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# Randomized, Double-Blind, 3-Month Parallel Study of the Effects of Pramipexole, Pergolide, and Placebo on Parkinsonian Tremor

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***Abstract:*** **We compared the antitremor effect of pramipexole, pergolide, or placebo in Parkinson's disease (PD). A double-blind, randomly controlled, parallel protocol was deployed to examine the effects of placebo, pergolide, and pramipexole [doses escalated to 1.5 mg three times daily (t.i.d.) over 3 months] on a compound Tremor Index (TI) and Unified Parkinson's Disease Rating Scale (UPDRS) part III. Thirty PD patients (19 men, 11 women; mean age 69 years, range 54–80 years; mean disease duration 3.9 years, range, 0.5–10 years) participated in the study, with 10 patients in each arm. Six subjects failed to complete the study (4 on pergolide and 2 on placebo). Analysis of covariance demonstrated strong evidence for a treatment effect on both TI and UPDRS III. There was no significant difference between the active treatments on either TI or UPDRS III. Both pergolide and pramipexole were significantly better than placebo. The results indicate that pergolide and pramipexole (1.5 mg t.i.d.) have similar anti–PD tremor and UPDRS III actions that are significantly superior to placebo. Patients on pergolide were more likely to drop out because of adverse events than those on pramipexole.**


**Key words:** Parkinson's disease, tremor, pergolide, pramipexole, randomized controlled trial, dopamine receptors

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Tremor is the most common initial symptom of Parkinson' disease (PD) and typically spreads from one hand to the ipsilateral arm and then foot before affecting the opposite side of the body. Various types of tremor occur in PD, including rest, postural, and kinetic tremors.[1] Clinical observation has shown that PD tremor responds variably to medication and when refractory may require surgical intervention.[2]

Over the past decade, interest in the direct-acting dopamine agonist class of drugs has increased, because these drugs have less propensity than levodopa to produce dyskinesia or motor complications.[3] However, studies designed specifically to assess the effects of the newer direct-acting dopamine agonists on PD-tremor are sparse.[4–6] Ropinirole was found retrospectively, using data taken from three multicentre randomised controlled trials (RCTs), to have significant anti–PD rest but not action tremor properties relative to placebo.[4] Similarly, a subanalysis performed on 11 patients in a large RCT showed that pramipexole reduced rest tremor by 61% compared to baseline. However, the effect on action tremor was not studied.[5] More recently, the effect of pramipexole on drug-resistant PD tremor was compared to placebo in a multicentre randomly assigned trial involving 84 patients.[6] The results showed that pramipexole, used as adjunctive therapy at a mean dose of 4.1 mg, significantly decreased PD *on* tremor (scored using a tremor index that summed items 16 [symptomatic tremor] and 20 and 21 [signs of rest and action tremor] of the Unified Parkinson's Disease Rating Scale [UPDRS]) by a mean of 34.7% compared to placebo with this result supported by long-term electromyographic recordings.[6]

Thus, the issue of whether pramipexole has a greater tremorlytic action than the other direct dopamine agonists arises. However, minimal data are available about the relative anti–PD tremor potencies of the individual direct-acting dopamine agonist drugs, although in a previous pilot study, we demonstrated that the anti–rest tremor effects of a single 0.5-mg dose of pergolide or

pramipexole were similar and were superior to placebo.[7] This finding is of particular interest because of their differential effects on the dopamine receptor types, as it has been postulated that pramipexole may have a stronger antiparkinsonian tremor effect than pergolide, because the former has preferential affinity for the D3 receptor, whereas the latter mainly stimulates D2 receptors, although it also has some weak activity at the D1 and D3 as well as non–dopamine receptor sites.[8–13] Conversely, a recent study of the actions of an apparently selective dopamine D3 receptor antagonist S33084 on the motor function of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine–lesioned marmosets showed that S33084 potentiated the antiparkinsonian actions of levodopa and ropinirole, suggesting that stimulation of D3 receptors compromised motor function.[14]

Although our pilot study demonstrated that the anti–PD rest tremor effects of a single 0.5-mg dose of pergolide or pramipexole were similar, the possibility that a difference in the antitremor efficacies of the two drugs may be present at a higher dose and with chronic administration led us to perform a randomly assigned placebo controlled trial involving these two drugs at increasing doses (up to 1.5 mg t.i.d.) over a 3-month period in patients with Parkinson's disease.[7]

## PATIENTS AND METHODS

### Study Design, Ethics, and Study Dates

A 3-month duration double-blind parallel study comparing the effects of pergolide, pramipexole, and placebo on PD tremor. Following ethical approval the study was carried out from February to November 2001. Written informed consent was obtained from all participants before enrollment in the study.

### Participants: Entry Criteria

Patients had (1) idiopathic PD, according to UK Parkinson's Disease Society brain bank criteria; (2) a symptomatic tremor of an upper limb that reached at least grade 2/10 in severity on a validated tremor rating scale[1,15,16]; and (3) previously had not taken any direct-acting dopamine agonist class medication, although other antiparkinsonian medications were permitted.

### Recruitment and Assessment Sites

Patients were recruited from the neurological clinics of the Charing Cross and West Middlesex University Hospitals, London, and Harold Wood Hospital, Essex. The assessments were performed at Charing Cross and Harold Wood Hospitals. A total of 40 appropriate patients attending the above clinics and fulfilling the study's entry criteria were asked to take part in the study; 10 declined.

### Randomisation, Study Design, and Intervention

Thirty patients were randomly assigned in blocks of three by using a computer to receive pergolide (n = 10), pramipexole (n = 10), or placebo (n = 10) in addition to their previous treatment. The randomisation was performed by the research pharmacist at Charing Cross Hospital; who also administered the medications so that patients and assessors were blind to treatment allocation. The medications were encapsulated in an identical manner and were supplied by Pharmacia. Patients were pretreated with domperidone 10 mg orally with each dose of (placebo or active) treatment for the first week. Subsequently, they could continue taking domperidone if nausea returned. After baseline assessment, the dose of the assigned medication was gradually titrated upward as shown in Table 1.

### Assessment Protocol

Patients were assessed at baseline and then for approximately 1 hour on three separate mornings at monthly intervals, commencing at the same time of day on each occasion. The patients continued to take their usual medications at the same time on each assessment day. Patients were asked to perform a verbal fluency task for 40 seconds while tremor was scored/recorded. The follow-

**TABLE 1.** *Weekly dosage regimen for the patients in the trial*

| Week | Dose level | Placebo | Pramipexole (mg) | Pergolide (mg) |
|---|---|---|---|---|
| 1, day 1–3 | 1[a] | 1 o.d. | 0.125 o.d., etc. | 0.1 o.d., etc. |
| 1, day 4–7 | 2[a] | 1 b.i.d. | 0.125 b.i.d., etc. | 0.1 b.i.d., etc. |
| 2 | 3 | 1 t.d.s. | 0.125 t.d.s., etc. | 0.1 t.d.s., etc. |
| 3 | 4 | 1 t.d.s. | 0.25 t.d.s., etc. | 0.25 t.d.s., etc. |
| 4 | 5 | 1 t.d.s. | 0.5 t.d.s., etc. | 0.5 t.d.s., etc. |
| 5 | 5 | 1 t.d.s. | 0.5 t.d.s., etc. | 0.5 t.d.s., etc. |
| 6 | 6 | 1 t.d.s. | 0.75 t.d.s., etc. | 0.75 t.d.s., etc. |
| 7 | 7 | 1 t.d.s. | 1.0 t.d.s., etc. | 1.0 t.d.s., etc. |
| 8 | 7 | 1 t.d.s. | 1.0 t.d.s., etc. | 1.0 t.d.s., etc. |
| 9 | 8 | 1 t.d.s. | 1.25 t.d.s., etc. | 1.25 t.d.s., etc. |
| 10 | 9 | 1 t.d.s. | 1.5 t.d.s., etc. | 1.5 t.d.s., etc. |
| 11 | 9 | 1 t.d.s. | 1.5 t.d.s., etc. | 1.5 t.d.s., etc. |
| 12 | 9 | 1 t.d.s. | 1.5 t.d.s., etc. | 1.5 t.d.s., etc. |

[a]Domperidone 10 mg taken with each dose of medication for first week and then as required for the remainder of the study.

The placebo capsules looked identical and were of the same number as those of pergolide and pramipexole at each dose level.

The 0.1-mg capsule of pergolide, actually contained 2 × 0.05 mg of pergolide within each capsule, as neither 0.1 nor 0.125 mg are manufactured. o.d., every day; b.d., twice daily; t.d.s., three times daily.

ing assessments were carried out on each occasion: (1) tremor rating, using a (0–10) tremor scale, of rest and postural tremors and tremor in a spiral (the most affected arm was assessed)[7,15,16]; (2) UPDRS motor subsection (part III)[17]; (3) upper limb rest and postural tremor were recorded from the most tremulous arm, while the patients were sitting, using a technique previously described[15,16]; (4) Nine-hole pegboard test[15,18]; (5) Becks Depression Rating Scale/HADS[19,20]; (6) Euroqol EQ-5D health status scores[21]; (7) sitting and standing blood pressure and pulse rate; and (8) the incidence of adverse effects and blinding was systematically collected.

### Outcome Measures

The primary outcomes were final (3-month) UPDRS part III and a Tremor Index (TI). The latter was the sum of the measured tremor scores for rest tremor (RT), postural tremor (PT), and spiral tremor (ST). So that TI = RT + PT + ST. As RT, PT, and ST were individually scored from 0 to 10, the range of TI is 0 to 30 (30 being maximum). The other measured variables were looked at for clinical interest (secondary outcomes).

### Sample Size and Data Analysis

A prestudy power calculation estimated that with 10 patients in each arm (at $P = 0.05$) the trial had an approximately 90% chance of detecting a 40% difference in TI between active treatments.[7] Analysis of covariance (ANCOVA) was performed on the primary outcomes adjusting for baseline UPDRS part III or TI, respectively, and all three pair-wise treatment post hoc comparisons made, with treatment differences reported after Bonferroni correction. The secondary outcome measures were analysed in a similar way. The tremor data obtained by accelerometry was $Log_{10}$ transformed before analysis because of a high-end skew and information that log tremor magnitude correlates better with tremor-related disability.[22]

## RESULTS

### Participants' Characteristics

Thirty patients were entered into the study (19 men and 11 women). Their mean age was 69 years (range, 54–80 years), mean disease duration was 3.9 years (range, 0.5–10 years), and mean on medication Hoehn & Yahr score was 1.5 (range, 1–3). Twenty-four of the patients were also taking other antiparkinsonian medications, which in every case remained unchanged throughout the study. The demographics of the patients by treatment group are given in Table 2.

### Numbers Analysed

The number of patients reaching each assessment and the reasons for dropping out are shown in Tables 3 and 4, respectively. There was a relationship between drop-

**TABLE 2.** *Patient demographics by treatment group*

| | Placebo | Pergolide | Pramipexole |
|---|---|---|---|
| Patients entered (n) | 10 | 10 | 10 |
| Gender, M/F (n) | 6/4 | 6/4 | 7/3 |
| Age (yr) | 70 (62–78) | 71 (54–80) | 66 (55–80) |
| Disease duration (yr) | 3 (0.8–7) | 5 (0.6–8) | 4 (0.5–10) |
| H & Y score | 2 (1–3) | 1 (1–2) | 1 (1–2) |
| S & E score % | 91 (80–100) | 89 (75–100) | 88 (70–95) |
| UPDRS part III | 32 (18–43) | 30 (21–38) | 35 (22–50) |
| Rest tremor (0–10) | 4.45 (3–6) | 4.2 (2–5) | 4.3 (2–6) |
| Patients on other anti-PD tx (n) | 6 | 8 | 10 |
| L-Dopa (no. of patients) | 4 | 6 | 6 |
| Mean dose, mg (range) | 550 (300–800) | 383 (300–700) | 400 (200–600) |
| Selegeline (no. of patients) | 1 | 4 | 3 |
| Mean dose, mg (range) | 10 | 8.75 (5–10) | 10 |
| Propranolol (no. of patients) | 0 | 3 | 3 |
| Mean dose, mg (range) | 0 | 107 (80–160) | 93 (40–160) |
| Benzhexol (no. of patients) | 0 | 1 | 2 |
| Mean dose, mg (range) | 0 | 6 | 6 (4–8) |
| Orphenadrine (no. of patients) | 1 | 0 | 1 |
| Mean dose, mg (range) | 300 | 0 | 100 |
| Amantadine (no. of patients) | 1 | 0 | 4 |
| Mean dose, mg (range) | 200 | 0 | 225 (200–300) |

Values are expressed as mean (range), unless otherwise indicated.

H & Y, Hoehn and Yahr; UPDRS, Unified Parkinson's Disease Rating Scale; PD, Parkinson's disease; tx, treatment.

**TABLE 3.** *Number of patients completing each assessment by treatment group*

| Treatment | Baseline | 4-Week | 8-Week | 12-Week |
|---|---|---|---|---|
| Placebo | 10 | 8 | 8 | 8 |
| Pergolide | 10 | 6 | 6[a] | 6[a] |
| Pramipexole | 10 | 10 | 10 | 10[b] |

[a]One patient (Case 26) on pergolide, having been on 0.5 mg three times daily at the 4-week assessment, received 0.25 mg three times daily from week 5 for the remainder of the study because of dyskinesia and hallucinations.

[b]One patient (Case 27) on pramipexole remained on 1.0 mg three times daily from the 8-week assessment to the end of the study because of dyskinesia.

ping out and treatment (Fisher's exact test, $P = 0.054$), with the majority of those dropping out having been on pergolide. All the patients taking placebo remaining in the study were on the appropriate dose level at each assessment. However, because of adverse events, one patient in each active treatment arm could not achieve the target dosage by the relevant assessment and were excluded from analysis (case 26 on pergolide was reduced to 0.25 mg t.i.d. from week 5 and case 27 on pramipexole was kept on 1 mg t.i.d. from week 8 for the remainder of the study).

## Adverse Events

One patient on placebo treatment died from a pulmonary embolus during week 3. The numbers of patients experiencing adverse events by treatment group are shown in Table 5. Symptomatic postural hypotension was not encountered and no significant effect of treatment was found on patients' supine and standing pulse rates or blood pressure (BP), except for sitting diastolic BP, which fell more on pergolide (mean ± SD, 60.8 ± 10.7 mm Hg) than on pramipexole (76.0 ± 15.1 mm Hg) at the final assessment ($P < 0.05$).

**Table 4.** *Reasons for patients dropping out by each assessment*

| Treatment | Reason for dropout | 4-Week | 8-Week | 12-Week |
|---|---|---|---|---|
| Placebo | Death | 1 | | |
| | Ineffective | 1 | | |
| Pergolide | Nausea | 3 | | |
| | Headache | 2 | | |
| | Constipation | 1 | | |
| | Drowsiness | 1 | | |
| | Dizziness | 1 | | |

Three patients on pergolide had multiple adverse events that led to their withdrawal from the trial before the 4-week assessment.

**Table 5.** *Number of patients experiencing adverse effects during the study by treatment group*

| Treatment | Placebo patients (n) | Pergolide patients (n) | Pramipexole patients (n) |
|---|---|---|---|
| Adverse effects | 5 | 10 | 9 |
| Death | 1 | 0 | 0 |
| Drowsiness | 2 | 5 | 5 |
| Constipation | 3 | 2 | 2 |
| Hallucinations | 0 | 4 | 3 |
| Nausea | 0 | 3 | 0 |
| Sleep disturbances | 1 | 3 | 0 |
| Headache | 0 | 2 | 1 |
| Dyskinesia | 0 | 1 | 1 |
| Dizziness | 0 | 1 | 0 |

## Blinding

Of the 9 surviving patients on placebo, 8 correctly considered themselves to have been on placebo. All patients treated with pergolide and 8 of 10 receiving pramipexole correctly thought that they had received active treatment but these patients answered "do not know" to the question "which active drug do you think you have received?", despite having been informed of the drugs' potential side-effects.

## Primary Outcomes

The Shapiro-Francia W′ test indicated that baseline UPDRS III and TI data could be modelled by the normal distribution. The mean and ranges for baseline UPDRS part III were as follows: pergolide, 29.8 (range, 21–38); placebo, 32.1 (range, 18–43); pramipexole, 35 (range, 22–50). For baseline TI, the values are as follows: pergolide, 9.96 (range, 5.5–15.25); placebo, 11.45 (range, 8–19); pramipexole, 11.95 (range, 6.5–22). The values of the baseline TI (for all 30 patients) were significantly correlated with the baseline UPDRS items [20 + 21] and items [16 + 20 + 21] subscores (respectively, $r = 0.728$ and 0.729, both $P < 0.01$).

## Results for the TI

The changes in the TI over time are displayed in Figure 1. This graphic shows that the TI decreased over time in each group, although more in those on active treatment. However, toward the end of the study, the TI increased in some subjects in each group. Subjects with a high initial TI tended to have a high TI at the final assessment. ANCOVA demonstrated strong evidence for a treatment effect on the TI ($F(2,20) = 6.53$; $P = 0.007$). Log transformation of the baseline TI data did not change this conclusion ($F(2,20) = 4.79$; $P = 0.019$). Post hoc analysis showed that there was no significant differ-

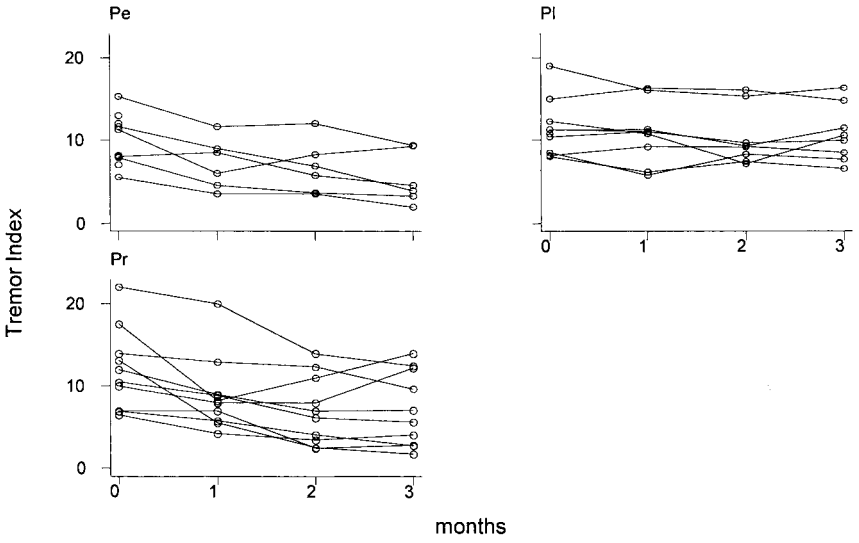


**FIG. 1.** Tremor index over time for pergolide (Pe), pramipexole (Pr), and placebo (Pl).

ence between the effects of the two active drugs on TI and that both drugs had a significantly greater antitremor effect than placebo (Table 6).

### Results for the UPDRS Part III

The changes in the UPDRS part III over time are displayed in Figure 2. Inspection of these profiles demonstrates that the UPDRS part III decreased more over time in the groups receiving active treatment. ANCOVA also provided strong evidence for a treatment effect on the UPDRS part III ($F(2,20) = 10.11$; $P = 0.001$). However, post hoc analysis showed that there was no significant difference between the effects of the two active drugs on the UPDRS part III, although both drugs had significantly greater anti-UPDRS part III effect than placebo (Table 7).

### Secondary Outcomes

The effects of each treatment on the secondary outcome measures are shown in Table 8. The effect of treatment on the three subcomponents of the TI, namely tremor at rest, on posture, and in spirals is shown in Table 8. There was a significant effect of treatment on postural tremor scored clinically, with pergolide having a significantly ($P < 0.01$) greater anti–postural tremor effect than placebo, while pramipexole did not. There was also a trend suggesting that treatment decreased rest tremor, but again only pergolide was significantly superior to placebo ($P < 0.05$). The effect of treatment on tremor in spirals was not significant. It is notable that, within the TI, the baseline (0–10) scores for upper limb rest tremor were significantly correlated with the (0–10) scores for postural tremor ($r = 0.764$; $P < 0.01$), but neither the (0–10) rest tremor nor the (0–10) postural tremor scores were significantly correlated with the (0–10) spiral scores (respectively, $r = 0.322$ and $r = 0.341$).

The results of the $\log_{10}$ transformed tremor magnitudes measured by accelerometry support those of the clinical ratings, as there was a significant effect of treatment on postural tremor (with pergolide having significantly greater anti–postural tremor action than placebo) but the effect on rest tremor did not reach significance. No significant differences were found between treat-

**TABLE 6.** *Post hoc analysis of treatment effects on the Tremor Index*

| | Effect size - 95% CI At mean value of baseline | $F$ | $P$ | |
|---|---|---|---|---|
| | | | Unadjusted | Bonferroni adjusted |
| Pr-Pe | 0.14 (−1.47,1.75) | F(1, 20) = 0.12 | 0.732 | 1.000 |
| Pl-Pr | 2.96 (1.30, 4.61) | F(1, 20) = 9.88 | 0.005 | 0.015 |
| Pl-Pe | 3.09 (1.66, 4.53) | F(1, 20) = 9.31 | 0.006 | 0.018 |

CI, confidence interval; Pr, pramipexole; Pe, pergolide; Pl, placebo.

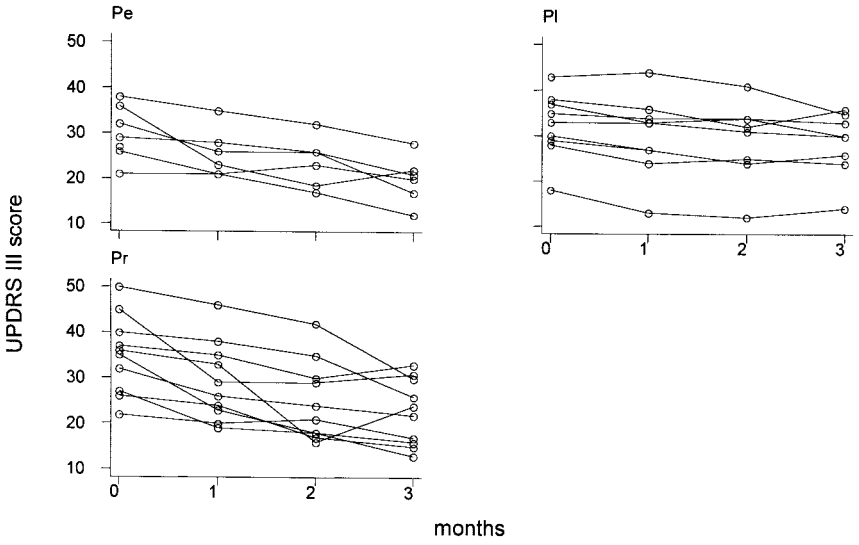


**FIG. 2.** Unified Parkinson's Disease Rating Scale part III (UPDRS III) over time for pergolide (Pe), pramipexole (Pr), and placebo (Pl).

ments in their effects on the nine-hole peg-test performance, Euroquol-EQ-5D health status scores or total scores for HADS or Beck's depression inventory (Table 8).

## DISCUSSION

A multicentre trial had demonstrated that pramipexole alleviated drug-resistant PD tremor significantly more than placebo.[6] The latter study raised the question of whether or not this tremorlytic property was unique to pramipexole or shared by other direct-acting dopamine agonist drugs.[6] Our results demonstrate that the efficacy of pramipexole (salt) and pergolide against PD tremor is similar and that these drugs are significantly more effective than placebo at reducing the severity of PD-tremor, when continuously administered up to a maintenance dose of 1.5 mg t.i.d. (Table 6). Our data also indicates that pramipexole and pergolide are useful chronic treatments for PD tremor in a "real life" clinic based sample in which better symptomatic control of tremor was required. Furthermore, these drugs were effective, despite that 24 patients were on other anti-PD medications (16 already on levodopa).

Examining the data (presented in Table 6) concerning the three components of the TI shows that treatment had a greater statistical effect on postural compared to rest or spiral tremor. The accelerometric data also shows a similar pattern, with treatment producing a statistically significant influence on postural but not rest tremor magnitude. Whether these secondary results reflect a genuine differential response of PD (postural $>$ rest $>$ spiral) tremor or merely experimental noise/low power is difficult to know. It is interesting that we found that baseline rest and postural tremor scores were highly correlated with each other but not with tremor in spirals, perhaps because spiral (kinetic) tremor involves a different mechanism to that producing rest and postural tremors. In this regard, a multicentre study showed that pramipexole reduced rest tremor by 37.9% and postural tremor by 35.6% compared to placebo; suggesting that the two tremor components had a comparable response to the

**Table 7.** *Post hoc analysis of treatment effects on the UPDRS part III*

| | | *P* | | |
|---|---|---|---|---|
| Effect size - 95% CI | *F* | At mean value of baseline | Unadjusted | Bonferroni adjusted |
| Pr-Pe | −1.35 (−4.70, 2.00) | F(1, 20) = 0.14 | 0.708 | 1.000 |
| Pl-Pr | 5.61 (2.63, 8.59) | F(1, 20) = 11.13 | 0.003 | 0.010 |
| Pl-Pe | 4.26 (0.87, 7.65) | F(1, 20) = 17.79 | 0.000 | 0.001 |

UPDRS, Unified Perkinson's Disease Rating Scale; CI, confidence interval; Pr, pramipexole; Pe, pergolide; Pl, placebo.

**TABLE 8.** *Effect of treatment on secondary outcome measures: rest tremor, postural tremor, tremor in spirals, accelerometry (rest and postural tremor) and 9-hole peg-test*

| Assessment | Baseline | 4-week | 8-week | 12-week | ANCOVA (post hoc) *F* | ANCOVA (post hoc) *P* |
|---|---|---|---|---|---|---|
| Rest tremor (0–10) | | | | | 3.317 | 0.059 |
| Placebo | 4.45 ± 0.98 | 4.1 ± 1.36 | 3.63 ± 1.09 | 3.63 ± 1.33 | | |
| Pergolide | 4.2 ± 0.95 | 3.0 ± 1.41 | 3 ± 1.41 | 2.25 ± 1.44 | | Pe-Pl: <0.05 |
| Pramipexole | 4.3 ± 1.48 | 3.2 ± 1.30 | 2.25 ± 1.55 | 2.28 ± 1.28 | | |
| Postural tremor (0–10) | | | | | 4.62 | 0.024 |
| Placebo | 3.7 ± 1.55 | 3.7 ± 1.48 | 3.6 ± 1.29 | 3.6 ± 1.37 | | |
| Pergolide | 2.6 ± 1.60 | 1.8 ± 1.08 | 1.5 ± 0.89 | 0.8 ± 0.46 | | Pe-Pl: <0.01 |
| Pramipexole | 3.7 ± 1.93 | 2.6 ± 2.06 | 2.1 ± 1.62 | 2.1 ± 1.96 | | |
| Spiral score (0–10) | | | | | 2.861 | 0.083 |
| Placebo | 3.3 ± 1.96 | 3.1 ± 1.47 | 3.1 ± 1.90 | 3.5 ± 2.0 | | |
| Pergolide | 3.2 ± 1.74 | 2.4 ± 1.05 | 2.2 ± 1.37 | 2.3 ± 1.83 | | |
| Pramipexole | 4.0 ± 2.38 | 3.2 ± 2.06 | 2.8 ± 1.64 | 3.0 ± 1.74 | | |
| Accelerometry: Rest tremor (Log10 mV) | | | | | 2.320 | 0.128 |
| Placebo | 1.67 ± 0.46 | 1.73 ± 0.51 | 1.74 ± 0.33 | 1.69 ± 0.57 | | |
| Pergolide | 1.71 ± 0.60 | 1.29 ± 0.93 | 1.38 ± 0.75 | 0.98 ± 0.68 | | |
| Pramipexole | 1.73 ± 0.44 | 1.16 ± 0.86 | 1.18 ± 0.87 | 1.42 ± 0.46 | | |
| Accelerometry: Postural tremor (Log10 mV) | | | | | 6.805 | 0.007 |
| Placebo | 1.35 ± 0.73 | 1.47 ± 0.67 | 1.52 ± 0.46 | 1.68 ± 0.59 | | |
| Pergolide | 1.10 ± 0.92 | 1.03 ± 0.51 | 0.70 ± 0.44 | 0.44 ± 0.32 | | Pe-Pl: <0.01 |
| Pramipexole | 1.45 ± 0.71 | 1.23 ± 0.73 | 1.10 ± 0.65 | 1.04 ± 0.75 | | |
| 9-Peg test (sec) | | | | | 0.073 | 0.930 |
| Placebo | 23.7 ± 12.97 | 21.2 ± 9.11 | 20.4 ± 6.63 | 20.4 ± 5.64 | | |
| Pergolide | 21.5 ± 7.66 | 19.8 ± 4.53 | 21.7 ± 7.50 | 20.7 ± 6.30 | | |
| Pramipexole | 30.3 ± 27.89 | 28.7 ± 25.34 | 27.1 ± 17.6 | 23.9 ± 10.72 | | |
| Euroquol-Health Status | | | | | 0.344 | 0.713 |
| Placebo | 76.5 ± 16.0 | | | 80.1 ± 15.8 | | |
| Pergolide | 71.0 ± 15.8 | | | 80.2 ± 12.3 | | |
| Pramipexole | 73.1 ± 11.9 | | | 78.2 ± 19.2 | | |
| Becks DI | | | | | 0.82 | 0.455 |
| Placebo | 6.7 ± 4.9 | | | 5.7 ± 4.8 | | |
| Pergolide | 9.0 ± 5.8 | | | 11.0 ± 7.8 | | |
| Pramipexole | 14.0 ± 8.2 | | | 13.9 ± 10.6 | | |
| HADS | | | | | 0.276 | 0.762 |
| Placebo | 3.6 ± 4.3 | | | 4.9 ± 3.3 | | |
| Pergolide | 6.4 ± 3.0 | | | 6.2 ± 4.7 | | |
| Pramipexole | 6.8 ± 4.9 | | | 5.9 ± 5.8 | | |

Values are expressed as mean ± SD, unless otherwise indicated.
ANCOVA, analysis of covariance

drug.[6] Conversely, the differential response of individual tremor components to treatment with levodopa/carbidopa (200/50 mg), subcutaneous apomorphine (1.5–6 mg), and primidone administered to a single PD patient with rest, postural, and kinetic tremors was reported recently.[23] Furthermore, although pergolide and pramipexole had a very similar "effect size" on the main outcome measure (TI) used in this study (Table 6), it is interesting that the decrease in postural tremor (measured clinically or by accelerometry) and clinical ratings of rest tremor by pergolide compared to placebo reached statistical significance (respectively, $P < 0.01$ and $P < 0.05$), which was not the case for pramipexole; although this may have been a threshold effect on the significance levels for these secondary outcomes (Table 8). Curiously, these drugs appear to be effective at reducing PD tremor in both the *off* and routine *on* state.[6,7] Pogarell and colleagues also showed that pramipexole had a significant antitremor effect in the *on* state, with a median levodopa dose of 300 mg.[6] It is also unlikely that pramipexole reduced PD tremor by increasing levodopa bioavailability.[24]

Our results demonstrate that pramipexole (salt) and pergolide had similar beneficial actions on the patients' UPDRS motor subsection scores, which were significantly better than that of placebo, suggesting that the mechanisms by which pramipexole or pergolide improve the UPDRS part III and PD tremors is not dependent on

their relative affinities for the dopamine receptor subtypes, either acutely or over a 3-month period.[7–13] Whether or not doses of pramipexole (salt) or pergolide in excess of 1.5 mg t.i.d. have an even greater anti-PD tremor or anti-UPDRS III action is unknown, although the tolerability of long-term treatment with pergolide in excess of 5 mg per day has been described.[25]

The number of patients experiencing adverse effects was approximately twice as great for the active treatments as placebo. This finding and the ineffectiveness of placebo resulted in many patients correctly ascertaining whether or not they were on active or placebo treatment. However, they were unable to distinguish which of the two active drugs had been administered. There was a significant differential effect of treatment on compliance, as 4 of 10 pergolide-treated patients withdrew from the study, whereas all the pramipexole-treated patients completed the study. Symptomatic postural hypotension did not occur, although pergolide decreased sitting diastolic blood pressure significantly more than pramipexole.

We conclude that chronic administration of pergolide or pramipexole (salt) 1.5 mg t.i.d. produced significant beneficial anti-TI and anti-UPDRS motor score effects, with similar effect sizes, despite having different affinities for dopamine receptor subtypes. However, the patients were more likely to discontinue pergolide than pramipexole therapy.

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