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Long-Term Efficacy and Safety of Pramipexole in Advanced Parkinson's Disease: Results From a European Multicenter Trial

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Abstract: **A double-blind, placebo-controlled study with a subsequent open-label phase was conducted in 354 patients with Parkinson's disease (PD) and motor fluctuations under individually adjusted therapy with levodopa. During the double-blind phase 174 patients received pramipexole and 180 placebo. In agreement with previous studies, pramipexole treatment improved UPDRS sum scores of parts II and III by 30% and *off* times by approximately 2.5 hours per day. Differences between the treatment groups became significant at a daily dose of 0.75 mg of pramipexole dihydrochloride. We, furthermore, performed post hoc analyses with respect to resting tremor and depression. Patients with pronounced resting tremor derived a clear benefit from pramipexole treatment compared with placebo. In addition, pramipexole significantly improved the subitems motivation/initiative and depression in a subpopulation with increased Unified Parkinson's Disease Rating Scale I scores at the time of inclusion. There were 262 patients who were subsequently enrolled into the open-label study featuring a maximum duration of up to 57 months. Statistical analysis revealed good long-term efficacy and tolerability of pramipexole. Overall, only a low prevalence of somnolence was found. In summary, this study provides additional level I evidence of the usefulness of pramipexole, suggests a particular tremorlytic and a possible antidepressant action of this compound, and addresses for the first time its efficacy and safety during long-term administration in advanced PD.** © 2005 Movement Disorder Society

Key words: pramipexole; controlled trial; tremor; depression

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Parkinson's disease (PD) is a progressively disabling neurodegenerative disorder usually treated by dopamine replacement with the precursor levodopa and/or the administration of dopamine agonists (DA). Pramipexole, a nonergoline DA, was introduced for the symptomatic treatment of PD in 1997. It acts as an agonist on the D2 dopamine receptor family and features a preferential affinity to the D3 dopamine receptor. The efficacy and safety of the compound in early and advanced PD have been investigated in several trials.[1–11] In parallel to a large US trial in advanced PD,[3] a multinational study, including 354 PD patients suffering from motor fluctuations was conducted in Europe. The results of this double-blind study were coanalyzed with the subsequent long-term open-label phase of up to 57 months and are presented in this manuscript. This is the fourth study providing level I evidence of the efficacy and safety of pramipexole and the first study on its open-label long-term administration in advanced PD. Besides special attention will be paid to the suggested particular tremorlytic and antidepressant effects of pramipexole and to a safety issue related to somnolence and sudden onset of sleep.[12,13]

PATIENTS AND METHODS

A detailed description of the methods is provided in the online Appendix. Briefly, the double-blind study was designed to compare the efficacy, safety, and tolerability of pramipexole with that of placebo in advanced PD. At least for 30 days before randomization DA had to be washed out, and patients had to experience motor fluctuations characterized as end-of-dose phenomena while receiving an individually adjusted stable dosage of L-dopa. The trial included an ascending-dose phase of up to 7 weeks and a maintenance phase of up to 24 weeks. Pramipexole dihydrochloride or matching placebo was administered t.i.d. as an adjunct to L-dopa in seven dosages from 0.375 to 4.5 mg per day (corresponding to 0.26–3.15 mg of pramipexole). The daily dosage of L-dopa could be reduced in case of dyskinesias, hallucinations, and other psychiatric side effects and subsequently increased if necessary, but not to a level exceeding the original daily dosage. Primary endpoints were the change from baseline to end-of-maintenance of the average Unified Parkinson's Disease Rating Scale (UPDRS) II score during *on* and *off* and the average UPDRS III score during *on*. The UPDRS III ratings were performed during defined *on* periods, i.e., 2 hours after intake of L-dopa and the study medication. Secondary endpoints were based on the change from baseline to end-of-maintenance for the following scales: UPDRS II during *on* periods only; UPDRS I and IV and the total UPDRS scores; average percentage and severity of *off* time during waking hours; dosage of concomitant L-dopa; modified Schwab–England Disability Scale for *on* and *off* periods; modified Hoehn & Yahr Scale for *on* and for *off* periods; Parkinson dyskinesia scale; timed walking test; individual items of UPDRS II and III; and Global Clinical Assessment. Furthermore, the area under the change-from-baseline curve (AUC) during the maintenance period was calculated for the average UPDRS II and III *on* and *off* ratings. The null hypothesis of the double-blind study was that of no difference between the two treatment groups with the alternative hypothesis being that a difference exists.

The protocol specified that the study would be considered successful if using the last observation carried forward (LOCF) analysis on the intent-to-treat (ITT) data set both primary endpoints were significant at the 0.05 level. Because statistical significance required changes in both endpoints, no correction of the alpha level was performed. A sample size of 150 patients per treatment group was calculated to detect a mean difference in the UPDRS III score of 1.8 to 3.6 points at a significance level of 0.05 and with a power of 90%. For statistical analysis of secondary endpoints, see the online appendix. Because of a previously reported benefit of pramipexole on patients with tremor-dominant PD, an unplanned post hoc analysis was performed to explore this effect in all patients and in tremor-dominant patients only.[13] Tremor dominance was arbitrarily defined by two approaches: (1) patients with a baseline sum score of UPDRS III items 16, 20, and 21 during *on* of at least 8 (or 6 if the tremor occurred one-sided only), and (2) patients with a predominant relative contribution of UPDRS tremor items to the baseline UPDRS II and III scores of equal to or more than 20%. In addition, a post hoc analysis was performed with respect to the changes of the UPDRS I subitems in patients with an UPDRS I score >0 at the time of inclusion. This multicenter 32-week, double-blind, placebo-controlled, parallel-group study was followed by an open-label extension trial with a maximum duration of 57 months. The 255 patients who previously participated in the double-blind study ($n = 139$ from the pramipexole group and $n = 116$ from the placebo group) and 7 patients who received pramipexole in an earlier phase II study entered the open-label study ($n = 262$). This study also began with an ascending-dose phase lasting up to 7 weeks. Then patients entered the maintenance phase with a planned duration of 25 months. An additional amendment allowed for the extension of the maintenance phase to a maximum of 55 months if the patient wished to continue the treatment. Primary endpoints of the open-label study were the changes of the average UPDRS II score during *on* and *off*, the UPDRS III score during *on*, and the total UPDRS II–IV score compared to baseline. The open-label study was ana-

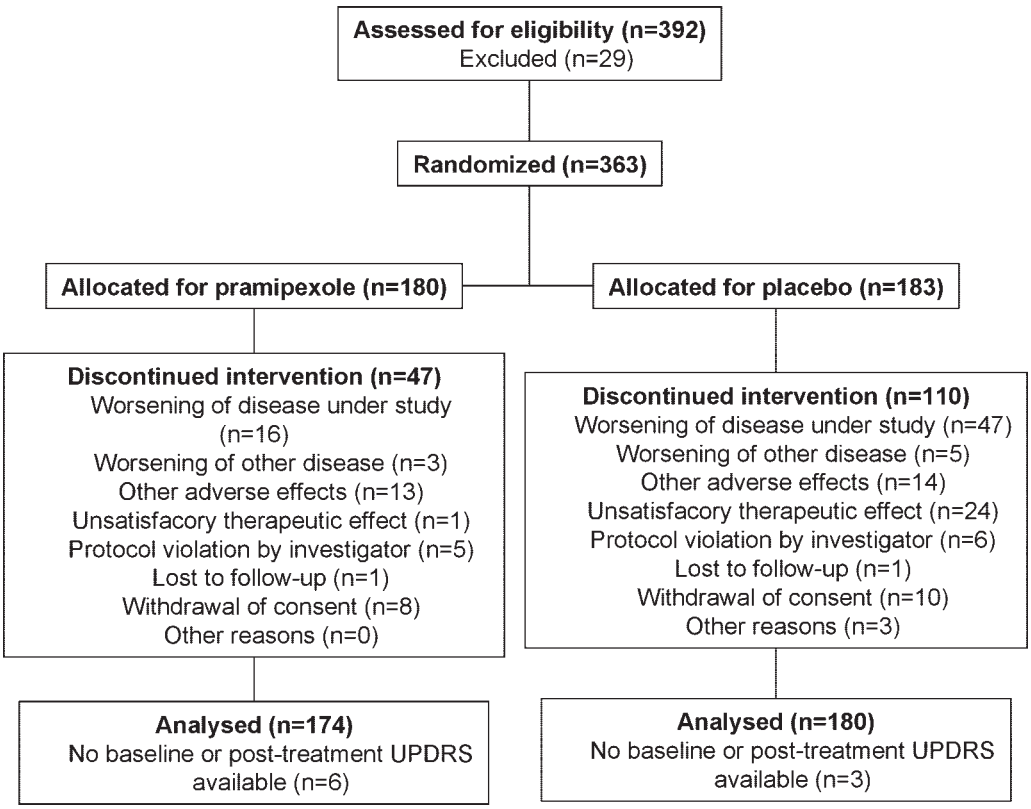

FIG. 1. Randomized patients per treatment group according to the CONSORT statement (double-blind study).

lyzed by descriptive statistics. For the assessment of adverse events, the WHO preferred terms were used.

RESULTS

Demographic Data

The demographic data for the double-blind study are summarized in Figure 1 and Table 1. Of 392 screened patients, 363 were randomized and 206 patients (56%) completed the protocol as planned, i.e., 133 patients of the pramipexole group (64.6%) and 73 patients of the placebo group (35.4%). The ITT population consisted of 354 patients (97.5%) with 174 patients in the pramipexole and 180 patients in the placebo group. A total of 6 patients in the pramipexole and 3 patients in the placebo group were not included into the ITT population, because no baseline or posttreatment UPDRS value was available. The average daily dose in the pramipexole group was 3.7 mg. Of the 160 patients who entered the maintenance phase, 57% were treated with the maximum dose of 4.5 mg pramipexole dihydrochloride per day. With respect to most demographic data, pramipexole- and placebo-treated patients were comparable (Table 1). Demographic or baseline differences were indicated by P values < 0.1. Accordingly, placebo-treated patients were slightly more impaired at baseline than pramipexole-treated patients. Of the 262 patients who entered the open-label study, 137 (52.3%) completed the planned maintenance phase of 25 months. Eighteen patients (6.9%) entered the fifth year of the study. Overall, the mean duration of pramipexole treatment was 32.1 months. The average daily dose of pramipexole dihydrochloride varied between 3.51 and 3.85 mg during the maintenance period. The concomitant daily dose of L-dopa increased slightly from 575 mg at baseline to 584 mg at the last assessment.

Efficacy

Analysis of the results of the double-blind study proved that pramipexole treatment as adjunct to L-dopa treatment was superior to placebo treatment (Table 2). The UPDRS II score (average of *on* and *off*) in the pramipexole group improved from 12.3 at baseline to 8.0 at end-of-maintenance compared with 13.6 and 11.8, respectively, in the placebo group ($P = 0.0001$). The UPDRS III score during defined *on* in the pramipexole group decreased from 27.5 at baseline to 17.2 at end-of-

TABLE 1. *Patient demographics at baseline (double-blind study)*

Characteristics of ITT population	Pramipexole	Placebo	Total	*P*
Patients (n)	174	180	354	
Gender, n (%)				0.27
M	108 (62.1)	122 (67.8)	230 (65.0)	
F	66 (37.9)	58 (32.2)	124 (35.0)	
Age, yr (mean)	63.4	64.7	64.0	0.32
Duration of PD (yr)	7.6	7.9	7.8	0.50
Smokers and ex-smokers	58 (33.3)	59 (32.8)	117 (33.0)	0.64
Alcohol consumption	84 (48.3)	95 (52.8)	179 (50.6)	0.46
Daily levodopa dose, mg (mean)	637.7	648.8	643.3	0.82
L-deprenyl use	82 (47.1)	84 (46.7)	166 (46.9)	1.00
Anticholinergics use	55 (31.6)	47 (26.1)	102 (28.8)	0.29
UPDRS total score during *on* (mean)	46.7	50.7	48.7	0.04
UPDRS II (average of *on* and *off*)	12.3	13.6	13.0	0.07
UPDRS III during *on* (mean)	27.5	29.8	28.7	0.07
Hoehn and Yahr stage during *on*				0.02
1	1 (0.6)	1 (0.6)	2 (0.6)	
1.5	2 (1.1)	1 (0.6)	3 (0.8)	
2	90 (51.7)	78 (43.3)	168 (47.5)	
2.5	58 (33.3)	56 (31.1)	114 (32.2)	
3	21 (12.1)	37 (20.6)	58 (16.4)	
4	2 (1.1)	7 (3.9)	9 (2.5)	

Values are expressed as n (%), unless otherwise indicated.
ITT, intention to treat; PD, Parkinson's disease; UPDRS, Unified Parkinson's Disease Rating Scale.
T1: Please indicate the significance of boldface values.

maintenance compared with 29.8 and 25.3, respectively, in the placebo group ($P = 0.0007$). A visit-by-visit analysis of UPDRS II and III scores showed that pramipexole was significantly superior to placebo after 2 weeks of treatment at a scheduled daily dose of 0.75 mg of pramipexole dihydrochloride ($P < 0.0036$; data not shown). The beneficial effect of the study drug was maintained over all visits as demonstrated by a significant difference in AUC reduction of UPDRS II and III scores (Table 2). Because of the slight baseline imbalance in UPDRS II and III scores, additional statistical analyses (analysis of covariance) were performed, confirming the above results of a favorable treatment effect by pramipexole for both endpoints ($P < 0.0001$). Superiority of pramipexole over placebo could also be shown for the secondary endpoints (Table 2). The decrease in percentage of *off* time of 15.2% equals a reduction of approximately 2.5 hours per day. The only (expected) exception was the Parkinson's dyskinesia scale. Besides the difference between both groups was not significant for the Hoehn & Yahr scale during *on* (Table 2). Defining responders as patients with an improvement in the total UPDRS score by 30% or more, 56.9% (n = 99) of the pramipexole-treated patients were responders compared with 28.3% (n = 51) in the placebo group. Furthermore, 39.1% of the patients in the pramipexole group reduced the L-dopa dosage versus 12.8% of the placebo-treated patients. Accordingly, the mean reduction of L-dopa was higher in the pramipexole group than in the placebo group (103 mg vs. 18 mg). The relatively high number of premature withdrawals in the placebo group (61.1%) did not generate biased results, as the LOCF technique guaranteed a balanced sample for analysis. However, it has to be acknowledged that a significant center effect was observed when testing the primary endpoints. Confidence intervals for the mean effect per center revealed that, in five small centers, placebo was superior to pramipexole, whereas the treatment effect was in favor of pramipexole in the remaining centers. A total of 256 patients of the open-label study could be used for the analysis of efficacy, because they had both baseline and at least one postbaseline UPDRS assessment. Pramipexole decreased the score of the primary endpoints with a gradual decline of improvement over time. The results for the total UPDRS II–IV score are shown in Table 3.

Safety

During the double-blind study the most commonly reported drug-related adverse events (≥ 10%) were dyskinesia (30.0% in the pramipexole group vs. 8.7% in the placebo group), asymptomatic orthostatic hypotension (23.3% vs. 20.2%), nausea (16.1% vs. 12.0%), visual hallucination (11.1% vs. 4.4%), and dizziness (10.6% vs. 7.1%). The global judgment on tolerance was comparably good in both treatment groups (86.8% for pramipexole, 88.9% for placebo). A total of 27% of all patients (17.8% in the pramipexole group and 36.1% in

TABLE 2. *Analysis of efficacy endpoints (double-blind study)*

	Pramipexole	Placebo	*P*
Primary endpoints			
UPDRS Part II (average of *on* and *off*)[a]	−4.3 (4.6)	−1.80 (4.2)	0.0001
UPDRS Part III *on*[a]	−10.3 (12.0)	−4.43 (11.1)	0.0001
Secondary endpoints*			
UPDRS II AUC (average of on and *off*), change[a]	−88.9 (85.3)	−39.5 (80.4)	0.0001
UPDRS III AUC (during *on*), change[a]	−209.7 (223.6)	−98.6 (218.3)	0.0001
UPDRS IV, i.e. motor complications, change[a]	−1.1 (2.3)	−0.5 (2.2)	0.0114
UPDRS total score, change[a]	−16.4 (16.5)	−7.0 (15.3)	0.0001
UPDRS II during on, change[a]	−2.5 (4.1)	−1.2 (3.8)	0.0007
Average change of *off* time during waking hours (Percentage)[a]	−16.2 (21.6)	−1.0 (25.9)	0.0001
Timed-walking test (sec), Final[a]	26.1 (38.9)	32.8 (50.2)	0.0334
UPDRS I[b]			0.020
Missing	0 (0.0)	0 (0.0)	
Increase	22 (12.6)	43 (23.9)	
No change	74 (42.5)	69 (38.3)	
Decrease	78 (44.8)	68 (37.8)	
Daily levodopa dose[b]			0.001
Increase	5 (2.9)	8 (4.4)	
No change	101 (58.0)	149 (82.8)	
Decrease	68 (39.1)	23 (12.8)	
Parkinson dyskinesia scale[b]			0.194
Missing	0 (0.0)	0 (0.0)	
Increase	37 (21.3)	25 (13.9)	
No change	97 (55.7)	111 (61.7)	
Decrease	40 (23.0)	44 (24.4)	
Average severity of *off* periods[b]			0.035
Missing	13 (7.5)	18 (10.0)	
Increase	23 (13.2)	36 (20.0)	
No change	60 (34.5)	63 (35.0)	
Decrease	78 (44.8)	63 (35.0)	
Global clinical assessment of efficacy[b]			<0.001
Good (+, ++)	147 (84.5)	60 (33.3)	
Poor (−,− −)	21 (12.1)	109 (60.6)	
Not assessable	6 (3.4)	11 (6.1)	
Modified Schwab-England in *on*[b]			<0.001
Missing	0 (0.0)	0 (0.0)	
Increase	73 (42.0)	39 (21.7)	
No change	89 (51.1)	101 (56.1)	
Decrease	12 (6.9)	40 (22.2)	
Modified Schwab-England in *off*[b]			<0.001
Missing	0 (0.0)	1 (0.6)	
Increase	111 (63.8)	70 (38.9)	
No change	44 (25.3)	66 (36.7)	
Decrease	19 (10.9)	43 (23.9)	
Modified Hoehn and Yahr in *on*[b]			0.059
Missing	0 (0.0)	0 (0.0)	
Increase	15 (8.6)	22 (12.2)	
No change	86 (49.4)	99 (55.0)	
Decrease	73 (42.0)	59 (32.8)	
Modified Hoehn and Yahr in *off*[b]			<0.001
Missing	0 (0.0)	1 (0.6)	
Increase	6 (3.4)	19 (10.6)	
No change	62 (35.6)	108 (60.0)	
Decrease	106 (60.9)	52 (28.9)	

*Pramipexole, n = 174; placebo, n = 180.
[a]Values are expressed as mean (SD).
[b]Values are expressed as n (%).

the placebo group) had an adverse event that led to discontinuation of the study medication. With respect to single adverse events resulting in withdrawal from the trial, aggravated parkinsonism was reported in 7.2% of the patients treated with pramipexole and in 25.7% of the patients treated with placebo. No further single adverse event was noticed as a predominant reason for premature discontinuation of the trial. During the open-label study,

TABLE 3. *Total UPDRS II–IV scores (open-label study)*

Selected time point	N	Baseline	End	Difference	% Change
End of first year	229	40.0 (18.5)	26.8 (15.7)	−13.2 (15.8)	−27.1 (49.6)
End of second year	186	39.2 (18.7)	29.0 (17.6)	−10.2 (17.3)	−18.3 (48.5)
End of third year	116	37.5 (18.0)	29.2 (16.7)	−8.4 (15.6)	−13.7 (49.1)
Last observation after year 3	98	36.7 (17.8)	29.9 (18.3)	−6.8 (15.9)	−11.0 (50.6)
Last assessable observation	255	41.4 (19.6)	34.2 (19.3)	−7.2 (17.0)	−9.5 (50.2)

Values are expressed as mean (SD), unless otherwise indicated.
UPDRS, Unified Parkinson's Disease Rating Scale.

frequent drug-related adverse events (≥ 5%) were asymptomatic orthostatic hypotension (35.5%), dyskinesia (34.4%), visual hallucination (13.0%), symptomatic orthostatic hypotension (11.1%), nausea (9.5%), vertigo (8.8%), dizziness (8.0%), confusion (5.3%), hyperkinesia (5.0%), and fatigue (5.0%). Of all patients, 23.7% had an adverse event that resulted in discontinuation of the study medication. The most frequent adverse events leading to premature discontinuation were aggravated parkinsonism (6.9%), visual hallucination (3.1%), dyskinesia (2.3%), hypokinesia (1.5%), confusion (1.5%), and insomnia (1.5%). Pleural fibrosis was not observed. The rate of adverse events did not increase with time but remained constant. None of the fatal adverse events (n = 15) was assessed as drug-related.

Resting Tremor, Depression, and Somnolence

Post hoc analysis showed that the change in the tremor scores from baseline was significant in favor of pramipexole within the whole ITT population (P = 0.0001) as well as in the investigated subpopulations (Wilcoxon–Mann–Whitney test; Table 4). Furthermore, the subgroup analysis of patients with an UPDRS I score > 0 at the time of inclusion showed that the decrease in the UPDRS I score was mainly due to improvement in the subitems motivation/initiative (P = 0.0022) and depression (P = 0.0121; Table 5). Depression as treatment-emergent side effect was reported by 0.6% in the pramipexole group and 4.9% in the placebo group (P = 0.012). Recent publications have drawn attention to treatment-induced somnolence and its consequences when occurring during activities of daily living such as driving.[12] In the double-blind study, somnolence was spontaneously reported by 3 patients in the pramipexole group (1.7%) versus four in the placebo group (2.2%). In the open-label study, somnolence was observed in 7 patients (2.7%). No motor vehicle accidents or events of falling asleep at the wheel were recorded. Furthermore, somnolence was not related to

TABLE 4. *Post hoc analysis of tremor (double-blind study)*

	Pramipexole n = 174	Placebo n = 180	*P*
Tremor score (UPDRS Items 16, 20, 21)			
Baseline	4.6 (4.7)	4.4 (4.3)	
Final	2.1 (3.2)	3.9 (4.3)	
Change	−2.5 (4.1)	−0.5 (3.8)	0.0001
Low tremor score at baseline (N)	132	141	
Tremor score < 6 (one-sided)/8 (two-sided)			
Baseline	2.4 (2.4)	2.5 (2.3)	
Final	1.5 (2.3)	2.5 (3.2)	
Change	−0.9 (2.4)	0.0 (2.9)	0.0029
High tremor score at baseline (N)	42	39	
Tremor score ≥ 6 (one-sided)/8 (two-sided)			
Baseline	11.5 (3.2)	11.3 (2.7)	
Final	3.5 (4.5)	7.6 (5.4)	
Change	−8.00 (4.2)	−3.7 (5.7)	0.0002
Low tremor contribution at baseline (<20%)			
N	137	158	
Change	−1.4 (3.1)	−0.3 (3.5)	0.0015
High tremor contribution at baseline (≥ 20%)			
N	37	22	
Change	−6.6 (4.8)	−2.4 (5.5)	0.0049

Values are expressed as mean (SD), unless otherwise indicated.
UPDRS, Unified Parkinson's Disease Rating Scale.

TABLE 5. *Post hoc analysis of UPDRS I subitems in patients with an UPDRS I score > 0 (double-blind study)*

	Placebo	Pramipexole	Total
Depression			
Improved	41 (45.6)	58 (67.4)	99 (56.3)
Unchanged	44 (48.9)	24 (27.9)	68 (38.6)
Worsened	5 (5.6)	4 (4.7)	9 (5.1)
Total	90 (100.0)	86 (100.0)	176 (100.0)
Motivation/initiative			
Improved	40 (43.5)	53 (63.1)	93 (52.8)
Unchanged	40 (43.5)	30 (35.7)	70 (39.8)
Worsened	12 (13.0)	1 (1.2)	13 (7.4)
Total	92 (100.0)	84 (100.0)	176 (100.0)

Values are expressed as mean (SD).
UPDRS, Unified Parkinson's Disease Rating Scale.

premature discontinuation of the double-blind or open-label trial.

DISCUSSION

The double-blind study has demonstrated that pramipexole dihydrochloride administered at doses between 0.375 and 4.5 mg per day as an adjunct therapy to L-dopa was superior to placebo treatment as assessed by both primary endpoints. The therapeutic benefit started early, i.e., it was significant at a scheduled daily dose of 0.75 mg of pramipexole dihydrochloride. Because the protocol of this study asked the investigators to ascend dosages to maximally tolerated levels over a period of 7 weeks, dosages were often further increased without causing relevant dose-related toxicity, safety, or tolerability problems. The therapeutic benefit was maintained over the whole duration of the double-blind study without an indication of loss of efficacy over time. Further evidence for the robustness of the treatment effect was provided by the significant superiority of pramipexole over placebo in the secondary endpoints. The reduction of *off* time by approximately 2.5 hours per day (compared with 10 minutes in the placebo group) revealed clinical benefit immediately perceived by the patients. Other signs for the efficacy of pramipexole in the treatment of advanced PD were the high responder rate (improvement in the total UPDRS score of more than 30%) and the dose reduction of L-dopa in a considerable proportion of the pramipexole patients (partly due to dys- or hyperkinesia). Furthermore, a substantially greater number of patients under pramipexole than under placebo treatment completed the trial. Because the LOCF technique on the ITT data set was used, the efficacy of pramipexole was possibly underestimated due to the hypothetically pronounced influence of disease progression in the pramipexole group. Thus, the results of this large European phase III trial are overall in line with the observations of a similar US trial and confirm the outcome of other smaller studies on the efficacy of pramipexole in advanced PD.[2–4,7,13,14] Compared with the US trial, percentage improvement of UPDRS Part III during *on* phase was more pronounced in the present study (37% vs. 22%), which may be due to the examination of the patients during defined *on* periods, i.e., 2 hours after drug intake. This phenomenon may reflect a reduced severity of the beginning *off* period, i.e., a prolonged *on*. Alternatively, this observation can also be due to the lower mean L-dopa dose/day at baseline in our patient population (643.3 mg vs. 831.9 mg), possibly entailing the more marked improvement in our pramipexole-treated patients than in those of the US trial. Other minor differences include a higher number of premature discontinuation due to worsening of disease or unsatisfactory therapeutic effect in the placebo group and a significant effect of pramipexole in the timed-walking test and a lower L-dopa dose reduction (16% vs. 27%) in the pramipexole group of this study.

A study on the use of pramipexole versus L-dopa over 23.5 months in early PD patients suggested that pramipexole delays the occurrence of motor fluctuations.[10] However, to our knowledge, no data have been published on the efficacy of pramipexole in advanced PD over a period of more than 36 weeks.[4] The moderate decrease in clinical improvement during the long-term open-label phase in our study was anticipated, taking the usual disease progression into account. This is, therefore, the first study to provide evidence that pramipexole is efficient in the long-term treatment of advanced PD, i.e., over a period of more than 4 years in some patients, which reflects the clinical experience with this compound.

A particular tremorlytic action of pramipexole has been proposed by a previous study on a subset of patients from this trial.[8] Another study, which included long-term electromyographic recordings, provided further evidence of a pronounced tremorlytic effect.[13] Therefore, the effect of pramipexole on parkinsonian tremor was explored in more detail in this study. Tremor was significantly improved in the subpopulations with either a high tremor score or a high contribution of tremor to the total UPDRS II and III scores. It is noteworthy that placebo also led to a moderate improvement in patients with a high tremor score. While this subanalysis does not allow the conclusion that pramipexole acts predominantly on tremor, its tremorlytic action as outlined by the results of this study seems remarkable. This notion has been called into question by a recent small study in 30 PD patients comparing the tremorlytic effects of pramipexole, pergolide, and placebo.[15] This double-blind, single-dose, cross-over trial was powered to detect a 40% difference in the used tremor index

between the active treatments. In the future, larger controlled trials comparing the antitremor efficacy of different DA will be of pharmacological and clinical relevance.

Apart from its antiparkinsonian potency, pramipexole is also characterized by an antidepressant action in patients with major depression.[16] Most previous studies in advanced PD patients, however, did not detect a significant difference in the UPDRS I subscore assessed as a secondary endpoint.[3,4,9] In line with the publication by Wermuth and The Danish Pramipexole Study Group,[7] we observed significant improvement in the UPDRS I subscore in our study. An analysis of the UPDRS I subitems demonstrated that the difference between the treatment groups was due to an amelioration of motivation/initiative and depression, whereas no significant changes were observed with respect to intellectual impairment and thought disorder. Additional supportive evidence of an antidepressant action of pramipexole is provided by the observation that depression as an adverse event was significantly less frequently reported in the pramipexole group than in the placebo group. However, the study design did not allow to distinguish between primary (i.e., pharmacological) and secondary (i.e., through improvement of motor functions) antidepressant effects of pramipexole. A recent small open-label study has reported that pramipexole but not pergolide led to significant improvement in the Montgomery and Asberg Depression Rating Scale in patients suffering from both depression and advanced PD.[17] Thus, further studies are justified to investigate whether or not pramipexole has a specific antidepressant effect in PD patients.

The safety profile of the study drug within the tested dose range of 0.375 to 4.5 mg of pramipexole dihydrochloride per day seemed to be manageable and was expected for a DA and for patients of this age. A noteworthy difference in the safety profile was seen with regard to a considerably increased rate of visual hallucination under pramipexole treatment (11.1% vs. 4.4%). With respect to orthostatic hypotension, nausea, and dizziness, only minor differences were observed. These results are in agreement with those of the previous studies and underline the overall good tolerability of pramipexole in terms of the classic peripheral dopaminergic side effects. Good tolerability can also be achieved by the antiparkinsonian efficacy of relatively low doses of pramipexole. The open-label study provides the first data on the long-term (i.e., more than 4 years in some cases) tolerability and safety of pramipexole in advanced PD. If elicited by the occurrence of adverse events, premature discontinuation of the open-label study was usually due to worsening of disease or to central nervous system–related side effects such as visual hallucinations but not to classic peripheral dopaminergic side effects. Overall, the obtained data show that pramipexole represents a safe and well-tolerated option in the long-term treatment of advanced stages of PD.

The occurrence of somnolence during DA treatment and its potential impact on activities of daily living recently has been brought to attention by the occurrence of motor vehicle mishaps under pramipexole treatment.[12] In the present study, no apparent difference in the overall low somnolence rates between the treatment groups was observed. Recent studies have shown that more than half of all PD patients suffer from excessive daytime sleepiness and that up to 23% have experienced falling asleep while driving.[18,19] In these (and other) studies, all DAs were shown to be associated with these somnolence-related side effects. However, sudden onset of sleep has been described only after the end of the present study. The low rate of somnolence in our study, therefore, probably indicates that excessive daytime sleepiness and sudden onset of sleep are usually not reported spontaneously, which underlines the need for a detailed assessment of somnolence-related side effects by the physician.

In summary, the present study confirms the efficacy and safety of pramipexole in the treatment of advanced PD and shows for the first time that pramipexole is a safe and well-tolerated drug also during long-term administration. It may be of particular interest to the clinician for two principal reasons. First, pramipexole seems to have a low frequency of cardiovascular and gastrointestinal side effects. Second, pramipexole may possess a particular antitremor efficacy and, therefore, can be tried in PD patients with predominant resting tremor. Its antidepressant action in PD awaits further clarification.

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HIV Encephalitis Simulating Huntington's Disease

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Abstract: **Complications from human immunodeficiency virus (HIV)/acquired immune deficiency syndrome are notorious for mimicking other neurological diseases. We describe a case of HIV encephalitis presenting with the classic clinical features of Huntington's disease in a woman without known HIV risk factors or other clinical stigmata suggestive of immunosuppression. This case reminds us that HIV should be part of the differential diagnosis in unexplainable neurological diseases.** © 2005 Movement Disorder Society

Key words: HIV; encephalitis; dementia; chorea

Pathological hyperkinetic movements in those infected with human immunodeficiency virus (HIV) are rare. Unilateral chorea or ballismus are the most reported forms, usually betraying a toxoplasmosis abscess in a contralateral basal ganglia.[1–6] We report a case of slowly progressive generalized chorea, behavioral changes, and

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