder remains to be determined. Furthermore, if pramipexole were discontinued in an effort to minimize these potential complications, it is unknown how long patients would continue to remain well. Finally, it could be argued that our findings were due to the imbalanced randomization in age in which patients randomized to pramipexole were older than patients randomized to placebo; however, covarying for age in our analysis did not alter the size of the treatment effect.

Strengths of this study are that it is a randomized, placebo-controlled trial; the requirement of a nonresponse to lithium or divalproex sodium therapy before randomization; the use of a 2-week single-blind placebo lead-in period and a 2-week washout of psychotropic medications; and the high completion rates. Finally, patients participating in this study were considered treatment-resistant, as all were required to have failed a trial of a mood stabilizer before being randomized and most had failed multiple adequate trials of antidepressants and other treatments during the current episode; however, it is important to point out that while there is general agreement on what treatment refractoriness is in major depression, in bipolar depression no general consensus has been reached (Yatham et al 2003).

In conclusion, the neurotrophic D_2/D_3 dopamine agonist pramipexole was effective in acute bipolar II depression and was associated with low switch rates into hypomania/mania. These results suggest that agents that provide trophic support and enhance throughput through the circuits implicated in mediating motivation, hedonic drive, and motoric activity may be ideal

treatments for bipolar depression. Larger controlled studies are clearly needed to replicate the present findings; such studies should be of a fixed dose design to identify the effective dose range of pramipexole in bipolar depression.

DSC and HKM contributed equally to this work.

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