PAPER

Pramipexole in patients with Parkinson's disease and marked drug resistant tremor: a randomised, double blind, placebo controlled multicentre study

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Objective: To compare the tremorlytic properties of pramipexole, a non-ergoline dopamine agonist to those of placebo as add on medication in patients with Parkinson's disease.
Methods: Eighty four patients with early or advanced Parkinson's disease and marked, drug resistant tremor under a stable and optimised antiparkinsonian medication were included in a double blind, randomised, placebo controlled, multicentre study and assigned to add on treatment (7 week dose titration interval, 4 week maintenance period) with either pramipexole (n=44) or placebo (n=40) as adjunct. The primary end point was the absolute change in tremor score, defined as the sum of tremor related items (16, 20, 21) of the unified Parkinson's disease rating scale (UPDRS) in "on" periods. Secondary end points included the percentage change in tremor score, the absolute and percentage changes in long term EMG tremor registration, and the change in tremor self rating scales. Safety and tolerability were assessed on the basis of adverse events, laboratory tests, ECG, and vital signs.
Results: Pramipexole was significantly superior to placebo with a difference between treatment groups in the mean absolute change in tremor score of –4.4 (95% confidence interval (95% CI) –6.2 to –2.5) ($p<0.0001$), corresponding to a difference in the mean percentage change of –34.7% in favour of pramipexole. The secondary end points were consistent with the significant change in tremor score and provided further evidence for the benefit of pramipexole compared with placebo. Long term EMG registration as an objective measure showed a difference in mean absolute change in tremor occurrence of –15.2% (95%CI –21.4 to –9.0) ($p<0.0001$), and a difference in the mean percentage change of –45.7% in favour of pramipexole. The treatment effects increased during dose titration and remained stable during the 4 week maintenance dose period until the end of the study. The average daily pramipexole dose during maintenance was 4.1 (SD 0.9) mg. Safety analysis showed an increased rate of fatigue, insomnia, nausea, abdominal pain, and headache under pramipexole, comparable with previous studies.
Conclusion: Pramipexole proved to be an effective agent for patients with Parkinson's disease and drug resistant tremor.

Tremor at rest is one of the cardinal symptoms of Parkinson's disease and the first sign in about 75% of patients. A minority of patients will present with tremor as the predominant symptom throughout the course of the disease (tremor dominant Parkinson's disease).[1] Antiparkinsonian drugs usually provide effective treatment for bradykinesia and rigidity, whereas drug treatment of tremor may be more difficult: parkinsonian tremor is sometimes resistant to currently available medication or sufficient pharmacotherapy may cause intolerable side effects and lead to discontinuation of treatment (drug resistant tremor).[2] Stereotactic neurosurgery with deep brain stimulation (nucleus ventralis intermedius thalami, subthalamic nucleus) or thalamotomy may lead to excellent tremor reduction, but is—at least in the short term—an expensive approach with rare but potentially severe side effects,[3–6] and is limited to specialised centres. Therefore, new antiparkinsonian compounds are to be investigated with respect to their efficacy on predominant and drug resistant parkinsonian tremor.

Pramipexole is a novel non-ergoline dopamine agonist with high binding specificity for the dopamine D2 receptor family and with preferential affinity to the dopamine D3 receptor subgroup.[7–9] Clinical trials with pramipexole as monotherapy and as an adjunct to levodopa have shown the compound to be safe, well tolerated, and efficacious.[10–14] Recently, sudden onset of somnolence (sleep attacks) was reported to occur in a few patients with pramipexol.[15] This topic is presently under further investigation.

Compared with placebo, pramipexole treated patients showed an improvement in both activities of daily living (ADL) and motor scores as assessed by the unified Parkinson's disease rating scale (UPDRS) in early and advanced Parkinson's disease, and a reduction of duration and severity of "off" periods in advanced Parkinson's disease.[10–14] In most of these trials, tremor items were not analysed separately or there were no systematic investigations of patients with predominant tremor. However, descriptive analyses of placebo controlled trials of pramipexole showed that the incidence of tremor, reported as a newly occurring symptom during the studies (507 patients, 251 under pramipexole, 256 under placebo) was less frequent in patients taking pramipexole compared with placebo.[16] Based on an exploratory subanalysis of patients from one study centre of a placebo controlled multicentre trial in advanced Parkinson's disease, pramipexole seemed to have potent tremorlytic activity: besides overall antiparkinsonian

Abbreviations: UPDRS, Unified Parkinson's disease rating scale; ADL, activities of daily living; LOCF, last observation carried forward; SAEs, serious adverse events

effects, pramipexole led to a statistically significant improvement in UPDRS tremor scores in a subgroup of 16 patients with previously drug resistant tremor.[17]

As a consequence of these findings, the present trial was conducted to investigate the tremorlytic properties of pramipexole compared with placebo as an add on therapy in patients with early or advanced Parkinson's disease presenting with marked and previously drug resistant tremor.

METHODS

Study design

The study followed a double blind, placebo controlled, randomised, multicentre, parallel group comparative design. The trial was conducted according to the principles of good clinical practice and was approved by local ethics committees at each centre. Written informed consent had to be given by all participants. A total of four study sites were involved in two European countries. Trial duration was up to 12 weeks. The treatment groups were pramipexole and placebo as add on therapy to a stable and optimised antiparkinsonian medication. The study drugs were administered as tablets with identical appearance and taste. A computer generated randomisation plan that included stratification by centre and block (with a block size of four) was used to ensure a balanced distribution (1:1) of treatment groups within centres. No person directly involved in management or analysis of the trial had access to the treatment assignment during the conduct. After a blinded report planning meeting where the analysis plan was finalised, the database was locked, treatment assignment was added, and no further changes were made to the database.

Inclusion/exclusion criteria

Patients of both sexes with Parkinson's disease (Hoehn and Yahr stage I-IV as assessed after at least 12 hours off medication) according to the United Kingdom Parkinson's disease brain bank criteria were included.[18] Patients had to fullfill the criteria of marked and drug resistant tremor during their medical history—subjects either failed to experience a clinically relevant and useful improvement in tremor under an optimised antiparkinsonian therapy with various agents, or side effects encountered under an effective antitremor therapy were intolerable. Marked tremor was clinically defined by the presence of a sum score of at least eight of 32 of the UPDRS tremor items 16, 20, and 21 (referred to as tremor score) or, if the tremor was present on one side only, by the presence of a tremor score of at least six of 32. The generation of this sum score is based on the validity of the UPDRS regarding tremor,[19] and the clinical experience, that the UPDRS tremor items reflect different but similarly important aspects of Parkinsonian tremor, including the impairment of activities of daily living by tremor.

Tremor was assessed during "on" periods—that is, 2 to 3 hours after the last intake of antiparkinsonian medication.

Patients with atypical parkinsonian syndromes (multiple system atrophy, progressive supranuclear palsy, etc), severe dementia, epilepsy, previous neurosurgery, electroconvulsive therapy within 90 days before randomisation, or severe other physical diseases were excluded. Also excluded were patients with symptomatic orthostatic hypotension—that is, a decline in systolic (diastolic) blood pressure at 1 minute after standing by 20 mm Hg or more compared with supine blood pressure obtained after 5 minutes of quiet rest. Female patients of childbearing potential were required to use medically accepted means of contraception.

The patients had to receive a stable antiparkinsonian medication with levodopa/decarboxylase inhibitor preparations, and/or selegiline, and/or amantadine for at least 30 days before randomisation. Before study inclusion, the medication had to be optimised regarding the symptomatic effects on parkinsonian signs and symptoms and the dose related side effects in each individual patient. Optimisation was mainly performed by adjusting the levodopa dose either by increasing the number of doses or increasing the dosage in each dose.

Concomitant treatment with the following agents was not allowed during the past month (neuroleptic drugs and metoclopramide: the past 2 months) before randomisation: dopamine agonists, MAO inhibitors except for selegiline, anticholinergic drugs, budipine, reserpine, (classic) neuroleptic drugs, metoclopramide, methylphenidate hydrochloride, amphetamine derivatives, α methyldopa, cinnarizine, and flunarizine.

Efficacy criteria

The primary end point was the absolute change in tremor score during "on" periods from baseline to the end of maintenance. Secondary end points were (1) absolute and relative (percentage) changes in separate tremor score items, and other UPDRS scores, (2) changes in two tremor self rating scales based on a patient's diary, (3) absolute and relative (percentage) changes in "tremor occurrence" as measured by a long term EMG registration, and (4) a global assessment of the effect on tremor.

Tremor score

Tremor score was calculated as the sum of UPDRS items 16, 20, and 21. Evaluation was done during an "on" period. "On"periods were defined as 2 to 3 hours after the last intake of study medication together with levodopa preparations and/or other antiparkinsonian drugs, if applicable.

UPDRS scores

UPDRS part II (ADL) was evaluated for "on" and "off" periods and the average calculated, a procedure consistent with other Parkinson's disease studies.[10 11] UPDRS part III (motor examination) was evaluated during "on" periods. The sum of both was calculated as the combined UPDRS II/III score.

Patient's diary

The patient's diary consisted of two tremor self rating scales[19]: (1) Impairment of daily living by tremor and (2) severity of tremor.

(1) Impairment of daily living by tremor is a 21 item checklist of daily living tasks (for example, cutting with a knife, using a spoon, brushing teeth etc). The best performance for each item per day is rated using a four point scale (0, no difficulty; 1, slight difficulty; 2, considerable effort; and 3, cannot be fulfilled). The maximum score is 63 points.

(2) Severity of tremor is rated on a five point scale (0, missing; 1, mild; 2, moderate but occasionally occurring; 3, moderate but persisting; and 4 severe) with the items rest tremor, postural tremor, and impairment by tremor (maximum score 12 points). Ratings were performed every 2 hours of the waking day. In both scales a reduction in total score indicates improvement. Each scale was used on the 3 consecutive days preceding each visit. The scores of these 3 days were averaged.

Long term EMG

A long term EMG tremor registration at baseline and end of maintenance was used as an objective measure to quantify the occurrence of tremor, expressed as a time percentage of a registration period of 10 waking hours. The tremor recording was performed with a long term EMG appliance via skin electrodes placed bilaterally over the muscle venters of extensor carpi radialis and flexor carpi ulnaris muscles with reference electrodes placed 10 cm distally. Registration and tremor analysis were performed according to a standardised protocol of EMG tremor registration.[20 21] Only the side with the most pronounced tremor was evaluated. The analysed time periods were identical at baseline and end of maintenance in individual patients.

Global assessment

The effect on tremor at the end of the trial was assessed globally on a three point scale (clear improvement, no clear effect, clear deterioration) by both investigators and patients, with the end points clear improvement versus no clear effect or deterioration used in the analysis.

Safety criteria

Safety was assessed by physical examination, supine and standing blood pressure measurements, laboratory tests (red blood cells, white blood cells, enzymes, electrolytes, urinalysis), 12 lead ECG, documentation of adverse events, and the investigators' global impression of tolerance.

Study procedures

At the screening visit medical history, physical examination, vital signs, laboratory tests, ECG, modified Hoehn and Yahr scale ("on" and "off"), UPDRS part II and III with derived tremor scores were performed and the patients' diaries with self rating scales distributed.

After a 2 week screening period the patients were randomly assigned to either pramipexole or placebo under double blind conditions in a 1:1 ratio (baseline visit). Baseline assessments comprised those for all end points, adverse events, and changes in concomitant medication.

Subsequently the patients underwent an ascending dose interval up to 7 weeks (weekly visits) with individual dose adjustments from 0.375 mg to 4.5 mg/day pramipexole or matching placebo using a three times a day regimen (3×0.125, 0.25, 0.5, 0.75, 1.0, 1.25, and 1.5 mg). The dosage was increased in weekly steps until the patient showed a stable and optimal improvement or received the maximally tolerated dose (up to a maximum dose of 4.5 mg daily). Dose adjustment was followed by a 4 week maintenance period. At the end of maintenance there was a 1 week dose reduction period to gradually withdraw study medication.

Additional antiparkinsonian medication (levodopa/decarboxylase inhibitor preparations and/or selegiline and/or amantadines) had to remain stable from 30 days before randomisation and throughout the course of the study.

The following assessments were performed at each visit after baseline—that is, at weekly visits during the ascending dose interval, at the end of the maintenance period, and after dose reduction: tremor score, UPDRS II ("on" and "off"), UPDRS III ("on"), evaluation of patients' diaries, adverse events, changes in concomitant non-antiparkinsonian medication. Just before the end of maintenance there was a second EMG registration of at least 10 hours of waking time. After dose reduction physical examination, vital signs, laboratory tests, and ECG were reassessed.

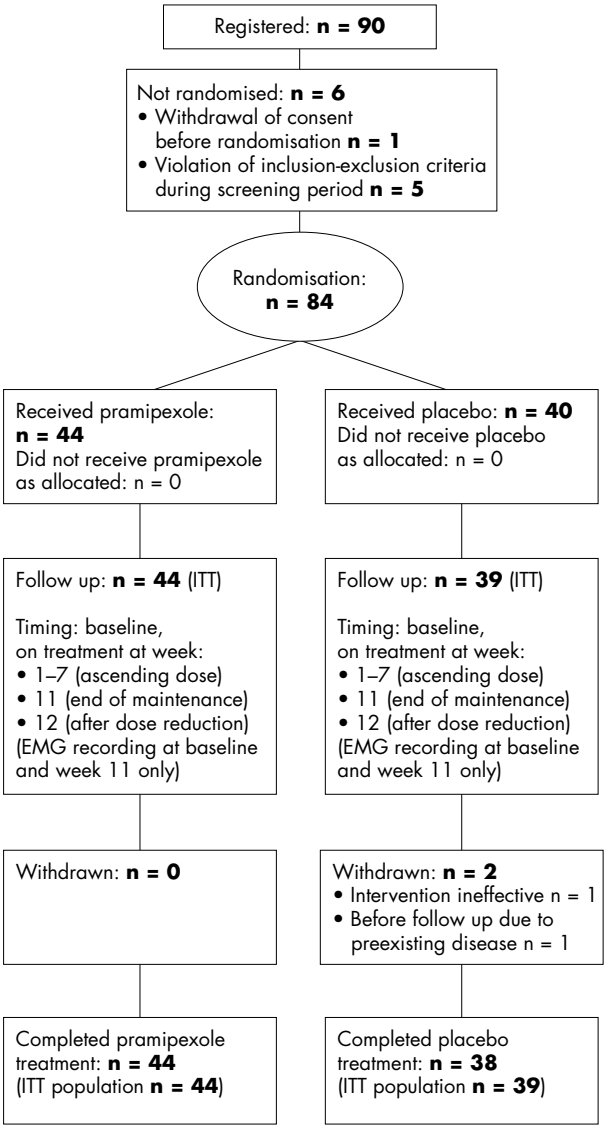

Figure 1 Profile of the randomised trial: flow diagram with the progress of the patients throughout the trial.

Statistical analysis

Baseline comparability of treatment groups was exploratively assessed by χ^2 test (sex), two way analysis of variance (ANOVA; age, UPDRS), Mantel-Haenszel test (Parkinson's disease duration, Hoehn and Yahr stage) and Wilcoxon-Mann-Whitney test (levodopa dose) with factors treatment and centre.

Analysis of variance with factors treatment and centre (for normally distributed data), and the Wilcoxon-Mann-Whitney test as alternative were applied for statistical evaluation of differences in efficacy between the treatment groups regarding the primary end point, the UPDRS derived secondary end points, the self rating scales, and EMG tremor registration. As the interaction treatment×centre was not significant ($p=0.12$) this factor was removed from the ANOVA and only the main effects remained. 95% Confidence intervals and p values were calculated for differences in the mean absolute changes between the treatment groups. The patients'and investigators' global assessments of the effect on tremor of pramipexole or placebo were compared using the Mantel-Haenszel test (clear improvement *v* deterioration or no clear improvement), confidence intervals for the differences of proportions were calculated using normal approximation. The null hypothesis for statistical tests was that there is no difference between the mean change from baseline to the end of maintenance in the pramipexole and placebo treatment groups (intent to treat population) and was tested for primary and secondary end points. Post hoc subgroup analyses to determine the influence of antiparkinsonian drugs other than study medication, adverse events (fatigue), presence of "off" periods at baseline, low or high tremor scores were performed for the primary end point. Incidences of adverse events were descriptively evaluated using Fisher's exact test for the occurrence per treatment group.

The intent to treat population included all patients who were randomised to treatment, received at least one dose of medication, and had at least one postbaseline efficacy assessment. Missing data of the intent to treat population were estimated using the "last observation carried forward" technique. Previous power calculations had suggested that a sample size of 42 in each treatment arm would be required to detect a statistically significant difference with 80% probability at the 5%

level of significance, if the difference in the mean change of tremor score between treatment groups was 2.2 units.

RESULTS

Treatment population

Eighty four patients gave informed consent, were included, and were randomised. One patient was withdrawn after the first treatment dose (placebo) without postbaseline efficacy measurements, as immediate cardiac surgery for an hitherto undetected aortic valve stenosis was required. Thus the intention to treat population consisted of 83 patients (60 male, 23 female), 44 in the pramipexole group, 39 in the placebo group. Eighty two (44 pramipexole, 38 placebo) patients completed the trial according to protocol. One placebo patient discontinued during the ascending dose period because of an unsatisfactory therapeutic effect (fig 1).

The mean age of the intention to treat population was 63.6 (SD 8.9) years with a range from 35 to 80 years and a mean disease duration of 6.3 (SD 3.8) years. The mean duration of drug treatment was 3.8 (SD 3.3) years. Seventy three patients were treated with levodopa with a median daily dose of 300 mg. Forty three patients (52%) received daily dosages of 300 mg levodopa or less, and 30 (36%) of more than 300 mg. Selegiline and amantadine were used by 12 (10 pramipexole, two placebo) and 14 (nine pramipexole, five placebo) patients, respectively.

The severity of Parkinson's disease was estimated at screening by Hoehn and Yahr staging during "on" and "off" periods. In "on" periods most of the patients were in Hoehn and Yahr stages 2 and 2.5. Thirty seven patients had no "off" periods at screening and most of the 46 patients with fluctuations were in Hoehn and Yahr "off" stages 2.5 and 3.

At baseline the mean UPDRS II scores (average of "on" and "off") were 13 (SD 6.4) in the pramipexole group and 11.5 (SD 4.6) in patients on placebo. Mean UPDRS III ("on") baseline scores were 34.2 (SD 15.3) compared with 32.1 (SD 11), pramipexole and patients with placebo, respectively. The mean tremor score in "on" was 11.9 (SD 5) in the pramipexole versus 10.9 (SD 3.5) in the placebo group with a mean proportion of the tremor score relative to the UPDRS II and III sum scores of 28% and 27%, respectively. Both treatment groups were comparable with respect to demographic and clinical features. Exploratory and descriptive analyses were not suggestive of significant differences at baseline (table 1).

Table 1 Demographics and baseline characteristics of the intent to treat population (n=83) with mean (SD), n (%), or median, where appropriate

	Pramipexole (n=44)	Placebo (n=39)	Total (n=83)
Sex (n (%)):			
Male	30 (68)	30 (77)	60 (72)
Female	14 (32)	9 (23)	23 (28)
Age (y):			
Mean (SD)	62.0 (10.1)	65.4 (7.1)	63.6 (8.9)
Range	35–80	47–80	35–80
Duration of PD (y):			
Mean (SD)	6.5 (4.0)	6.0 (3.5)	6.3 (3.8)
Range	0.9–17	2.0–16	0.9–17
Duration of drug treatment (y):			
Mean (SD)	3.9 (3.1)	3.6 (3.5)	3.8 (3.3)
Levodopa dose (mg):			
Median	300	300	300
Range	50–700	100–1700	50–1700
Patients (n (%)):			
With no levodopa	5 (11)	5 (13)	10 (12)
≤300 mg	25 (57)	18 (46)	43 (52)
>300 mg	14 (32)	16 (41)	30 (36)
Patients without "off" periods (at baseline) (n (%))	22 (50)	16 (41)	38 (46)
Hoehn and Yahr Stage: in "on" periods (n (%)):			
I	6 (14)	4 (10)	10 (12)
I.5	4 (9)	5 (13)	9 (11)
II	22 (50)	20 (51)	42 (51)
II.5	10 (23)	7 (18)	17 (20)
III	2 (4)	3 (8)	5 (6)
IV	0	0	0
Hoehn and Yahr Stage: in "off" periods (n (%)):			
I	0	1 (3)	1 (1)
I.5	0	2 (5)	2 (2)
II	3 (7)	6 (15)	9 (11)
II.5	12 (27)	10 (26)	22 (27)
III	7 (16)	4 (10)	11 (13)
IV	0	1 (3)	1 (1)
Tremor score (mean (SD))	11.9 (5)	10.9 (3.5)	11.4 (4.3)
Item 16 (reported)	2.2 (0.8)	2.1 (0.7)	2.2 (0.7)
Item 20 (rest)	6.3 (3.4)	5.8 (2.2)	6.1 (2.9)
Item 21 (action/postural)	3.3 (1.6)	3.0 (1.8)	3.2 (1.7)
UPDRS (mean (SD)):			
UPDRS II/III sum score	47.2 (21.1)	43.6 (14.4)	45.5 (18.2)
UPDRS II(mean "on/off")	13 (6.4)	11.5 (4.6)	12.3 (5.7)
UPDRS III ("on")	34.2 (15.3)	32.1 (11)	33.2 (13.4)
Patient's diary (mean (SD)):			
Daily living	20.2 (14.9)	17.3 (10.8)	18.8 (13.1)
Severity	6.1 (2.9)	5.7 (2.3)	5.9 (2.6)
Long term EMG:			
Tremor occurrence (%, mean (SD))	41.8 (21.5)	49.5 (21.6)	45.5 (21.8)

Table 2 Synopsis of primary and secondary end points for the intent to treat population (last observation carried forward technique): absolute changes from baseline to end of maintenance

	Pramipexole (n=44)	Placebo (n=39)	Difference between groups (95% CI)	Difference in mean relative changes (%)	
Tremor scores (UPDRS):					
Tremor score	–5.8 (5)	–1.5 (3.2)	–4.4 (–6.2 to –2.5)	–34.7	p<0.0001
Item 16	–0.7 (0.9)	–0.2 (0.7)	–0.6 (–0.9 to –0.2)	–21.5	p<0.01
Item 20	–3.6 (3.3)	–1.0 (2.2)	–2.6 (–3.8 to –1.4)	–37.9	p<0.0001
Item 21	–1.5 (1.6)	–0.3 (1.1)	–1.2 (–1.8 to –0.6)	–35.6	p<0.0001
UPDRS scores:					
UPDRS II/III (sum score)	–18.8 (13.9)	–3.8 (8.3)	–15 (–20 to –10)	–30.9	p<0.0001
UPDRS II (average "on"-"off")	–3.6 (3.8)	–0.1 (2.6)	–3.5 (–4.9 to –2.0)	–25.2	p<0.0001
UPDRS III ("on")	–15.2 (11.6)	–3.7 (6.8)	–11.5 (–15.7 to –7.4)	–34.1	p<0.0001
Patient's diary:					
Daily living	–4.7 (8.6)	3.4 (8.0)	–8.1 (–11.7 to –4.5)	–43.4	p<0.0001
Severity	–1.6 (2.1)	0.6 (2.2)	–2.2 (–3.1 to –1.3)	–39.5	p<0.0001
Long term EMG:					
Tremor occurrence (%)	–19.3 (14.8)	–4.1 (13.2)	–15.2 (–21.4 to –9.0)	–45.7	p<0.0001
Global assessment (patients with improvement (%)):					
Investigator's assessment	56.8	12.8	44.0 (26.1 to 61.9)	NA	p<0.0001
Patient's assessment	56.8	17.9	38.9 (20.0 to 57.7)	NA	p<0.0001

Values are mean (SD) or n (%) for pramipexole and placebo group; differences in the mean absolute changes between groups (mean and 95% confidence intervals (95% CIs); and differences in mean relative changes between groups ((%)); p values are given for the differences in the mean absolute changes (controlled for differences between study centres); NA, not applicable.

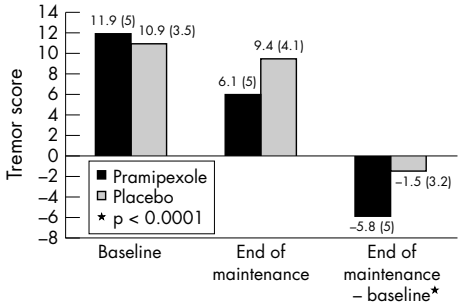

Figure 2 Mean tremor score (SD) at baseline (left) and end of maintenance (middle) of pramipexole (n=44) and placebo (n=39) group. Right: mean change from baseline to end of maintenance.

Efficacy

Primary end point

The change in tremor score showed a statistically significant difference between pramipexole and placebo group (p<0.0001). The difference in the mean absolute change between the treatment groups was –4.4 (95% confidence interval –6.2 to –2.5), corresponding to a difference in the mean relative change of –34.7% in favour of pramipexole (table 2, fig 2). The visit by visit analysis of the change in tremor score showed that the improvement under pramipexole increased in a dose dependent manner during the ascending dose interval and seemed to remain stable between the beginning and end of maintenance (fig 3).

Single tremor items

The separate analysis of the single UPDRS tremor items (UPDRS II item 16 "on": reported tremor in the ADL, UPDRS III items 20 and 21: tremor at rest and action or postural tremor, resp) disclosed similar results, with a statistically significant difference in favour of pramipexole for rest tremor and postural tremor (p<0.0001), as well as for reported tremor (p<0.01). The differences in the mean absolute change between the treatment groups were –2.6 (95% CI –3.8 to –1.4) and –1.2 (95% CI –1.8 to –0.6) for items 20 and 21, respectively, and –0.6 (95% CI –0.9 to –0.2) for item 16.

Subgroup analyses

The change in tremor score (primary end point) was further evaluated according (1) to the presence or absence of "off" periods at baseline, (2) to low or high baseline tremor scores, and (3) to the presence or absence of fatigue (table 3). In addition, the influence of antiparkinsonian medication other than pramipexole or placebo was analysed.

(1) Pramipexole treatment was significantly superior to placebo in both patients with and without "off " periods at baseline, with a difference in the mean change in tremor score between the treatment groups by –5.8 (p=0.0001), and –3.2 (p=0.006), respectively. Interaction tests (ANOVA with factors treatment and "off" status) disclosed that the reduction in

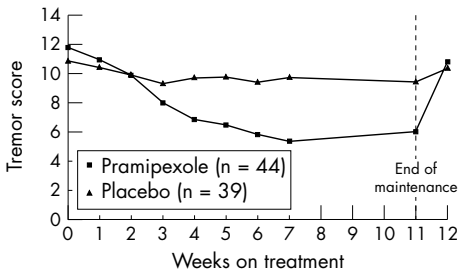

Figure 3 Development of the mean tremor score per week on treatment with pramipexole (ppx) and placebo (pbo) (intent to treat, last observation carried forward), at week 0 (baseline), weeks 1–7 (ascending dose interval), weeks 7–11 (maintenance period), week 11–12 (dose reduction).

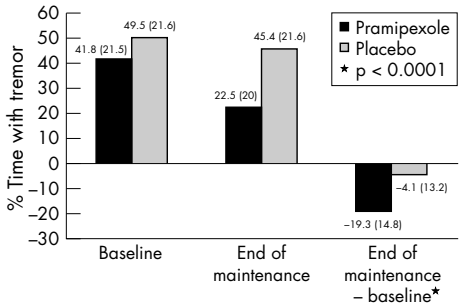

Figure 4 Mean occurrence of tremor by long term EMG registration (% time of waking hours (SD)) at baseline (left) and end of maintenance (middle) of pramipexole and placebo group. Right: Mean change from baseline to end of maintenance.

Table 3 Subgroup analyses of primary end point data (tremor score): stratification of the intent to treat population according to the presence or absence of "off"periods at baseline, high or low tremor scores, and patients with and without fatigue, reported as adverse event

	Pramipexole	Placebo	Mean difference between groups (p value)	Interaction test (treatment×subgroup qualifier)
"Off" status (yes/no)	22/22 patients	23/16 patients		p=0.038
Patients with "off"	−8.1 (5.4)	−2.3 (3.6)	−5.8 (p=0.0001)	
Patients without "off"	−3.6 (3.3)	−0.4 (2.3)	−3.2 (p=0.006)	
Tremor score (high/low)	24/20 patients	18/21 patients		p=0.01
Tremor score ⩾11	−8.0 (5.4)	−1.9 (3.7)	−6.1 (p=0.0001)	
Tremor score <11	−3.3 (2.6)	−1.1 (2.8)	−2.2 (p=0.03)	
Fatigue (yes/no)	10/34 patients	4/35 patients		NA
Patients with fatigue	−5.4 (5.6)*	−0.8 (3.3)	NA	
Patients without fatigue	−6 (4.8)*	−1.6 (3.3)	NA	

*p=0.73 for pramipexole treated patients.
NA; not applicable; change in tremor score from baseline to end of maintenance; difference in the mean change between treatment groups (p value for the difference between treatment groups); and interaction tests with factors treatment×subgroup qualifiers ("off" status, tremor score). Change in tremor score in patients with or without fatigue per treatment group.

tremor was significantly greater in the subgroup with "off" periods at baseline (p=0.038, "with off" *v* "without off").

(2) As the median tremor score at baseline was 11, a high score was defined as⩾11 and a low score as<11. The difference between the treatment groups in the mean change in tremor score was −6.1 (p=0.0001) in the high score group, and −2.2 (p=0.03) in the low score group, both in favour of pramipexole. The interaction between the factors treatment and baseline tremor score was statistically significant (p=0.01, "high" *v* "low score")—that is, the improvement under pramipexole was stronger in patients with a high baseline tremor score.

(3) To investigate whether the reduction in tremor was influenced by side effects such as increased tiredness or fatigue, the pramipexole treated patients without these adverse events (n=34) were descriptively compared to those patients, who experienced fatigue or increased tiredness during treatment (n=10). There was no significant difference in the mean change in tremor score from baseline to end of maintenance between these subgroups (p=0.73). The improvement was even slightly more pronounced in the group without compared with the group with fatigue/tiredness (mean change by −6 (SD 4.8) *v* −5.4 (SD 5.6)), so there is no evidence that additional fatigue during the trial contributed to a reduction in tremor.

Further post hoc analyses indicated that levodopa, selegiline, or amantadine use did not influence treatment outcome; neither did levodopa dose, when stratified as>300 mg versus⩽300 mg.

UPDRS parts II and III

The mean improvement in the combined UPDRS II/III sum score was significantly superior under pramipexole (p<0.0001). The difference in the mean absolute change between the treatment groups was −15 (95% CI −20 to −10)—that is, a percentage difference in UPDRS II/III sum scores of −30.9% in favour of pramipexole. The single UPDRS II and III scores also showed a significant improvement (p<0.0001) in the pramipexole group compared with the placebo group. The differences between groups were −3.5 (95% CI −4.9 to −2.0) for UPDRS II and −11.5 (95% CI −15.7 to −7.4) for UPDRS III, indicating an overall efficacy of pramipexole on activities of daily living and motor performance.

Patients' diaries

The tremor self rating with respect to impairment of daily living and severity of tremor, as based on the patients' diaries disclosed a difference in the mean improvement between the treatment groups of −8.1 (95% CI −11.7 to −4.5) and −2.2 (95% CI −3.1 to −1.3) in favour of pramipexole (p<0.0001), respectively.

Long term EMG

The EMG recordings of tremor activity were consistent with the patients' subjective estimation (fig 4): Long term EMG during waking hours displayed a mean occurrence of tremor (as percentage of a time interval of 10 consecutive hours) at baseline of 41.8 (SD 21.5)% in the pramipexole group and 49.5 (SD 21.6)% in the placebo group. To the end of maintenance the mean tremor occurrence decreased with a group difference of −15.2 (95% CI −21.4 to −9.0) (p<0.0001), corresponding to a difference in the mean relative change of -45.7% in favour of pramipexole.

Global assessment

The investigators' assessment of the effect on tremor showed a clear improvement in 25 (56.8%) pramipexole patients versus five (12.8%) placebo patients. This corresponded with the patients' estimation: clear improvement was reported by 25 patients (56.8%) of the pramipexole and seven patients (17.9%) of the placebo group. The differences between pramipexole and placebo groups were 44.0% (95% CI 26.1 to 61.9) and 38.9% (95% CI 20.0 to 57.7) in favour of the pramipexole group (p<0.0001), respectively.

Safety

The safety population consisted of all 84 patients who have received at least one administration of the test dose (44 pramipexole, 40 placebo). Safety and tolerance were generally assessed as good in most cases. Global clinical impression of tolerance was rated as good in 94% of the patients and did not differ between treatment groups. No deaths were reported.

The mean duration of treatment was comparable in the treatment groups: 48.8 (SD 9.5) versus 46.4 (SD 9.1) days ascending dose interval, 31.2 (SD 4.8) versus 29.4 (SD 3.9) days maintenance, and 4.9 (SD 1.4) versus. 4.7 (SD 1.3) days dose reduction phase, pramipexole and placebo group, respectively. The average daily dose in the pramipexole group was 4.1 (SD 0.9) mg and 4 (SD 0.8) mg in the placebo group.

A descriptive analysis of adverse events showed a higher overall incidence of side effects in patients treated with pramipexole. A total of 72 patients (85.7%) reported at least one adverse event, 41 (93.2%) and 31 (77.5%) in the pramipexole and placebo group, respectively (p=0.06). Common treatment emergent adverse events—that is, with an incidence of at least 10% in either treatment group were

Table 4 Occurrence of adverse events (AEs)/treatment group

	pramipexole (n=44)	placebo (n=40)	p Value
Any AE	41 (93.2)	31 (77.5)	0.06
Fatigue	10 (22.7)	4 (10)	0.15
Dizziness	8 (18.2)	6 (15)	0.78
Insomnia	9 (20.5)	3 (7.5)	0.12
Nausea	7 (15.9)	3 (7.5)	0.32
Aggravation of parkinsonism	4 (9.1)	4 (10)	1.00
Abdominal pain	6 (13.6)	1 (2.5)	0.11
Tremor	2 (4.5)	5 (12.5)	0.25
Headache	6 (13.6)	1 (2.5)	0.11
Serious AE	2 (4.5)	2 (5)	1.00
Assessed as drug related	1 (2.3)	0	1.00

Values are number of patients (%) with at least one AE; common treatment emergent adverse events, occurring in at least 10% of patients in either treatment group; and serious adverse events; p values (Fisher's exact test) for the differences between treatment groups

fatigue (10 pramipexole/4 placebo patients), dizziness (8/6), insomnia (9/3), nausea (7/3), aggravated parkinsonism (4/4), abdominal pain (6/1), tremor (2/5), and headache (6/1). Except for aggravated parkinsonism and tremor each of these adverse events were reported more often in the pramipexole group (table 4). Adverse events with a risk difference in excess of 5% (more than two patients) between treatment groups, were fatigue, insomnia, nausea, abdominal pain, and headache. Tremor was reported in more placebo patients (12.5% versus 4.5%). The differences between the treatment groups in the incidence of these adverse events did not reach statistical significance. In this trial, new occurrence of dyskinesias was not seen in the pramipexole group and hallucinations were reported in two (4.5%) patients on pramipexole. Serious adverse events (SAEs) occurred in four (4.8%) patients, two in each treatment group. Only one SAE (orthostatic hypotension with a short loss of consciousness in a pramipexole treated patient) was assessed as drug related. One patient (placebo group) dropped out due to a serious adverse event (cardiac surgery for hitherto undetected aortic valve stenosis), but this was not related to the study drug. No other adverse events led to discontinuation. Laboratory assessments, ECG, vital signs, and physical findings seemed not to be systematically changed by pramipexole treatment.

DISCUSSION

The present study shows that pramipexole is not only an effective antiparkinsonian agent with respect to improvement in ADL or UPDRS motor scores as a whole, but also leads to a statistically significant reduction of parkinsonian tremor when added to a stable antiparkinsonian medication. With respect to the tremor scores, the difference in mean relative improvement between the treatment groups was −34.7% in favour of pramipexole. The corresponding difference in the change in UPDRS II/III sum score was −30.9%. Accordingly, there could be a slightly pronounced efficacy of pramipexole on tremor in these patients, and it seems that the reduction in tremor is not merely due to an overall antiparkinsonian effect. However, our findings are only descriptive, and in the literature there are no comparable data on selective efficacy of antiparkinsonian agents.

The long term EMG recordings as an objective measure of tremor activity over time were consistent with the change in tremor score, showing a difference in the mean relative reduction in tremor occurrence by –45.7% in favour of pramipexole. Furthermore, both patients' and investigators' assessments as well as the patients' self rating scales showed superiority of pramipexole in this trial and thus underlined the clinical relevance and benefit in daily living of the observed effects.

The differences between pramipexole and placebo increased dose dependently during titration and were maintained until the end of the study. As indicated by the analysis of the single tremor score items, pramipexole favorably influenced not only—as might have been anticipated—rest tremor, but also both action and postural components of tremor.

Subgroup analyses disclosed that patients with "off" periods, indicating an advanced stage of the disease, and patients with higher tremor scores at baseline derived best benefit from pramipexole treatment. However, the treatment effect of pramipexole remained significant in the subgroups without "off" periods, or with lower baseline tremor scores.

Pramipexole has been reported to cause "sleep attacks".[15] A non-specific sedative effect could, conceivably, be responsible for the improvement of tremor. As there was no correlation between the reduction in tremor and the presence or absence of fatigue or increased tiredness in the subgroup analysis, efficacy end points do not seem to be influenced by this side effect profile of the study drug.

Two points should be made concerning the inclusion criteria and study population. Firstly, there is, unfortunately, no accepted UPDRS derived measure to define "tremor dominant", so that certainly some patients with mixed type Parkinson's disease and severe tremor were included. By clinical impression, though, most patients were characterised as tremor dominant Parkinson's disease. As the mean tremor score was 11.4 at baseline, all patients had at least marked parkinsonian tremor in "on", regardless of being tremor dominant or not.

Secondly, patients were required to receive an optimised antiparkinsonian therapy before inclusion. As the median levodopa dose was relatively low (300 mg in all study arms), this condition does not seem to be fulfilled at first glance. However, most patients had Hoehn and Yahr scores of 2 in the "on" periods and only 2.5 in the "off" periods indicating a sufficient global therapeutic response, and a mild to moderate disease severity of the study population. In addition, before study inclusion, antiparkinsonian therapy was optimised by balancing the best possible ratio of symptomatic benefit to side effects provided at an individual base, which might favour lower levodopa doses.

The improvement in tremor in this patient group is remarkable, as the patients enrolled into the trial had shown a marked to severe parkinsonian tremor throughout their medical history, despite an otherwise optimised medication. Add on therapy with pramipexole led to a further significant improvement in parkinsonian symptoms and particularly in tremor throughout the study. Upon discontinuation of the trial medication, the tremor scores rapidly returned to baseline values (fig 3), consistent with a drug relation of the observed effect. A maintenance period of 4 weeks as in this study is relatively short. However, other clinical trials with longer observation periods proved a sustained treatment effect of pramipexole.[10 11 13]

The safety data showed a good overall tolerability, although the number of patients with at least one adverse event was higher in the pramipexole group (93.2% *v* 77.5%, p=0.06). The most prominent adverse events were fatigue, insomnia, nausea, abdominal pain, and headache, which is in line with previous studies and similar to those of other dopamine agonists.[2 10 12 14] None of these single adverse events showed a statistically significant difference between treatment groups; however, these exploratory analyses are limited by the few patients and should not be overrated. There were no unexpected safety results or deaths. "Sleep attacks", recently reported in patients under non-ergoline dopamine agonists,[15] did not occur during this trial, and increased tiredness or fatigue did not contribute to the treatment effects. Pramipexole was regarded as safe and tolerable within the tested dose range from 0.375 to 4.5 mg daily with an average daily dose of 4.1 mg in the population studied.

Positive effects of dopamine agonists as adjunct to levodopa therapy on parkinsonian tremor have been reported earlier.[22–24] Pergolide improved parkinsonian tremor in an open label trial in patients unresponsive to bromocriptine therapy (retrospective analysis),[22] and in a placebo controlled double blind trial[23] as part of an overall antiparkinsonian effect. Both lisuride and bromocriptine showed a significant improvement in tremor when added to long term levodopa treatment in patients with wearing off phenomena.[24] None of these studies were designed to investigate the effects on tremor separately in a homogeneous sample of patients.

The reported trial is the first controlled, double blind study of a dopamine agonist focusing on this cardinal symptom, including tremor scales and objective EMG recordings. The study was planned to test previous—methodologically limited—findings that have suggested tremorlytic properties of pramipexole and was designed to compare pramipexole with placebo.[17] As no other dopamine agonist has been investigated with a special attention to tremor, the magnitude of the tremorlytic response of pramipexole cannot be directly compared with other substances. Data available on budipine, a butyldiphenylpiperidine with affinities to various neuroreceptors and an antiparkinsonian agent, suggested to be tremorlytic, have shown an improvement of 33.7%[25] and 40%[26] as measured with long term EMG. Our result of 45.7% difference in relative tremor reduction between pramipexole and placebo is even more pronounced. Thus further active comparator studies are warranted to directly compare pramipexole to other substances with tremorlytic potential. Nevertheless, we conclude that in patients with early or advanced Parkinson's disease and insufficient control of tremor, add on pramipexole is an effective dopamine agonist and thus seems to provide a therapeutic option for this subgroup of patients with Parkinson's disease.

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