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COMPARISON OF PRAMIPEXOLE, FLUOXETINE, AND PLACEBO IN PATIENTS WITH MAJOR DEPRESSION

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Pramipexole, a dopamine D_2 receptor agonist, was tested in 174 patients with major depression, with or without melancholia and without psychotic features. Three daily dose levels (0.375 mg, 1.0 mg, and 5.0 mg) were compared to fluoxetine (Prozac) at 20 mg and placebo in a randomized, double-blind, parallel-group study. After a 1 week placebo run-in period, patients were treated for 8 weeks, had a post-study follow-up (week 9), and were evaluated primarily with the Hamilton Psychiatric Rating Scale for Depression (HAM-D), the Montgomery-Asberg Depression Rating Scale (MADRS), and the Clinician's Global Impressions-Severity of Illness scale (CGI-SI). All patients who received one dose of study medication were included in the observed-case analysis (no missing data were replaced). Results indicated that by endpoint (week 8), patients receiving pramipexole at the 1.0 mg per day dose had significant improvement over baseline compared to the placebo group by measure of the HAM-D, MADRS, and CGI-SI. Significant improvement in this dose group was seen at other timepoints as well. The most obvious improvement was seen in the pramipexole 5.0 mg group, although a substantial dropout rate for this group precluded statistical tests vs. placebo late in the study. Patients taking fluoxetine also showed significant improvements at endpoint on the MADRS and earlier in the study on the HAM-D. No new or unusual safety concerns were generated during this study. Pramipexole helped safely alleviate the symptoms of depression at 1.0 mg per day and especially in those patients who could tolerate the escalation to 5 mg per day. Depression and Anxiety 11:58–65, 2000.

Key words: ***Hamilton psychiatric rating scale for depression; clinician's global impressions; Montgomery-Asberg depression rating scale; Mirapex®; Prozac®; dopamine agonist antidepressant***

INTRODUCTION

The role of dopamine in psychotic disorders is well established both through animal models of psychosis and the efficacy of neuroleptic agents that block dopamine. The role of dopamine in mood disorders is less clearly defined, although dopaminergic neuroanatomical pathways are involved in the regulation of motivation and reward circuits in animal models [Piercey, 1998]. Furthermore, although serotonergic-specific reuptake inhibitors (SSRIs) are currently the mainstay

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This study was conducted at University of Tennessee Medical Center in Memphis; Anxiety and Depression Center in Columbia South Carolina; University of Florida at Gainesville; McMaster University at Ontario; Southlake Professional Group in Renton, Washington; Glenbeigh Hospital of Orlando in Winter Park, Florida; VA Medical Center in Palo Alto, California; and Delaware Valley Research Associates in King of Prussia, Pennsylvania.

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in the treatment of depression, established compounds, such as buproprion, which increase dopamine levels centrally, clearly have antidepressant properties [Kapur and Mann, 1992]. Patients with Parkinson's disease, characterized by degeneration of nigro-striatal dopamine-containing neurons, suffer from increased rates of depression compared to age-matched controls [Dooneief et al., 1992; Cummings, 1992]. Recently, reports of antidepressant effects of pramipexole, a direct-acting agonist, in depressed patients have emerged, supporting the role of dopamine dysregulation in some patients with depression.

Pramipexole, a synthetic aminothiazole derivative, is a dopamine D_2 receptor agonist that currently is approved for use in Parkinson's disease. It is structurally distinct from the ergot-derived drugs (e.g., bromocriptine and pergolide). It is also pharmacologically unique in that it is a full agonist and has receptor selectivity for the dopamine D_3 receptor subtype of the D2 subfamily of receptors. These properties may confer advantages in terms of both efficacy (full agonist with potential for greater therapeutic effects) and safety (receptor selectivity may reduce unwanted side effects) compared to currently available dopamine agonists [Piercey, 1998].

Theoretically, higher doses of pramipexole should act as a direct agonist at the postsynaptic receptor to relieve symptoms of depression. Pramipexole proved to be active in diverse tests of animal behavior simulating symptoms of depression, including Willner's Anhedonia Test [Willner et al., 1994], Fixed Interval Test [Schaefer et al., 1996], Forced Swimming Test, and REM Sleep Inhibition Test. These tests showed indications of antidepressant properties after a dose of 0.1 mg/kg.

In a small pilot study in depressed patients, Schaefer and colleagues [1996] studied the maximum tolerated dose and examined the reduction in total scores from the Montgomery-Asberg Depression Rating Scale (MADRS), Hamilton Psychiatric Rating Scale for Depression (HAM-D), Clinical Global Impressions (CGI), and the Bech-Rafaelson Melancholia Scale (not used in this study). Specifically, 9 out of 13 patients taking pramipexole had a greater than 30% decrease in the HAM-D total score from baseline. The doses chosen for this current study are based on these results, in which pramipexole in daily doses of 1.75, 3.5, and 4.875 mg were considered safe and effective.

The half-life of pramipexole is estimated to be 9–12 hr and therefore pramipexole was administered twice daily in this study. Prozac (Dista Products-Eli Lilly) is an antidepressant whose action is presumed to be linked to the inhibition of the CNS neuronal uptake of serotonin. Prozac was chosen as a comparator at a dose of 20 mg per day (package insert, prepared June 1994).

The present study was conducted to assess the effect of pramipexole in patients with major depression and to assess the safety and tolerance of this medication in this patient population. We hypothesized that increasing doses of pramipexole, compared to placebo, would improve the symptoms of major depression in a dose-response manner.

METHODS

This was a double-blind, randomized, placebo-controlled, parallel-group, clinical trial using fixed doses of pramipexole and fluoxetine. The protocol was approved by an Institutional Review Board at each participating study center. All patients signed an Informed Consent Form after the nature of the study was explained to them and before undergoing any study procedures. Patient selection criteria are listed in Table 1. One hundred seventy-four eligible patients with a DSM-III-R diagnosis of major depression (single or recurrent episode, with or without melancholia and without psychotic features) were assigned to one of five treatment groups: placebo group, fluoxetine group, or one of three pramipexole groups. Patients received a 1 week placebo run-in, 8 weeks of treatment, and a 1 week post-study follow-up assessment (week 9).

During the titration period, patients in the pramipexole 0.375 mg group (36 patients), fluoxetine 20 mg group (35 patients), and placebo group (35 patients) were started at their fixed-dose assignment. Patients in the pramipexole 1.0 mg group (35 patients) and 5.0 mg group (33 patients) were titrated up to their assigned fixed dose over a maximum of 14 days and then held at their dose assignment for the remainder of the 8 week treatment period.

Efficacy was measured primarily by the change from baseline in the HAM-D (17-item version) total score, MADRS total score, and the CGI-Severity of Illness (SI) score. Supplemental evaluations were done using the Beck Depression Inventory (BDI) and the CGI-Global Improvement (GI) score. Tolerance and safety were evaluated by assessing adverse events, laboratory tests, and vital signs.

All statistical tests were two-sided and a p-value of ≤ 0.05 was considered significant for this report. Analyses were performed on the intent-to-treat population, which included randomized patients who received at least one tablet of study medication and who had at least one post-baseline evaluation. Patients were categorized by the scheduled visit and not the date of visit. Statistical tests were done at each visit for those patients with observations within the specified window. The principal analysis emphasized tests conducted at week 8 of treatment, the end of the fixed-dose treatment period, and results from the analysis at this timepoint are reported here.

The statistical model was Response = Mean + Treatment + Investigator + Treatment × Investigator + Error, where all effects were additive. For most analyses, the Response term was the change from baseline value. In addition, group comparisons were based on adjusted group mean changes (predicted by the model) rather than on actual mean changes. However, only actual

TABLE 1. Patient selection criteria

Inclusion criteria	Exclusion criteria
Met DSM-III-R criteria for major depression, single episode or recurrent episode, with or without melancholia and without psychotic features (296.21, 296.22, 296.23, 296.31, 296.32, or 296.33).	History of clinically relevant medical disease.
Between ages of 18 and 65 years, inclusive.	Clinically significant changes on the ECG suggestive of ischemia or clinically abnormal laboratory value (i.e., one that required further investigation or treatment of the patient) or positive hepatitis B screen.
Had a total score of ≥ 18 on the HAM-D (17-item version), and a score of ≥ 2 on the depressed mood item of the HAM-D at the screen visit and at the baseline visit.	Lifetime history of hypomania/mania, psychotic disorder, dementia, and borderline or antisocial personality disorders.
Male or female (post-menopausal LH>50 mIU/ml, or surgically sterile, or using a reliable barrier method contraception).	History of a serious suicidal attempt in the past 12 months; presence of serious suicidal tendencies/potential; the suicide question on the HAM-D must not have been rated > 2.
Patients on certain antidepressants with prolonged effects (e.g., MAOI, fluoxetine) may have needed longer than 2 weeks post-discontinuation to obtain relatively uncontaminated baseline evaluations.	Women who were pregnant or lactating; women taking a low-estrogen "mini-pill" contraceptive.
Agreed not to start psychotherapy or behavior therapy while participating in the trial. Patients currently on these types of therapy for at least 3 months were eligible for the study and could continue to receive therapy during the study.	Positive urine screen for benzodiazepines, cocaine/cocaine metabolites, cannabinoids, amphetamines, barbiturates, and opiates or history of substance abuse (drugs or alcohol, DSM-III-R criteria) within the past 6 months of the screen visit.
Consented to participate voluntarily and signed a written Patient Informed Consent prior to any study procedures at Screen visit.	Non-responders to at least two trials of antidepressant treatment in the past.
	Use of fluoxetine (Prozac) in the past 6 months or use of another investigational drug within 1 month prior to the baseline visit.
	Inability to be withdrawn from any psychoactive drug(s) being taken at the time of screening.
	Evidence of hypersensitivity, intolerance, or contraindication to dopamine agonists (i.e., bromocriptine, selegiline) or lactose.

mean changes are reported here. Pairwise comparisons were conducted to test for differences between each active treatment versus placebo. Orthogonal contrasts and regression analyses were performed on the HAM-D and MADRS total scores (mean change from baseline). A responder analysis was conducted on the number of patients with at least a 50% decrease from baseline compared to placebo on the HAM-D and MADRS and on the number of patients with a score of 2 or less (much improved or greater) on the CGI—global improvement scale.

Results are reported for the observed-case analysis, for which no missing data were replaced. Results at endpoint (week 8) and thereby represent a completer analysis and include only those patients who tolerated their dose through the full study. Results from an LOCF analyses (missing data were replaced by carrying the last observation forward) were not reported due to a notable dropout rate by the end of the study, especially in the pramipexole 5.0 mg group, which had 36% drop out in the ascending-dose interval due to adverse events (Table 2).

Because this was a Phase II hypothesis-generating study, all significant pairwise comparisons were discussed, regardless of the significance level of the overall comparison. For some tests later in the study, the N for the pramipexole 5.0 mg group was too low for valid statistical testing and no *P*-values were generated. In addition, no orthogonal contrast results were available after week 2 in the OC analysis due to the dropout rate.

RESULTS

All patients who were randomized (174) to this study received at least one dose of study medication and were included in the statistical analysis. The majority of patients in each treatment group completed the study (66–86%), with the exception of the pramipexole 5.0 group (42.4%). Dropout information is presented in Table 3. The average age of the patients was 42 years and most patients were white and female. With the exception of diastolic blood pressure, the treatment groups were statistically similar in demographic variables. The range of mean diastolic blood pressure among the groups was 74.1 to 79.0 mmHg. Baseline data is shown in Table 4. Baseline values for the HAM-D, MADRS, CGI-SI, and BDI were similar across the treatment groups. The CGI-GI evaluation does not have a baseline assessment.

At endpoint (week 8), the overall group comparison

TABLE 2. Number (%) of patients with adverse events (most commonly reported)*

	Placebo	PPX 0.375	PPX 1.0	PPX 5.0	Fluoxetine
Total patients	34 (100)	36 (100)	35 (100)	33 (100)	33 (100)
Number of patients with AEs	28 (82.4)	34 (94.4)	30 (85.7)	31 (93.9)	29 (87.9)
Headache	11 (32.4)	12 (33.3)	15 (42.9)	10 (30.3)	13 (39.4)
Nausea	7 (20.6)	9 (25.0)	16 (45.7)	25 (75.8)	6 (18.2)
Somnolence	2 (5.9)	4 (11.1)	6 (17.1)	12 (36.4)	3 (9.1)
Dizziness	3 (8.8)	5 (13.9)	6 (17.1)	9 (27.3)	3 (9.1)
Insomina	1 (2.9)	5 (13.9)	4 (11.4)	5 (15.2)	6 (18.2)
Infection	6 (17.6)	5 (13.9)	7 (20)	1 (3.0)	5 (15.2)
Asthenia	0	4 (11.1)	2 (5.7)	5 (15.2)	5 (15.2)
Anorexia	1 (2.9)	1 (2.8)	5 (14.3)	4 (12.1)	3 (9.1)
Vomiting	2 (5.9)	0	4 (11.4)	13 (39.4)	2 (6.1)

**AEs were summed across visits by maximum severity for each patient.*

TABLE 3. Disposition of patients: n (%)*

Number of patients	Placebo	PPX 0.375	PPX 1.0	PPX 5.0	Fluoxetine	Total
Randomized	35 (100)	36 (100)	35 (100)	33 (100)	35 (100)	174 (100)
ITT	35 (100)	36 (100)	35 (100)	33 (100)	35 (100)	174 (100)
Ascending-dose interval						
Entered	34 (97.1)	36 (100)	35 (100)	33 (100)	33 (94.3)	171 (98.3)
Completed	28 (80.0)	33 (91.7)	29 (82.9)	21 (63.6)	32 (91.4)	143 (82.2)
Discontinued	6 (17.1)	3 (8.3)	6 (17.1)	12 (36.4)	1 (2.9)	28 (16.1)
Nonserious adverse event	2 (5.7)	2 (5.6)	4 (11.4)	12 (36.4)	0	20 (11.5)
Personal request	1 (2.9)	0	1 (2.9)	0	0	2 (1.1)
Lost to followup	3 (8.6)	1 (2.8)	1 (2.9)	0	1 (2.9)	6 (3.4)
Maintenance dose interval						
Entered	28 (80.0)	33 (91.7)	29 (82.9)	21 (63.6)	32 (91.4)	143 (82.2)
Completed	23 (65.7)	27 (75.0)	23 (65.7)	14 (42.4)	30 (85.7)	117 (67.2)
Discontinued	5 (14.3)	6 (16.7)	6 (17.1)	7 (21.1)	2 (5.7)	26 (14.9)
Lack of efficacy	1 (2.9)	3 (8.3)	3 (8.6)	1 (3.0)	1 (2.9)	9 (5.2)
Serious adverse event	0	0	0	1 (3.0)	0	1 (1.0)
Nonserious adverse event	2 (5.7)	1 (2.8)	1 (2.9)	4 (12.1)	1 (2.9)	9 (5.2)
Personal request	2 (5.7)	1 (2.8)	1 (2.9)	0	0	4 (2.3)
Lost to followup	0	1 (2.8)	1 (2.9)	1 (3.0)	0	3 (1.7)
Post-treatment interval						
Entered	25 (71.4)	29 (80.6)	26 (74.3)	20 (60.6)	28 (80.0)	128 (73.6)

**Percentage denominator is ITT patients per group.*

for the HAM-D total score (mean change from baseline) was significant (F = 2.54, P = 0.0457, df = 4,84). At this visit, the pramipexole 1.0 mg group showed significantly better improvement (-13.26) over baseline than the placebo group (–9.13) (t = –2.735, P = 0.0076, df = 84). Significant improvement compared to placebo was seen at other timepoints as well for both the pramipexole 1.0 mg group and the fluoxetine group (data not shown). The pramipexole 5.0 mg group had the best improvement at week 8 (–15.00), but P values were not available for this test against placebo because of a decreased group N (see Methods). See Figure 1 for a graphical display of HAM-D total score means (no statistical tests were done on the actual means).

TABLE 4. Baseline values

Variable	Placebo (N=35)	PPX 0.375 (N=36)	PPX 1.0 (N=35)	PPX 5.0 (N=33)	Fluoxetine (N=35)	P value
HAM-D total score	20.8	21.4	22.0	21.8	22.0	0.2585
CGI-severity of illness	4.1	4.0	4.2	4.1	4.1	0.5501
MADRS total score	26.8	28.3	28.9	27.5	28.8	0.3515
BDI	21.5	23.5	24.1	24.7[a]	23.1[a]	0.5983

[a]Ns for this variable were one less than the N.

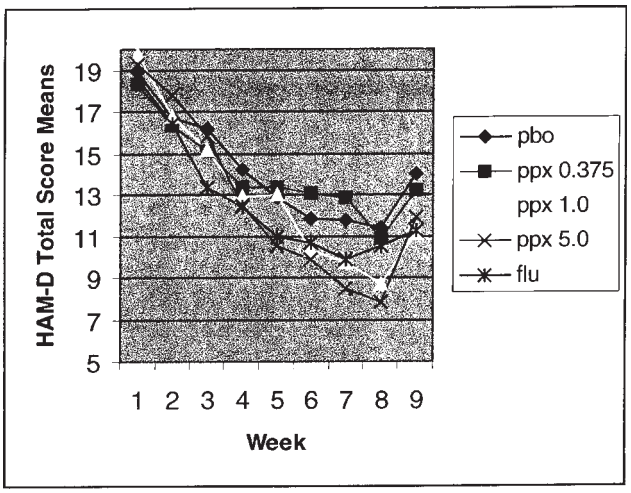

Figure 1. HAM-D total score group means over the 8 week treatment period and the post-study period (week 9). Although no statistical tests were done on the actual group means as shown, change from baseline analyses at endpoint (week 8) indicated that the pramipexole 1.0 mg group had significant improvement compared to placebo. At week 9, both the pramipexole 1.0 mg and fluoxetine groups had significant improvement compared to placebo. The fluoxetine group showed significant improvement earlier in the study as well. The pramipexole 5.0 mg group had the best improvement, but no *P* values were generated because of a low number of patients.

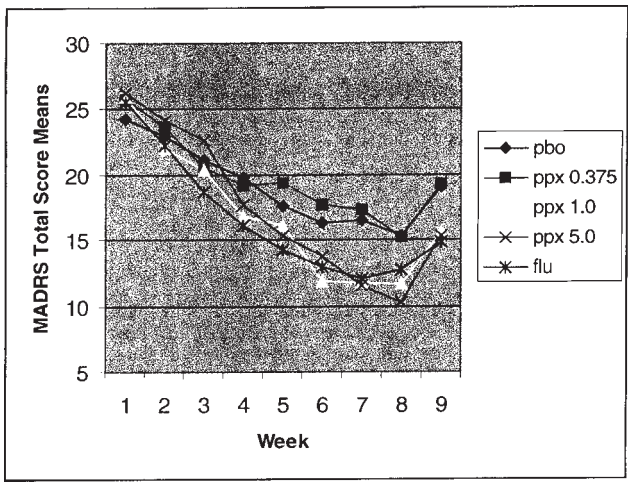

Figure 2. MADRS total score group means over the 8 week treatment period and the post-study period (week 9). Although no statistical tests were done on the actual group means as shown, change from baseline analyses and endpoint (week 8) indicated that the pramipexole 1.0 and fluoxetine groups had significant improvement compared to placebo. At week 9, the pramipexole 1.0 mg and fluoxetine groups had significant improvement compared to placebo. Both of these active drug groups showed significant improvement earlier in the study as well. The pramipexole 5.0 mg group had the best improvement, but no *P* values were generated because of a low number of patients.

Although the overall comparison for MADRS total score (mean change from baseline) was not significant at endpoint (week 8), individual group differences were significant at this visit. The pramipexole 1.0 mg group (–17.26) (t = –2.647, *P* = 0.0097, df = 84) and fluoxetine group (–15.73) (t = –2.034, *P* value = 0.0451, df = 84) had significantly better improvement compared to the placebo group (–11.22). Both of these active drug groups had significant improvement earlier in the study and at the post-study visit as well (data not shown). As with the HAM-D, the pramipexole 5.0 mg group had the best improvement (–18.60) at week 8, but *P* values vs. placebo were not available. See Figure 2 for a graphical display of MADRS total score means (no statistical tests were done on the actual means).

As with the MADRS, the overall comparison for the CGI-Severity of Illness scale (mean change from baseline) was not significant at endpoint (week 8). However, the pramipexole 1.0 mg group had significant improvement over baseline (–1.83) compared to placebo (–1.13) (t = –2.46, *P* value = 0.0159, df = 84) at this visit. The significant improvement observed in the pramipexole 1.0 mg group was also seen earlier in the study and at the post-study visit, when the fluoxetine group also had significant improvement compared to placebo (data not shown). At week 8, the pramipexole 5.0 mg group showed good improvement (–1.73) in severity of illness (no *P* value vs. placebo available). See Figure 3 for a graphical display of CGI-SI total score means (no statistical tests were done on the actual means).

Significant treatment effects were also seen in the supplemental evaluations (BDI and CGI-GI scales). The pramipexole 1.0 mg group had significantly better improvement on the BDI at endpoint (week 8) and at almost every study week compared to the placebo group (data not shown). The 5.0 mg group had similar improvements at several timepoints, although no *P* values vs. placebo were available. The fluoxetine group also had significant improvement over placebo at several study weeks. Results from the CGI-GI scale indicated no significant effects at endpoint. However, the pramipexole 1.0 mg group had significant global improvement compared to placebo at week 3 and the fluoxetine group had significant improvement compared to placebo at weeks 6 and 9.

No significant linear effect was detected by regression analysis for the HAM-D or MADRS total scores (mean change from baseline) and no results were available for the linear orthogonal contrasts after week 2 in the OC analysis due to the dropout rate.

A responder analysis was conducted on several variables at endpoint (week 8) and the results are presented in Table 5. At endpoint, the pramipexole 5.0 mg group (73.3% of patients who completed evaluations at this visit) had significantly more responders by the HAM-D (< 50% decrease from baseline in total score) compared to the placebo group (39.1%) (χ^2 = 4.71, *P* =

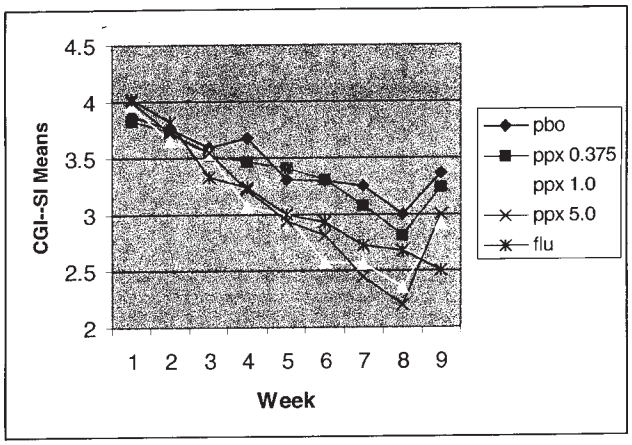

Figure 3. CGI-SI score group means over the 8 week treatment period and the post-study period (week (). **Although no statistical tests were done on the actual group means as shown, change from baseline analyses at endpoint (week 8) indicated that the paramipexole 1.0 mg group had significant improvement compared to placebo. The pramipexole 1.0 mg group showed significant improvement before and after endpoint as well. Results for the fluoxetine group were significant at week 9. The pramipexole 5.0 mg group had the best improvement, but no *P* values were generated because of a low number of patients.**

0.0299, df = 1). However, no active treatment groups had significantly more responders than the placebo group on the MADRS (< 50% decrease from baseline in total score) or the CGI-GI (score of 2 or less).

No new or unusual safety concerns were generated during this study. The adverse events that were reported with a frequency of at least 10% in each of the three pramipexole dose groups were: headache, nausea, somnolence, dizziness, and insomnia. These events were not unexpected and occurred with similar frequencies in the placebo and fluoxetine groups. No clinically significant abnormal changes were seen for laboratory tests or vital signs. One patient had a high platelet count at the screening visit and throughout the study. Although still above normal, the level did decrease by the end of the study. No diagnosis or medical consequences were noted by the investigator.

DISCUSSION

The patients in this study were at least moderately depressed, with an average baseline HAM-D score of greater or equal to 21. Based on results from the HAM-D, MADRS, and BDI total scores and the CGI-Severity of Illness score, patients in the pramipexole 1.0 and 5.0 mg groups had good improvement over baseline in symptoms of depression at the end of treatment. Fluoxetine also showed efficacy, although the results were not as consistent statistically.

Although the higher pramipexole doses did result in improvements, linear dose effects could not be assessed given the sample size and dropout rate for the high-dose group. The dropout rate may have been caused by the relatively rapid escalation to the 5 mg dose level. In this study, the escalation period was 14 days; in a previous study conducted in patients with Parkinson's disease, the escalation to the 4.5 mg dose occurred over 7 weeks [Lieberman et al., 1997; Shannon et al., 1997]. The 5 mg dose may be tolerated with a slower dose escalation, and therefore may be useful in those patients who do not respond to lower doses.

As we hypothesized, pramipexole was efficacious in treating depressive symptoms, especially for those patients who could tolerate the escalation into higher doses. This result lends support to the monoaminergic theories of depression, which hold that dysregulation of systems involving dopamine, in addition to serotonin and norepinephrine, may be involved in major depression [Siever and Davis, 1985]. The mechanism of action of currently available antidepressants is to re-equilibrate one or more neurotransmitter systems and restore relative efficiency at one or more synaptic sites, such as by altering post-synaptic receptor sensitivity [Siever and Davis, 1985; Heninger and Charney, 1982; Sugrue, 1983]. It is believed that pramipexole, in higher doses, acts as a direct agonist at the postsynaptic receptor thereby relieving some symptoms of depression.

The role of altered CNS dopamine neurotransmission in depression has been supported by the increased rate of depressive symptoms in patients suffering from Parkinson's disease. In a review by Cummings [1992], the mean frequency of depression was 40% of patients with Parkinson's disease across 26 studies. Cummings suggests that depression in these patients can differ subtly from idiopathic mood disorders both in symptomology and pathophysiology. However, dopamine, norepinephrine, and serotonin have all been implicated in the pathogenesis of depression in Parkinson's patients. His model for pathogenesis proposes that neuronal loss in brainstem nuclei leads to biochemical depletion of the cortex and basal ganglia. This depletion is associated with decreased reward mediation, environmental dependency, and inadequate stress response, which in turn results in apathy, hopelessness, and other symptoms of depression. Thus the morphological changes in Parkinson's disease can lead to biochemical disruption even in areas remote from the nuclei. Many of the dysfunctional events Cummings describes are mediated by prefrontal dopamine systems and he suggests that changes in other neurotransmitters systems further modify the characteristics of an individual's depressive illness.

An interesting finding by Bejjani and colleagues [1999] showed that high-frequency deep-brain stimulation used in the treatment of advanced Parkinson's disease led to transient acute depression in one of 19 patients when the stimulation was delivered to the left substantia nigra instead of the subthalamic nuclei. Although the neural pathways in this case have not been identified, the findings provide a basis for the involve-

TABLE 5. Number (no.) and percentage (%) of responders at endpoint (week 8)[†]

		Treatment group (N per patient population)					
Variable	Result/ patient population	Placebo cmptrs=23 ITT=35	PPX 0.375 cmpts=27 ITT=36	PPX 1.0 cmptrs=23 ITT=35	PPX 5.0 cmptrs=15 ITT=33	Fluoxetine cmptrs=30 ITT=35	*P*-value (overall)
HAM-D[a]	No. responders	9	15	13	11	17	0.4999
	% of completers	39.1	55.6	56.5	73.3*	56.7	
	% of ITT patients	25.7	41.7	37.1	33.3	48.6	
CGI-GI[b]	No. responders	10	14	14	11	20	0.4553
	% of completers	43.5	51.9	60.9	73.3	66.7	
	% of ITT patients	28.6	38.9	40.0	33.3	57.1	
MADRS[a]	No. responders	9	13	14	9	17	0.6727
	% of completers	39.1	48.1	60.9	60.0	56.7	
	% of ITT patients	25.7	36.1	40.0	27.3	48.6	

[†]*Percentages are based on the number of completers (cmptrs) of the maintenance phase and number of ITT patients overall. Note: the PPX 5 mg group had one patient who was considered discontinued in the patient disposition tabulation but who completed evaluations at the endpoint visit and is included with completers.*

*$P \leq 0.05$ *vs. placebo. Statistical comparisons done only for completer population, not ITT population.*

[a]*Responder, patient with > = 50% decrease in score at visit compared to baseline.*

[b]*Responder, patient with GI score of 2 or less (much improved or greater).*

ment of the dopamine system in depression. Antidepressants generally relieve symptoms of depression in Parkinson's patients. Recently, sertraline, a relatively selective serotonin reuptake inhibitor with dopamine reuptake inhibitor activity, significantly improved BDI scores, did not affect UPDRS scores, and was well tolerated by 13 of 15 patients with both Parkinson's disease and depression in an open-label pilot study [Hauser, 1997].

Studies with dopamine reuptake inhibitors such as nomifensine have shown clear antidepressant effects in major depression. Likewise, bromocriptine, a postsynaptic dopamine receptor agonist, has had efficacy comparable with standard tricyclic antidepressants [Van Scheyen et al., 1977; Waehrens and Gerlach, 1981; Theohar et al., 1981] and appears useful in antidepressant-resistant depression [Inoue et al., 1996] and in relapses during SSRI treatment [McGrath et al., 1995]. Other dopaminergic treatments such as the use of stimulant augmentation [Nelson, 1998] and ECT [Douyon et al., 1989] have been be useful for the treatment of depression, the latter in patients who also had Parkinson's disease. Finally, pramipexole has been described, with a handful of other dopamine-active compounds, as having rapid antidepressant action [Willner, 1997]. The combined results of preliminary evidence in human studies and of data from animal models of depression [Willner et al., 1994; Schaefer et al., 1996; Muscat et al., 1992] support the growing body of evidence for the efficacy of dopamine-related treatments for depressive illness.

CONCLUSIONS

This study presents evidence that pramipexole at 1.0 mg daily is effective and safe as a treatment for depression. Although no direct comparison to fluoxetine was conducted, pramipexole 1.0 mg provided similar or more statistically consistent improvement than fluoxetine 20 mg, when both groups were compared to placebo. Pramipexole 5 mg is probably the best dose for those patients who can tolerate it. Pramipexole is currently approved for use in Parkinson's disease and may prove to be useful to treat depressive symptoms in this patient population, as well as in those patients with other forms of depressive illness or in combination with SSRIs for refractory depression. We recommend that future studies evaluate higher doses, such as pramipexole 5 mg and up, with a slower dose titration to reach these doses safely.

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