Pramipexole for the treatment of depressive symptoms in patients with Parkinson's disease: a randomised, double-blind, placebo-controlled trial

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Summary

Background Depression is common in patients with Parkinson's disease, but evidence on the efficacy of antidepressants in this population is lacking. Because depression in patients with Parkinson's disease might be related to dopaminergic dysfunction, we aimed to assess the efficacy of the dopamine agonist pramipexole for treatment of depressive symptoms in patients with Parkinson's disease.

Methods We did a 12-week randomised, double-blind, placebo-controlled (1:1 ratio) trial of pramipexole (0·125–1·0 mg three times per day) compared with placebo in patients with mild-to-moderate Parkinson's disease. Patients from 76 centres in 12 European countries and South Africa were included if they were on stable antiparkinsonian therapy without motor fluctuations and had depressive symptoms (15-item geriatric depression scale score ≥5 and unified Parkinson's disease rating scale [UPDRS] part 1 depression item score ≥2). Patients were randomly assigned by centre in blocks of four by use of a randomisation number generating system. Clinical monitors, the principal investigator, and patients were masked to treatment allocation. The primary endpoint was change in Beck depression inventory (BDI) score and all treated patients who had at least one post-baseline efficacy assessment were included in the primary analysis. We also did a pre-specified path analysis with regression models to assess the relation between BDI and UPDRS part 3 (motor score) changes. This trial is registered with ClinicalTrials.gov, number NCT00297778, and EudraCT, number 2005-003788-22.

Findings Between March, 2006, and February, 2008, we enrolled 323 patients. Of 296 patients randomly assigned to pramipexole or placebo, 287 were included in the primary analysis: 139 in the pramipexole group and 148 in the placebo group. BDI scores decreased by an adjusted mean 5·9 (SE 0·5) points in the pramipexole group and 4·0 (0·5) points in the placebo group (difference 1·9, 95% CI 0·5–3·4; p=0·01, ANCOVA). The UPDRS motor score decreased by an adjusted mean 4·4 (0·6) points in the pramipexole group and 2·2 (0·5) points in the placebo group (difference 2·2, 95% CI 0·7–3·7; p=0·003, ANCOVA). Path analysis showed the direct effect of pramipexole on depressive symptoms accounted for 80% of total treatment effect (p=0·04). Adverse events were reported in 105 of 144 patients in the pramipexole group and 101 of 152 in the placebo group. Adverse events in the pramipexole group were consistent with the known safety profile of the drug.

Interpretation Pramipexole improved depressive symptoms in patients with Parkinson's disease, mainly through a direct antidepressant effect. This effect should be considered in the clinical management of patients with Parkinson's disease.

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Introduction

Depression is common in patients with Parkinson's disease, and although studies have reported a mean prevalence of major depressive disorder of 17% in patients with Parkinson's disease, 35% have clinically significant depressive symptoms.[1] Depression is a major determinant of poor quality of life[2] and is associated with increased disability and motor and cognitive decline in patients with Parkinson's disease.[3,4] Depression in patients with Parkinson's disease might be caused by dysfunction in brain serotoninergic, noradrenergic, and dopaminergic pathways,[3,5] and in particular by dopamine depletion in subcortical–cortical circuits that regulate mood, motivation, and reward.[5]

Despite the high incidence of depression in patients with Parkinson's disease, few controlled clinical trials have specifically investigated antidepressant treatments in these patients, and those trials have included small numbers of patients.[6–8] There is little evidence that patients with Parkinson's disease might benefit more from any one particular class of antidepressants than any others.[6–8] The selective serotonin reuptake inhibitor (SSRI) citalopram and the tricyclic antidepressant desipramine are more effective than placebo at improving major depression in patients with Parkinson's disease.[9] Recently, the tricyclic drug nortriptyline, but not the SSRI paroxetine, was also found to be better than placebo for treatment of Parkinson's disease-related depression.[10]

Open-label trials have suggested that D_2 dopamine receptor agonists, such as pramipexole and pergolide, might be effective in reducing depression in patients with Parkinson's disease.[11,12] In a randomised, double-

blind, placebo-controlled trial, pramipexole improved the symptoms of major depression in patients without Parkinson's disease.[13] Pramipexole is a non-ergot dopamine agonist that has high in-vitro specificity for the D_2 subfamily of dopamine receptors; it is a full agonist and has higher affinity for the D_3 receptor subtype than for the D_2 or D_4 receptor subtypes. Sustained administration of pramipexole can modify the spontaneous firing of dopamine, norepinephrine, and serotonin neurons in rat brains, suggesting that the therapeutic action of pramipexole might be attributed to increased dopaminergic and serotoninergic neurotransmission in the brain.[14]

The antidepressant effects of pramipexole were first observed in several animal models,[15–17] and studies in patients with Parkinson's disease have also suggested clinical benefits in depression. In an open-label comparison of pramipexole and the SSRI sertraline for the treatment of major depression in patients with Parkinson's disease, the treatments had similar benefit, but remission was more likely in patients treated with pramipexole.[18] A meta-analysis of controlled trials of pramipexole for treatment of motor symptoms in patients with Parkinson's disease reported an odds ratio of 2·41 (95% CI 1·78–4·13; p<0·001) for improvement in depression severity as measured by item 3 on part 1 of the unified Parkinson's disease rating scale (UPDRS).[19] However, this scale is best used for screening, and its sensitivity and responsiveness in clinical trials have not been adequately evaluated.[20] Furthermore, because the meta-analysis included patients with Parkinson's disease without a depressive disorder,[19] the relevance of the results for patients with Parkinson's disease who have depression is unclear. No trials of pramipexole have specifically assessed symptomatic reduction of depression as a primary outcome in patients with Parkinson's disease. Therefore, we did the present study to investigate the effects of pramipexole on clinically relevant depressive symptoms in patients with Parkinson's disease without motor fluctuations who were on stable antiparkinsonian treatment.

Methods

Patients

We enrolled patients from 76 centres in 12 European countries and South Africa. Patients were included in the study if they were at least 30 years old, had idiopathic Parkinson's disease (according to UK Brain Bank criteria)[21] at modified Hoehn and Yahr stages 1–3,[22] did not have motor fluctuations, and had Parkinson's disease motor symptoms under satisfactory control as judged by the local investigator. Use of levodopa (plus carbidopa or benserazide), amantadine, anticholinergic drugs, catechol-*O*-methyltransferase inhibitors, or monoamine oxidase B inhibitors was allowed if dosing was stable for at least 4 weeks before baseline and remained unchanged during the study. Use of a dopamine agonist was not allowed during the 30 days before baseline.

Patients were required to have clinically relevant depressive symptoms, as documented by baseline scores of at least 5 on the 15-item geriatric depression scale (GDS-15; score range 0–15, with higher scores suggesting increasing severity of depressive symptoms)[23–25] and of at least 2 on part 1, item 3 of the UPDRS (depression).[26] Antidepressant drugs such as SSRIs were allowed if the dose was stable for at least 6 weeks before baseline and remained unchanged during the study.

Exclusion criteria were a score of less than 24 on the mini-mental state examination;[27] severe depression, defined by the presence of suicidal ideation; present psychotherapy; use of typical neuroleptics, metoclopramide, α-methyldopa, methylphenidate, reserpine, flunarizine, cinnarizine, or amphetamine derivatives within the past 3 months; a history of malignant melanoma; or previous deep brain stimulation surgery. Women of childbearing potential were excluded if they were pregnant, lactating, or not taking adequate contraception.

Local ethics committees approved the study and all patients provided written informed consent before random allocation. There was no independent safety board monitoring because pramipexole, which has already received marketing authorisation in the European Union, the USA, and other countries, was used in this study under phase 4 conditions and within the approved indication and dose range. Therefore, no new safety risks were expected.

Randomisation and masking

The randomisation code was provided by the study sponsor using their validated, centralised, randomisation number generating system, and was stratified by study centre with a block size of four to provide a balanced distribution of the treatment groups within each centre and across the study as a whole. To preserve masking, access to the randomisation code was restricted to clinical trial support and pharmaceutical personnel, who generated the code and labelled and packaged the study drugs. Investigators, clinical monitors, and patients were masked to treatment allocation. Pramipexole and matching placebo tablets were prepared by Boehringer Ingelheim, Germany, by use of the same excipients, such that the tablets could not be differentiated.

Procedures

We did a double-blind, placebo-controlled, parallel-group trial with a 12-week treatment phase. Patients were randomly assigned (1:1) to pramipexole or placebo. For pramipexole, four different tablet strengths were used: 0·125 mg, 0·25 mg, 0·5 mg, and 1·0 mg. The study drugs were titrated for a maximum of 5 weeks, during which the dose (started at 0·125 mg three times per day for pramipexole) was increased each week until an antidepressant effect was achieved, as assessed by investigators reporting patients' symptoms as much or very much improved on the investigator-rated clinical

global impression of improvement scale (CGI-I) focused on mood improvement.[28] At each weekly assessment the dose could be decreased to the previously used dose to address intolerance. After titration, patients received at least 7 weeks of maintenance treatment (at 0·125, 0·25, 0·5, 0·75, or 1·0 mg of pramipexole three times per day, or matching placebo); the study drug was then tapered off for a maximum of 5 days, after which patients had a final follow-up visit. Patients visited study centres for assessment at screening and baseline (week 0), and at weeks 1, 2, 3, 5, 12 (end of treatment), and 13 (taper phase); assessments via telephone were done by local investigators at weeks 4, 6, 8, and 10.

The primary efficacy endpoint was the change between baseline and 12 weeks in total score on the Beck depression inventory version 1A (BDI; range 1–63, with higher scores suggesting more severe depression).[29,30] Secondary efficacy outcomes included the BDI responder rate (the proportion of patients with at least a 50% reduction in BDI score from baseline) and changes from baseline on the GDS-15,[23–25] UPDRS[26] parts 2 (activities of daily living) and 3 (motor examination), CGI-I categories,[28] 39-item Parkinson's disease questionnaire (PDQ-39),[31] EuroQol,[32] Snaith-Hamilton pleasure scale (SHAPS),[33] and 0–10 visual analogue scale for pain. Efficacy assessments were done at baseline, at the beginning of the maintenance phase (week 5), and at the end of study treatment (week 12).

An additional secondary analysis, which was predefined in the statistical analysis plan before database lock, was to use path analysis to differentiate between direct treatment effects on depressive symptoms and effects that were mediated indirectly through alleviation of motor symptoms. Path analysis is a statistical technique designed to enhance the imputation of causal relations by investigating the association among variables and measuring the contribution of direct and indirect effects of one variable on other variables or outcomes.[34] Path analysis is often used to explore which treatment pathways contribute to the overall efficacy of a drug; for example, path analysis was used in a depression treatment study to identify contributions of depressive and somatic symptoms to the effects of duloxetine on functional abilities.[35]

Three post-hoc (ie, after unmasking) analyses were done. The first analysis investigated the proportion of patients with a GDS-15 score of less than 5 (the recommended cut-off for separating non-depressed patients from depressed patients)[20] after 12 weeks. The second assessed the association between change in BDI total score and quality of life (PDQ-39 total score). The final analysis investigated whether antidepressant treatment status at baseline was a moderator of treatment response.

Safety parameters included medical examination findings; vital signs; clinical laboratory data; and the occurrence, type, and intensity of adverse events. Severe adverse events were defined as incapacitating or causing inability to work or undertake usual activities, and serious adverse events were defined as fatal, life-threatening, needing or prolonging a treatment in hospital, or resulting in significant disability.

Statistical analysis

All statistical analyses were done using SAS version 8.2. To detect a difference between groups of at least 3 points between baseline and 12 weeks in the change in BDI score for pramipexole compared with placebo,[36] at a two-sided 5% significance level with 90% power (and assuming an SD of 7·5), 266 patients (133 per treatment group) would need to be included. Random allocation of 280 patients (140 per group) would allow for a 5% dropout rate. This number of patients, a reduction from the 350 listed in the original protocol, was chosen on the basis of a masked data review of the sample size assumptions for the common standard deviation of the change from baseline to 12 weeks in the BDI total score. The original sample size calculation used a standard deviation of 8·0 and a dropout rate of 15%; the change to 280 patients was incorporated into a protocol amendment.

The treated set used for the safety analysis comprised all patients who received at least one dose of study drug. The full analysis set included all patients who received at least one dose of study drug and who had at least one on-treatment BDI assessment, with a last-observation-carried-forward strategy used for imputation of missing data. The per-protocol set included all patients in the full analysis set who had no important protocol violation (defined as any protocol violation that could potentially have an effect on efficacy). Changes in BDI score and GDS-15 score between baseline and week 12 and BDI response rate were assessed in per-protocol analyses.

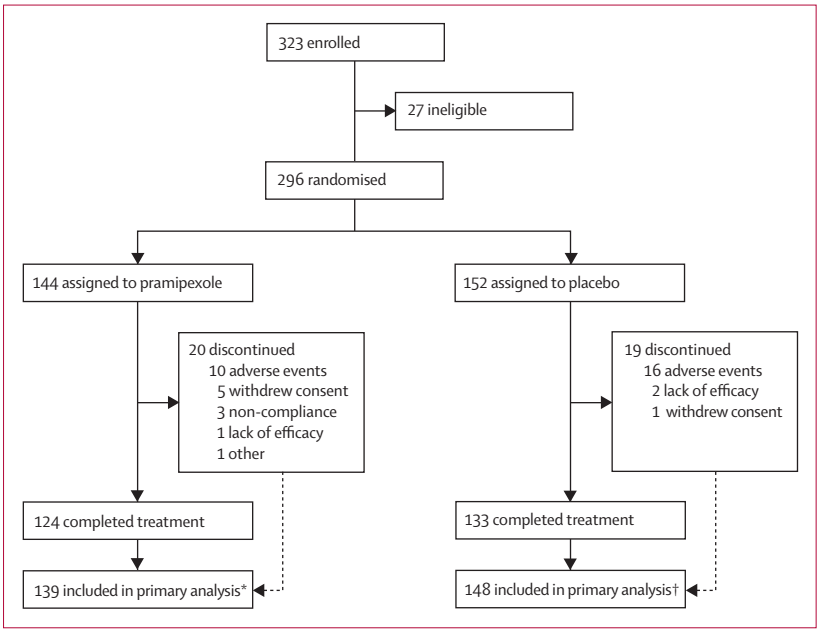

Figure 1: **Trial profile**
*5 patients had no post-baseline data. †4 patients had no post-baseline data.

For the primary efficacy endpoint, two-sided ANCOVA was used for the full analysis set data, with treatment and country (pooled for countries with less than four patients) as main effects, and baseline BDI score as a covariate. ANCOVA was also used for change in GDS-15 and UPDRS scores. For CGI-I categories, logistic regression was done, and the Wilcoxon Mann-Whitney rank test was used (with stratification for pooled countries) for the PDQ-39. For BDI responders, defined as at least a 50% reduction in BDI total score from baseline to week 12, logistic regression was done. For GDS-15 responders, defined as a GDS-15 score reduction to less than 5 from baseline to week 12, we did logistic regression.

Path analysis was done via three regression models: change in BDI modelled with terms for baseline BDI, baseline UPDRS part 3, change in UPDRS part 3, pooled country, and treatment (model 1); changes in motor symptom scores (UPDRS part 3) modelled with terms for baseline BDI, baseline UPDRS part 3, pooled country, and treatment (model 2); and change in BDI modelled with terms for baseline BDI, baseline UPDRS part 3, pooled country, and treatment (model 3). Model 1 provides the direct effect of treatment on depressive symptoms (via changes in the BDI), taking into account the indirect effect of treatment on depressive symptoms via changes in motor symptoms (UPDRS part 3). Model 2 in conjunction with model 1 provides the indirect effect of treatment on depressive symptoms via changes in motor symptoms (UPDRS part 3). Model 3 provides the total treatment effect on depressive symptoms via changes in the BDI. The main assumptions of the analysis were that relations between the variables are linear and that the effects observed are additive (ie, the direct plus indirect effect results in the total effect).

	Pramipexole (n=144)	Placebo (n=152)
Age (years)	67·4 (9·0)	66·6 (9·9)
Men	62 (43%)	78 (51%)
Duration of Parkinson's disease (years)	4·0 (4·5)	4·0 (3·9)
Hoehn and Yahr stage		
1	13 (9%)	18 (12%)
1·5	18 (13%)	18 (12%)
2	50 (35%)	56 (37%)
2·5	30 (21%)	35 (23%)
3	33 (23%)	25 (16%)
Parkinson's disease treatment*		
Any	134 (93%)	133 (88%)
Levodopa and derivatives†	109 (76%)	112 (74%)
Amantadine	36 (25%)	33 (22%)
Monoamine oxidase-B inhibitors	19 (13%)	20 (13%)
Anticholinergic drugs	9 (6%)	14 (9%)
Other dopaminergic drugs‡	7 (5%)	9 (6%)
Antidepressant treatment*	36 (25%)	32 (21%)
BDI score	18·7 (8·0)	19·5 (8·6)
GDS-15 score	8·4 (2·3)	9·2 (2·7)
UPDRS score		
Part 2	11·8 (5·3)	11·6 (4·9)
Part 3	26·3 (11·2)	24·9 (10·2)
PDQ-39 score	30·9 (1·6–69·1)	31·8 (5·1–72·3)

Data are mean (SD), number (%), or median (range). BDI=Beck depression inventory (version 1A). GDS-15=15-item geriatric depression scale. UPDRS=unified Parkinson's disease rating scale. PDQ-39=39-item Parkinson's disease questionnaire. *In addition to study drug, taken at any stage during the study treatment period. †Levodopa with or without carbidopa, levodopa plus carbidopa plus entacapone, or levodopa plus benserazide. ‡Entacapone or budipine.

Table 1: **Demographics and baseline characteristics**

Role of the funding source

The study sponsor participated in the study design, data management, data analysis, and writing of the report. The sponsor had no role in the collection or interpretation of the data, or in the decision to submit for publication. All authors had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

Between March, 2006, and February, 2008, 323 patients were enrolled (figure 1). 296 patients were randomly assigned to treatment: 144 to pramipexole and 152 to placebo. 39 patients withdrew from the study after random allocation: 20 in the pramipexole group and 19 in the placebo group. Of the 39 patients who withdrew, ten patients in the pramipexole group and 16 in the placebo group discontinued because of adverse events. Data from 287 patients (full analysis set) were included in the primary analysis: 139 in the pramipexole group and 148 in the placebo group. Data were available for 242 patients with no important protocol violations (per-protocol set): 117 in the pramipexole group and 125 in the placebo group. The most common protocol violations were no assessment of the primary endpoint at the maintenance phase (n=36) or not reaching the maintenance phase (n=31).

Demographics and baseline characteristics were similar between groups (table 1), although 43% of patients in the pramipexole group and 51% in the placebo group were men. 267 of 296 patients were receiving at least one Parkinson's disease drug and 68 of 296 used antidepressants. At final visits, pramipexole-treated patients were receiving a mean daily dose of 2·18 mg (SD 0·83) pramipexole and the placebo group were receiving a placebo dose equivalent to 2·51 mg (SD 1·66).

BDI scores in the pramipexole group decreased from a mean of 18·7 (SE 0·7) at baseline to an adjusted mean of 13·1 (0·5) at 12 weeks, compared with a decrease from 19·2 (0·7) to 15·0 (0·5) in the placebo group (figure 2). The adjusted mean change from baseline to week 12 was –5·9 (SE 0·5) in the pramipexole group and –4·0 (0·5) in the placebo group (difference –1·9, 95% CI –3·4 to –0·5; p=0·01). In the per-protocol set the adjusted mean change between baseline and week 12 was –6·1 (SE 0·6) in the pramipexole group and –4·3 (0·6) in the placebo group (difference –1·8, –3·3 to –0·3; p=0·02).

38 of 139 patients in the pramipexole group and 27 of 147 in the placebo group were BDI clinical responders (table 2). After adjusting for pooled country and baseline BDI score, the odds ratio for a decrease of at least 50% in BDI score was 1·8 (95% CI 1·0–3·1; p=0·05), with an adjusted odds ratio of 1·9 (1·0–3·5; p=0·05) in the per-protocol analysis.

GDS-15 scores decreased from a mean of 8·4 (SE 0·2) at baseline to an adjusted mean of 6·3 (0·3) at week 12 in the pramipexole group, compared with a decrease from 9·2 (0·2) to 7·1 (0·3) in the placebo group. The adjusted mean change was –2·5 (SE 0·3) in the pramipexole group and –1·7 (0·3) in the placebo group (difference –0·8, 95% CI –1·5 to –0·1; p=0·035). In the post-hoc analysis, 54 of 139 patients in the pramipexole group and 35 of 148 in the placebo group were GDS-15 responders (adjusted odds ratio 2·1, 1·2–3·6; p=0·01).

46 of 139 patients in the pramipexole group were rated as either much or very much improved on the CGI-I compared with 32 of 148 patients in the placebo group (odds ratio 1·8, 95% CI 1·2–2·8; p=0·006). The per-protocol analysis was consistent with these results (data not shown).

The mean adjusted difference between the pramipexole group and the placebo group in improvement from baseline to week 12 on the UPDRS part 3 (motor symptoms) was –2·2 (95% CI –3·7 to –0·7; p=0·003; figure 2), and the mean adjusted difference for UPDRS part 2 (activities of daily living) was –1·2 (–1·9 to –0·4; p=0·003). The per-protocol analysis also favoured pramipexole for these outcomes (data not shown). There were no between-group differences in change in either UPDRS part 1 total score or depression item alone, or part 4 scores (data not shown).

The difference between the pramipexole group and the placebo group in the median change from baseline to week 12 in overall PDQ-39 score was –1·3 (95% CI –3·3 to 0·8; p=0·19). There was a significant correlation (p<0·0001) between the change in total BDI and PDQ-39 scores; this effect was more pronounced for pramipexole (r=0·46) than for placebo (r=0·36). The difference between the pramipexole group and the placebo group in the adjusted mean change from baseline to week 12 in the EuroQol was 0·04 (95% CI 0·00–0·09; p=0·034). There were no between-group differences in change in pain or anhedonia scores.

The total effect of treatment on depressive symptoms (model 3) was represented by a path coefficient of –1·87 (p=0·01; webappendix). –1·49 (80%) of the effect of treatment on depressive symptoms was caused by a direct effect on depressive symptoms (model 1; p=0·04) and –0·38 (20%) was caused by its effect on motor function (model 2).

The post-hoc subgroup analysis that excluded all patients taking an antidepressant at baseline included 221 patients: 104 in the pramipexole group and 117 in the placebo group. Baseline BDI scores were 18·8 (SE 0·7) in the placebo group and 18·5 (0·8) in the pramipexole group. The adjusted mean difference in change in BDI total scores for those patients not on an antidepressant was –6·2 (SE 0·6) in the pramipexole group and –3·7 (0·6) in the placebo group (adjusted mean difference –2·5 (95% CI –4·1 to –0·8; p=0·004).

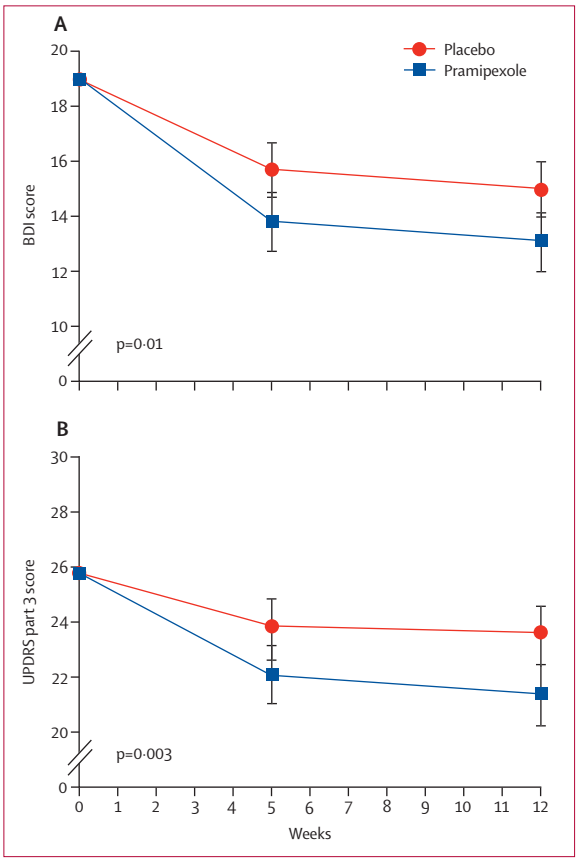

Figure 2: **Change in BDI and UPDRS part 3**
Mean baseline value for the total population and adjusted mean scores at 5 weeks and 12 weeks in the placebo and pramipexole groups on the BDI version 1A (A) and part 3 of the UPDRS (B). Vertical lines represent 95% CIs. p values are for the difference between pramipexole and placebo for adjusted mean change from baseline at 12 weeks. BDI=Beck depression inventory. UPDRS=unified Parkinson's disease rating scale.

105 of 144 patients in the pramipexole group and 101 of 152 in the placebo group had adverse events (table 3). The most common treatment-emergent adverse event was nausea, followed by headache, dizziness, and somnolence. 12 patients in the pramipexole group and six in the placebo group had severe adverse events, and six patients in the pramipexole group and six in the placebo group had serious adverse events.

Treatment-related adverse events were reported in 73 of 144 pramipexole recipients and 63 of 152 placebo recipients (table 3). The most common treatment-related adverse events were nausea, somnolence, dizziness, and dyskinesia. These events occurred in a similar number of people in the two groups, except for dyskinesia, which was more common in the pramipexole

See Online for webappendix

	Pramipexole (n=139)	Placebo (n=148)	Treatment group comparison	p
GDS-15 score	−2·5 (0·3)	−1·7 (0·3)	−0·8 (−1·5 to −0·1)*	0·035†
UPDRS part 2	−2·4 (0·3)	−1·2 (0·3)	−1·2 (−1·9 to −0·4)*	0·003†
UPDRS part 3	−4·4 (0·6)	−2·2 (0·5)	−2·2 (−3·7 to −0·7)*	0·003†
Visual analogue scale pain score	−3·5 (1·9)	−3·0 (1·8)	−0·5 (−5·6 to 4·6)*	0·85†
Snaith-Hamilton pleasure scale	0·0 (−2·0 to 0·0)	0·0 (−2·0 to 0·0)	0·0 (−1·0 to 0·0)‡	0·52§
PDQ-39 total score¶	−3·3 (−8·9 to 0·3)	−2·4 (−8·9 to 2·6)	−1·3 (−3·3 to 0·8)‡	0·19§
EuroQol total score**	0·07 (0·00 to 0·21)	0·00 (−0·06 to 0·12)	0·04 (0·00 to 0·09)‡	0·034§
BDI clinical responders††	38 (27%)	27 (18%)	1·8 (1·0 to 3·1)‡‡	0·05§§
CGI-I much or very much improved¶¶	46 (33%)	32 (22%)	1·8 (1·2 to 2·8)‡‡	0·006§§

Data are adjusted mean (SE), median (IQR), or number (%). GDS-15=15-item geriatric depression scale. UPDRS=unified Parkinson's disease rating scale. PDQ-39=39-item Parkinson's disease questionnaire. BDI=Beck depression inventory. CGI-I=clinical global impression of improvement. *Difference in adjusted means (95% CI). †ANCOVA adjusted for baseline BDI score and pooled country. ‡Hodges-Lehman estimate of difference in medians and stratified for pooled country (95% CI). §Wilcoxon rank sum test. ¶Pramipexole group n=108, placebo group n=127. **Pramipexole group n=136, placebo group n=144. ††Pramipexole group n=139, placebo group n=147; responder defined as at least a 50% reduction in BDI total score from baseline to week 12. ‡‡Odds ratio (95% CI). §§Logistic regression adjusted for baseline BDI score and pooled country. ¶¶Analysis done on all seven CGI-I categories, but for this summary we report only the two improved categories.

Table 2: **Secondary endpoints**

	Pramipexole (n=144)	Placebo (n=152)
Any	105 (73%)	101 (66%)
Severe	12 (8%)	6 (4%)
Serious	6 (4%)	6 (4%)
Treatment emergent*	105 (73%)	101 (66%)
Nausea	24 (17%)	26 (17%)
Headache	16 (11%)	12 (8%)
Dizziness	16 (11%)	9 (6%)
Somnolence	15 (10%)	12 (8%)
Dyskinesia	10 (7%)	4 (3%)
Vertigo	10 (7%)	4 (3%)
Fatigue	8 (6%)	9 (6%)
Insomnia	8 (6%)	4 (3%)
Treatment-related†	73 (51%)	63 (41%)
Nausea	20 (14%)	20 (13%)
Somnolence	12 (8%)	12 (8%)
Dizziness	12 (8%)	9 (6%)
Dyskinesia	10 (7%)	3 (2%)
Headache	7 (5%)	6 (4%)
Fatigue	6 (4%)	5 (3%)
Vertigo	6 (4%)	3 (2%)
Hallucination	6 (4%)	1 (1%)
Insomnia	5 (3%)	3 (2%)
Orthostatic hypotension	5 (3%)	3 (2%)

Data are number (%). Adverse events listed by medDRA preferred term. *All adverse events occurring during the study and reported by at least 5% of patients in either group. †Adverse events related to the investigational drug as assessed by the local investigator and reported by at least 3% of either group.

Table 3: **Adverse events**

group. Although no specific assessments of impulse control disorders were undertaken, no pramipexole recipient reported any adverse event that suggested development of an impulse control disorder or behaviours related to impulse control disorders (data not shown).

Discussion

We did a large placebo-controlled trial specifically evaluating treatment of depressive symptoms in Parkinson's disease. Although two placebo-controlled trials have assessed tricyclic antidepressants and SSRIs for the treatment of depression in patients with Parkinson's disease, the populations of those trials (n=48 and n=52) were substantially smaller than that of the present study.[9,10] The tolerability profile reported in this study was generally consistent with the known safety profile of pramipexole and showed no new adverse events.

Overall improvement in quality of life of patients in this study was modest, probably because the depressive symptoms and motor impairment of most patients were of mild-to-moderate severity. However, there was an overall association between improvement in depression severity and quality of life, consistent with previous research reporting that treatment of depression in Parkinson's disease improves quality of life.[37]

We report the efficacy of a dopamine agonist on depressive symptoms in patients with Parkinson's disease; scores on both the primary (BDI) and secondary (GDS-15) outcome measures showed substantially greater improvement with pramipexole than with placebo. The BDI is a recommended instrument for measuring severity of depression in Parkinson's disease.[20] Although the GDS-15 has not been validated as an outcome measure for treatment studies in patients with depression, it might be sensitive to changes in depression severity[20] and the GDS-15 is deemed to be appropriate for use in Parkinson's disease given its lack of focus on somatic symptoms.[23]

Dysfunction in dopaminergic pathways contributes to depression,[38] and an effect of pramipexole on individuals with major depression who do not have Parkinson's disease has previously been reported.[13] However, in patients with Parkinson's disease, depression can also arise as a result of specific Parkinson's disease-related symptoms, such as motor fluctuations, and any treatment

that improves motor symptoms could potentially improve a patient's mood. The two randomised trials that tested antidepressants in patients with Parkinson's disease did not differentiate between patients with and without motor fluctuations.[9,10] Furthermore, since neither of these studies used the BDI as either a primary or secondary outcome measure (one used the Montgomery-Asberg depression rating scale[9] and the other used the Hamilton depression rating scale[10]), they cannot be directly compared with the results reported here. In the present study, an inclusion criterion was that patients had motor symptoms under control and did not experience motor fluctuations. Additionally, in the path analysis, the effects of pramipexole were predominantly mediated by a direct effect on depressive symptoms (80%), with the remaining 20% of the total effect mediated through alleviation of motor symptoms.

This study has several limitations. The between-group difference of 2 points on the BDI at the end of the study suggests a small treatment effect. This relatively small difference is not surprising given that patients on average experienced depression of mild-to-moderate severity according to their mean baseline GDS-15 and BDI scores, which might have limited the potential size of treatment effect and the generalisability of the present findings to patients with severe depression. Recent research has confirmed that small treatment effects are seen in studies that enrol patients with milder forms of depression.[39] Nevertheless, the overall change in severity of depression was associated with improvement in quality of life, particularly in pramipexole-treated patients, suggesting that decreasing the severity of depression in this study did have tangible benefits.

Inclusion of patients in the study was on the basis of self-rated depression severity scales rather than formal diagnostic criteria applied in a research interview; we do not know whether results would have differed if patients had been enrolled on the basis of a formal diagnosis of depression. Also, the study population primarily included patients who had early and mild-to-moderate Parkinson's disease, thus limiting the generalisability of these findings. However, the selection of patients followed the recommendations of the European Union guideline on clinical investigation of medicinal products in the treatment of Parkinson's disease,[40] and according to Hoehn and Yahr disease stages, 238 patients (80%) had mild disease (stages 1–2·5) and 58 patients (20%) had mild-to-moderate disease (stage 3). Nevertheless, further evaluation of pramipexole as an antidepressant in patients with more advanced Parkinson's disease is warranted.

Although treatment unmasking was possible because of the motor effects of pramipexole, patients were required at baseline to have stable motor function or treatment with levodopa at an optimised dose; the maximum daily dose of pramipexole was limited to 3 mg per day, and improvement of motor symptoms was below the threshold of a minimal clinically relevant difference.[41] Hence, it is unlikely that patients and investigators were unintentionally unmasked during the study.

In conclusion, these results suggest that specific stimulation of dopaminergic pathways as provided by pramipexole should be considered in the management of patients with Parkinson's disease and clinically significant depressive symptoms. This strategy might offer a combined, although independent, benefit on motor disability, depressive symptoms, and quality of life. It remains to be established whether optimising the dose of pramipexole in patients with depressive symptoms already taking this drug can reduce depressive symptoms, and whether the drug is effective for more severe depressive symptoms or in patients with more advanced disease. Finally, direct comparisons between antidepressants and dopamine agonists such as pramipexole are needed to compare the effects of these two drug classes on depressive symptoms of patients with Parkinson's disease.

Contributors

PB was the international principal investigator, designed the study, contributed to the interpretation of the data, and wrote the draft of the report. WP contributed to the study design, recruitment of patients, interpretation of the data, and writing of the report. SA contributed to the study planning, data collection, and writing of the report. CD was the international clinical monitor for the sponsor and contributed to the study planning, data collection, and writing of the report. DM was the statistician and reviewed the final draft of the manuscript. OR and ET contributed to recruitment of patients, interpretation of the data, and writing of the report. DW contributed to the study design, interpretation of the data, and writing of the report.

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Conflicts of interest

PB has received compensation for consulting services and research support from Boehringer Ingelheim, and payment for consulting services and symposia from Novartis, Schwarz Pharma/UCB, Merck-Serono, Eisai, Solvay, General Electric, and Lundbeck. WP has received compensation for consulting services from GlaxoSmithKline, Novartis, Teva, Boehringer Ingelheim, Schwarz Pharma/UCB, AstraZeneca, and General Electric and has received a research grant from Teva. SA, CD, and DM are employees of Boehringer Ingelheim Germany, Boehringer Ingelheim France, and Boehringer Ingelheim UK, respectively. OR has acted as an adviser or consultant for drug companies including Boehringer Ingelheim, GlaxoSmithKline, Novartis, Teva, Lundbeck, Sanofi, Euthérapie, and Eisai, and has received financial support for research programmes from such companies. ET has received honoraria for consulting activities and scientific grants from Boehringer Ingelheim, GlaxoSmithKline, Lundbeck, Novartis, Orion, Medtronic, and Teva. DW has received consulting fees and grant support from Boehringer Ingelheim, and consulting fees from BrainCells, Merck Serono, Novartis, Ovation, Sanofi, and Wyeth.

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