

Preliminary Randomized, Double-Blind, Placebo-Controlled Trial of Pramipexole Added to Mood Stabilizers for Treatment-Resistant Bipolar Depression

Joseph F. Goldberg, M.D.
Katherine E. Burdick, Ph.D.
Carrie J. Endick, C.S.W.

Objective: Previous studies suggest that the dopamine agonist pramipexole may possess antidepressant properties. The authors conducted a preliminary randomized, placebo-controlled trial to determine the safety and antidepressant efficacy of pramipexole in treatment-resistant bipolar depression.

Method: Twenty-two depressed outpatients with DSM-IV nonpsychotic bipolar disorder were randomly assigned to receive placebo or flexibly dosed pramipexole (mean maximum dose = 1.7 mg/day, SD = 1.3) added to existing mood stabilizers for 6 weeks. The primary outcome measure was response, defined as improvement in Hamilton Depression Rating Scale score of 50%

or more over the baseline score; secondary analyses involved changes in Clinical Global Impression (CGI) severity scores.

Results: More patients given pramipexole (10 [83%] of 12) than patients given placebo (six [60%] of 10) completed the study. Eight (67%) of 12 patients taking pramipexole and two (20%) of 10 taking placebo had an improvement of at least 50% in their Hamilton depression scale scores. The mean percentage of improvement from baseline Hamilton depression scale scores was greater for patients taking pramipexole (48%) than for those taking placebo (21%). Mean improvements in CGI severity were also greater with pramipexole than placebo. No patients discontinued the study because of adverse events except for one patient who became hypomanic while taking pramipexole.

Conclusions: Pramipexole was a safe and effective antidepressant among patients with bipolar depression. Larger randomized, controlled trials are needed to affirm these initial observations.

(*Am J Psychiatry* 2004; 161:564–566)

Depression remains a persistent source of morbidity and mortality for patients with bipolar disorder. Controlled trials suggest that standard antidepressants may offer little therapeutic advantage beyond the effects of therapeutically dosed mood stabilizers (1, 2), and all appear to heighten risk for inducing mania or cycle acceleration (3).

Dopamine agonists have gained increasing attention for their possible antidepressant effects. Preclinical evidence of hypodopaminergic tone in depression derives from reduced homovanillic acid levels and increased mesolimbic function after tricyclic antidepressant therapy (4). Monoamine oxidase inhibitors may be advantageous for anergic depressions, partly because of their prodopaminergic effects (5). Pramipexole is a novel D2/D3 agonist previously shown to exert antidepressant efficacy comparable to that of fluoxetine for major depression (6). Case reports (7) and open trials (8, 9) suggest the utility of pramipexole in bipolar and treatment-resistant depression. The present pilot study was undertaken to provide a clearer estimate of the antidepressant efficacy and safety of pramipexole compared with placebo added to mood stabilizers in outpatients with treatment-resistant bipolar depression.

Method

Subjects for the present study were 22 outpatients with DSM-IV bipolar disorder experiencing major depression defined by DSM-IV criteria. The patients, recruited by advertisement, word of mouth, and clinic referral, were seen in the Bipolar Disorders Research Clinic of the Payne Whitney Clinic, New York Presbyterian

Hospital. All had not responded to at least two adequate trials of standard antidepressants with concomitant mood stabilizers during the current episode. We made research diagnoses of bipolar disorder based on the Structured Clinical Interview for DSM-IV. Depressive and manic symptoms were rated by using the 17-item Hamilton Depression Rating Scale (10) and the Young Mania Rating Scale (11) after achieving adequate interrater reliability. Clinical status was secondarily assessed by using the Clinical Global Impression (CGI) severity scale (12). Induction of mania or hypomania was defined as a Young Mania Rating Scale score greater than 15 after study initiation.

At baseline, all patients were nonpsychotic and had Young Mania Rating Scale scores less than 12 and Hamilton depression scale scores greater than 18. None took antipsychotic medications during the study, and all had been taking lithium, divalproex, carbamazepine, lamotrigine, and/or topiramate at stable doses for the month before random assignment to placebo or pramipexole; their doses of these drugs were held constant throughout the study. Concomitant lorazepam (up to 2 mg/day) or clonazepam (up to 1 mg/day) were permitted as needed for insomnia or agitation.

Patients were randomly assigned to placebo or active drug by an unblinded research assistant. Ten patients were assigned to placebo and 12 to active drug. Pramipexole administration was started at 0.125 mg twice a day and increased by 0.25 mg/day every 3–5 days to a target range of 1.0–2.5 mg/day. Higher doses (up to 5.0 mg/day) were permitted as needed. Dose escalations continued until 1) achievement of primary endpoint (defined as a reduction of 50% or more from baseline in Hamilton depression scale score for at least 2 successive weeks), 2) drug intolerance, or 3) 6-week protocol completion.

All patients provided written informed consent to participate in the study protocol, which was approved by the Institutional Review Board of the Weill Medical College of Cornell University–New York Presbyterian Hospital.

Efficacy and safety analyses were conducted on all patients who completed at least 1 week of treatment. Analyses were based on last observations carried forward. Proportions of responders and nonresponders in each condition were compared by chi-square or Fisher's exact tests. Changes from baseline are reported as differences in means and standard deviations and analyzed with Mann-Whitney tests. All statistical tests were two-tailed with an alpha level of 0.05.

Results

Characteristics of patients taking pramipexole or placebo are summarized in Table 1. The mean peak dose of pramipexole was 1.7 mg/day (SD=1.3). Six-week study completion rates were somewhat higher for patients taking pramipexole (10 [83%] of 12) than for patients taking placebo (six [60%] of 10) ($\chi^2=1.50$, $df=1$, $p=0.22$). Mean concomitant medications, dosed alone or in combinations, included lithium (N=6): mean=1137.5 mg/day (SD=381.6) (serum Li⁺ mean=0.70 meq/liter, SD=0.21); divalproex (N=9): mean=916.7 mg/day (SD=129.1) (serum valproate mean=80.7 μ g/ml, SD=15.4); carbamazepine (N=2): mean=400.0 mg/day (SD=282.8); lamotrigine (N=6): mean=283.3 mg/day (SD=144.3); and gabapentin (N=3): mean=450 mg/day (SD=212.1).

A reduction of 50% or more from baseline Hamilton depression scale was evident among eight (67%) of 12 patients taking pramipexole and two (20%) of 10 taking placebo ($p=0.04$, Fisher's exact test). The mean change from baseline in Hamilton depression scale scores was greater for patients taking pramipexole (mean=48.0%, SD=33.1%) than for those taking placebo (mean=21.4%, SD=36.3%) ($p=0.05$, Mann-Whitney test). Median time to response with pramipexole was 4 weeks. Among the patients who completed the study, response rates tended to be higher among those taking pramipexole (seven of 10) than those taking placebo (one of six) ($p=0.06$, Fisher's exact test). Remission, defined as a Hamilton depression scale score of 7 or less, occurred in two patients taking pramipexole and one patient taking placebo.

Mean CGI severity scores were lower at the end of the study for patients who took pramipexole (mean=2.7, SD=1.4) than for those who took placebo (mean=4.4, SD=1.3) ($p=0.02$, Mann-Whitney test). Improvement in CGI severity scores from baseline to study end was also significantly greater for patients who took pramipexole (mean=-2.4 points, SD=1.8) than placebo (mean=-0.30 points, SD=1.3) ($p=0.01$, Mann-Whitney test).

Lack of efficacy led to premature study discontinuation more often among the patients taking placebo (three of four patients) than among those taking pramipexole (one of two). No patients dropped out prematurely because of adverse events except for one patient taking pramipexole who developed mania with psychosis at week 6, despite concomitant divalproex (1000 mg/day, serum valproate=86 μ g/ml upon termination). No patients taking placebo became manic.

TABLE 1. Characteristics of 22 Depressed Patients With Bipolar Disorder Randomly Assigned to Treatment With Pramipexole or Placebo

Characteristic	Pramipexole (N=12) ^a		Placebo (N=10)		p
	N	%	N	%	
Female sex	8	67	3	30	0.20 ^b
White race	11	92	7	70	0.29 ^b
Bipolar I diagnosis	9	75	6	60	0.65 ^b
	Mean	SD	Mean	SD	
Age (years)	40.9	8.2	43.3	6.2	0.54 ^c
Baseline Hamilton depression scale score	20.2	5.9	19.3	4.7	0.97 ^c
Baseline Young Mania Rating Scale score	5.2	2.5	3.9	2.6	0.25 ^c
Baseline CGI severity score	5.1	0.9	4.7	0.7	0.31 ^c

^a Includes one patient who developed hypomania during treatment.

^b Fisher's exact test.

^c Mann-Whitney test.

Mean Young Mania Rating Scale scores at the end of the study did not differ significantly between the patients taking pramipexole (mean=4.4, SD=4.6) and those taking placebo (mean=2.0, SD=2.2) ($p=0.12$, Mann-Whitney test). Nausea tended to occur more often with pramipexole than placebo (seven [58%] of 12 versus two [20%] of 10, respectively) ($p=0.10$, Fisher's exact test). Other adverse events common with pramipexole included sedation (N=3 [25%]) and headache (N=3), but proportions did not differ significantly from placebo.

Discussion

This pilot study preliminarily demonstrates antidepressant efficacy for the dopamine agonist pramipexole in treatment-resistant bipolar depression. Pramipexole was safe and effective when combined with lithium or anti-convulsants, consistent with the results of case reports and open trials (7-9).

Although few patients achieved full remission within 6 weeks, longer treatment durations might be necessary for optimal benefits. The vast majority of patients who openly took pramipexole after study completion showed marked responses that were sustained at least through 12-week follow-up. Our impression was that faster dose escalations (e.g., 0.25 mg every 2-3 days) might accelerate time to response unless limited by gastrointestinal or other adverse effects. Nausea, while frequent and usually persistent until protocol cessation, was generally mild and manageable by coadministration with food or over-the-counter remedies.

Limitations of the current study include the small number of subjects, inclusion of both bipolar I and bipolar II patients, random assignment of more women to pramipexole than to placebo, and continuation of varied pre-study medications. It is possible that pharmacodynamic synergies occurred by combining pramipexole with different agents, although all patients had been nonresponsive

to previous treatments. In addition, heterogeneity of the group of patients studied might have affected outcome through some unidentified unmatched factor. The lower completion rate with placebo underscores patients' symptom severity, although greater efficacy and adverse effects with pramipexole could also have inadvertently compromised the double-blind.

These preliminary findings suggest high tolerability and safety with pramipexole in bipolar depression. Larger-scale controlled trials are needed to affirm these initial observations.

Presented in part at the 40th Annual Meeting of the American College of Neuropsychopharmacology, Waikoloa, Hawaii, Dec. 9–13, 2001, and the 155th Annual Meeting of the American Psychiatric Association, Philadelphia, May 18–23, 2002. Received April 9, 2003; revision received July 15, 2003; accepted July 17, 2003. From the Department of Psychiatry, Weill Medical College of Cornell University, New York; and the Bipolar Disorders Research Clinic, Payne Whitney Clinic, New York Presbyterian Hospital, New York. Address correspondence to Joseph F. Goldberg, M.D., The Zucker Hillside Hospital, 75-59 263rd St., Glen Oaks, NY 11004; jgoldber1@lij.edu (e-mail).

Supported by NIMH K23 Career Development Award MH-01936, research grants from the Theodore and Vada Stanley Foundation and the Nancy Pritzker Foundation, a National Alliance for Research on Schizophrenia and Depression Young Investigator Award, and resources from a fund established in the New York Community Trust by DeWitt Wallace (Dr. Goldberg).

Study drug and funds to compound matching placebo were provided by Pharmacia.

The authors thank Joseph R. Calabrese, M.D., for helpful comments.

References

1. Young LT, Joffe RT, Robb JC, MacQueen GM, Marriott M, Patelis-Siotis I: Double-blind comparison of addition of a second mood stabilizer versus an antidepressant to an initial mood stabilizer for treatment of patients with bipolar depression. *Am J Psychiatry* 2000; 157:124–126
2. Nemeroff CB, Evans DL, Gyulai L, Sachs GS, Bowden CL, Gergel IP, Oakes R, Pitts CD: Double-blind, placebo-controlled comparison of imipramine and paroxetine in the treatment of bipolar depression. *Am J Psychiatry* 2001; 158:906–912
3. Post RM, Altshuler LL, Frye MA, Suppes T, Rush AJ, Keck PE Jr, McElroy SL, Denicoff KD, Leverich GS, Kupka R, Nolen WA: Rate of switch in bipolar patients prospectively treated with second-generation antidepressants as augmentation to mood stabilizers. *Bipolar Disord* 2001; 3:259–265
4. Pallis E, Thermos K, Spyraiki C: Chronic desipramine treatment selectively potentiates somatostatin-induced dopamine release in the nucleus accumbens. *Eur J Neurosci* 2001; 14:763–767
5. Himmelhoch JM, Thase ME, Mallinger AG, Houck P: Tranylcypromine versus imipramine in anergic bipolar depression. *Am J Psychiatry* 1991; 148:910–916
6. Corrigan MH, Denahan AQ, Wright CE, Ragual RJ, Evans DL: Comparison of pramipexole, fluoxetine, and placebo in patients with major depression. *Depress Anxiety* 2000; 11:58–65
7. Goldberg JF, Frye MA, Dunn RT: Pramipexole in refractory bipolar depression (letter). *Am J Psychiatry* 1999; 156:798
8. Sporn J, Ghaemi SN, Sambur MR, Rankin MA, Recht J, Sachs GS, Rosenbaum JF, Fava M: Pramipexole augmentation in the treatment of unipolar and bipolar depression: a retrospective chart review. *Ann Clin Psychiatry* 2000; 12:137–140
9. Lattanzi L, Dell'Osso L, Cassano P, Pini S, Rucci P, Houck PR, Gemignani A, Battistini G, Bassi A, Abelli M, Cassano GB: Pramipexole in treatment-resistant depression: a 16-week naturalistic study. *Bipolar Disord* 2002; 4:307–314
10. Hamilton M: A rating scale for depression. *J Neurol Neurosurg Psychiatry* 1960; 23:56–62
11. Young RC, Biggs JT, Ziegler VE, Meyer DA: A rating scale for mania: reliability, validity and sensitivity. *Br J Psychiatry* 1978; 133:429–435
12. Guy W (ed): ECDEU Assessment Manual for Psychopharmacology: Publication ADM 76-338. Washington, DC, US Department of Health, Education, and Welfare, 1976, pp 218–222