Efficacy, safety, and tolerance of the non-ergoline dopamine agonist pramipexole in the treatment of advanced Parkinson’s disease: a double blind, placebo controlled, randomised, multicentre study

M M Pinter, O Pogarell, W H Oertel

Abstract

Objectives—Pramipexole, a non-ergot dopamine D2/D3 receptor agonist, was investigated as an add on drug in advanced parkinsonian patients with motor fluctuations to assess efficacy, safety, and tolerance.

Methods—Seventy-eight patients of either sex with advanced Parkinson’s disease and treatment complications such as motor fluctuations were enrolled into a double blind, placebo controlled, randomised, multicentre study (phase II) and assigned to add on treatment with pramipexole (n=34) versus placebo (n=44) to a previously stabilised antiparkinsonian medication (7 week dose titration interval, 4 week maintenance period). The primary end point of efficacy was the change from baseline in the total score of the unified Parkinson’s disease rating scale (UPDRS) in the on “period” (2 hours after intake of study medication). Safety and tolerability were assessed on the basis of adverse events, vital signs, laboratory measurements, and ECG recordings.

Results—There was a significant improvement of the pramipexole group in UPDRS total scores, subscores part II, III (activities of daily living and motor examination), and IV (complications of therapy). Mean UPDRS total score decreased by 37.3% under pramipexole compared with 12.5% under placebo (p<0.001). Patients under pramipexole reported an overall reduction in “off” periods of 12%—resulting in 1.7 more hours “on” a day—compared with an increase in “off” periods of 2% under placebo. There were no unexpected safety results. The adverse event profile disclosed a high tolerability. The most important adverse events under pramipexole were fatigue, dyskinesia, and vivid dreams.

Conclusion—Pramipexole administration is an efficacious and well tolerated add on therapy in patients with advanced Parkinson’s disease with an improvement in activities of daily living, motor function, and treatment associated complications.

Keywords: Parkinson’s disease, dopamine agonist, pramipexole

Pramipexole, a synthetic aminobenzothiazole derivative, is a non-ergot dopamine agonist with novel properties. It has the highest affinity of the dopamine D2 receptor subfamily and within this group it shows preferential affinity for the D3 receptor subgroup. There is no binding to the dopamine D1 receptor family and apart from dopamine receptors, it binds only to α2-adenoreceptors, but to an extent not clinically relevant.1,2 According to findings in animal models, the binding site of pramipexole on dopaminergic neurons is preferentially located presynaptically, where it acts as an agonist and inhibits dopamine synthesis and release. However, when the presynaptic dopaminergic neuron is impaired, as is the case in Parkinson’s disease, pramipexole acts as a potent postsynaptic dopamine D2 receptor agonist.3,4

The pharmacokinetic indices of pramipexole are linear and predictable, plasma concentrations increase proportionally with dosage. Pramipexole is well absorbed after oral administration with a bioavailability of more than 90% and a half life ranging from 8 to 12 hours. Peak plasma concentrations occur within 1 to 3 hours. Pramipexole undergoes minimal metabolism and is excreted virtually unchanged in the urine.5

Pramipexole has been investigated in preliminary studies in early and advanced Parkinson’s disease.4,6,7 Main findings in patients with advanced Parkinson’s disease with motor fluctuations have been that pramipexole improved motor functions, reduced the time of “off” periods, and decreased the disability and Parkinson’s disease severity during “on” and “off” periods.8,9,10

The purpose of this prospective, double blind, placebo controlled, randomised, multicentre clinical trial (phase II) was to compare the efficacy and tolerability of pramipexole as an add on drug with that of placebo in advanced Parkinson’s disease, and to assess the effect of pramipexole on complications associated with levodopa treatment such as motor fluctuations or abnormal involuntary movements.

Patients and methods

In this trial, patients with idiopathic Parkinson’s disease classified according to the UK Parkinson’s Disease Society Brain Bank11; who experienced motor fluctuations or abnormal involuntary movements on a stable levodopa...
regimen, were enrolled at nine study centres. Included were patients with severity of Parkinson's disease corresponding to Hoehn and Yahr classification stages II and IV. The use of concomitant antiparkinsonian drugs such as MAO-B inhibitors and amantadines was allowed, but—as with levodopa (plus decarboxylase inhibitor)—doses had to remain unchanged during the trial. Excluded were female patients of child bearing potential (contraceptives were not allowed), patients with Parkinson's disease caused by other neurodegenerative diseases, and patients with severe dementia, epilepsy, previous neurosurgery, or severe physical diseases. The concomitant treatment with dopaminergic agonists, MAO-A inhibitors, neuroleptics, α-methyldopa, clonidine, reserpine, and calcium antagonists was not allowed. The study was approved by local ethics committees and written informed consent was obtained from all patients.

**METHODS**

After a screening period of up to 2 weeks, patients were randomly assigned under double blind conditions to either pramipexole (34 patients) or placebo (44 patients). There was a stratification into four groups according to a high (>600 mg) or low (≤600 mg) daily levodopa dose, with or without other antiparkinsonian medication. Daily doses of trial medication were individually adjusted during a 7 week dose titration interval, with doses being increased weekly from 0.2 mg up to 5.0 mg/day (2×0.1 mg, 4×0.1, 0.25, 0.5, 0.75, 1.0, and finally 1.25 mg) followed by a 4 week maintenance period. At the end of the maintenance period, a reduction in dosage followed to gradually withdraw the study medication over the course of 1 week.

Unless otherwise specified, the following assessments were performed at each visit: the unified Parkinson's disease rating scale (UPDRS) including part I (mentation, behaviour, and mood), part II (activities in daily living), part III (motor examination) and part IV (complications of therapy). The motor examination was assessed in the “on” period, 2 hours after intake of study medication. Also assessed were the Hoehn and Yahr scale, the Schwab and England scale (best “on” period, worst “off” period within past week before visit) and the Parkinson dyskinesia scale in “on” period using a five point scale (0=normal, 1=intermittent, 2=generalised, 3=marginal, 4=incapacitating) for various body regions (head, upper and lower limbs, and trunk). Furthermore, a global clinical assessment scale with respect to efficacy, tolerance, and compliance (ratings=good, fair, unsatisfactory, not assessable) as judged by the investigators at the end of the maintenance period was also employed, as were patient diaries to record duration and severity of disability during waking hours “off” periods. The diaries were dispensed at screening and before the end of maintenance, and were evaluated by the investigator at baseline and at the end of the maintenance period.

The primary end point was the change in the UPDRS total score at the end of the maintenance interval compared with baseline. Secondary end points were changes in UPDRS subscores (parts I-IV), the Schwab and England scale, the Parkinson dyskinesia scale, the patients’ diary, and the global clinical assessment at the end of maintenance interval compared with baseline.

Safety and tolerance were assessed on the basis of neurological examinations, blood pressure and pulse rate measurements, ECG, routine laboratory investigations (blood cell count, erythrocyte sedimentation rate, enzymes, glucose, electrolytes, and urinary findings)—evaluated up to eight times throughout the study period—and adverse events (those events reported for the first time during the treatment phase or with higher intensity compared with baseline).

**STATISTICAL ANALYSIS**

To evaluate differences between the two treatment groups, the Wilcoxon-Mann-Whitney test was applied to the UPDRS total score and subscores of parts II, III, and IV. The subscore of UPDRS part II was defined as the sum of the averages of the individual “on” and “off” scores for each item. However, the subscores of UPDRS part I were classified in categories (improved, unchanged, and deteriorated) and were computed using the χ² test. In all tests, a probability level of p<0.05 was considered significant.

An evaluable patient analysis (per protocol), which comprised all patients with complete data for analysis, was performed, as this was a phase II trial. The obtained results were confirmed by an intent to treat (ITT) analysis using the last observation carried forward (LOCF) method. Considered suitable for ITT analysis were all patients with at least one dose of study medication and completion of at least one postbaseline assessment. The results of the ITT efficacy analysis (n=77) are presented, as these differed only marginally from the per protocol analysis (n=67).

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**Table 1 Demographics and baseline characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Pramipexole</th>
<th>Placebo</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of patients</strong></td>
<td>34*</td>
<td>44</td>
<td>78*</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>20 (58.8%)</td>
<td>31 (70.5%)</td>
<td>51 (65.4%)</td>
</tr>
<tr>
<td>Women</td>
<td>14 (41.2%)</td>
<td>13 (29.5%)</td>
<td>27 (34.6%)</td>
</tr>
<tr>
<td><strong>Age (y)</strong></td>
<td>59.5 (8.3)</td>
<td>60.7 (8.7)</td>
<td>60.1 (8.5)</td>
</tr>
<tr>
<td><strong>Duration (y) of Parkinson’s disease</strong></td>
<td>7.8 (4.3)</td>
<td>8.5 (5.2)</td>
<td>8.2 (4.8)</td>
</tr>
<tr>
<td>Hoehn and Yahr stage:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>7 (20.6%)</td>
<td>13 (29.5%)</td>
<td>20 (25.6%)</td>
</tr>
<tr>
<td>III</td>
<td>22 (64.7%)</td>
<td>20 (45.5%)</td>
<td>42 (53.9%)</td>
</tr>
<tr>
<td>IV</td>
<td>5 (14.7%)</td>
<td>11 (25.0%)</td>
<td>16 (20.5%)</td>
</tr>
<tr>
<td><strong>UPDRS total score</strong></td>
<td>53.6 (14.0)</td>
<td>50.2 (20.0)</td>
<td>51.7 (17.6)</td>
</tr>
<tr>
<td><strong>UPDRS part I</strong></td>
<td>1.5 (1.8)</td>
<td>1.1 (1.5)</td>
<td>1.2 (1.6)</td>
</tr>
<tr>
<td><strong>UPDRS part II</strong></td>
<td>13.0 (4.9)</td>
<td>12.7 (7.3)</td>
<td>12.8 (6.3)</td>
</tr>
<tr>
<td><strong>UPDRS part III</strong></td>
<td>33.5 (9.1)</td>
<td>30.5 (12.2)</td>
<td>31.8 (11.0)</td>
</tr>
<tr>
<td><strong>UPDRS part IV</strong></td>
<td>5.7 (4.0)</td>
<td>5.9 (5.5)</td>
<td>5.8 (3.7)</td>
</tr>
</tbody>
</table>

*One patient was randomised to both treatment groups. Values are mean (SD) or mean (%).
Pinter, Pogarell, Oertel

**Results**

In total, 78 patients (51 men, 27 women; aged 34 to 75 years) were enrolled in the trial. Thirty four patients received pramipexole, 44 placebo. The baseline demographic information of the total population (n=78) is listed in table 1. The pramipexole and placebo group were comparable for baseline characteristics and no significant discrepancies between study centres were noted. There were no significant differences between the two groups in age, duration of the disease, and baseline UPDRS total scores and subscores. The relative number of patients in Hoehn and Yahr stage III was higher in the pramipexole group, whereas relatively more patients on placebo were in Hoehn and Yahr stages II and IV. Stratification according to levodopa treatment and other antiparkinsonian medication resulted in a comparable representation of each stratum in both treatment groups. The mean levodopa dose at baseline was 537.5 (SD 314.4) mg/day in the pramipexole group and 592.6 (SD 264.0) mg/day in the placebo group.

One patient was dropped from the ITT efficacy analysis population (n=77), as he had been unintentionally enrolled and randomised twice, firstly in the placebo group, then in the pramipexole group. The consequent adaptation of baseline values in the pramipexole treated group showed only marginal changes. Ten patients (four pramipexole, six placebo) discontinued the study prematurely; two patients for administrative reasons (withdrawal of consent; protocol violation), and eight patients due to adverse events (see adverse event section). Overall, 67 (87%) patients (29 pramipexole, 38 placebo) completed the study according to the protocol and were considered in the per protocol analysis.

In the maintenance period, 43 patients (64%) received the maximum dose of 5 mg/day pramipexole or corresponding placebo; the maximum dose level was reached by 16 patients (53%) of the pramipexole group and 27 (71%) of the placebo group. The mean daily maintenance dosage was 3.59 (SD 1.79) mg (minimum of 0.4 mg/day) in the pramipexole group and 4.08 (SD 1.52) mg (minimum of 0.85 mg/day) in the placebo group. The mean levodopa dose at end of the maintenance period was 511.0 (SD 308.8) mg/day for the pramipexole group, and 583.5 (SD 273.3) mg/day for the placebo group.

Efficacy Evaluation

In the per protocol as well as in the ITT analysis, there was a significant improvement in both end point measurements—that is, the UPDRS total score and the subscores II to IV with respect to pramipexole in comparison with placebo. The reduction of UPDRS total score by 20.1 (37.3%) under pramipexole versus 5.9 (13.1%) under placebo was highly significant (p<0.001). The mean and median changes of the UPDRS total scores, as well as the subscores and the calculated significances for the ITT population, are presented in table 2. For the UPDRS total scores a significant difference between treatment and placebo was achieved as early as week 1 and sustained to the end of the maintenance period (fig 1). The median change in UPDRS part II subscore (fig 2) and part III subscore (fig 3) from baseline to end of maintenance, shows a significant difference between treatment and placebo.

An improvement in the Hoehn and Yahr staging was found in six patients (18%) of the pramipexole group compared with 12 patients (27%) in the placebo group. A deterioration was registered in two patients (6%) on pramipexole and in four patients (9%) in the placebo group. In the remaining patients (25 patients on pramipexole and 28 patients on placebo group, ADL score decreased by 20.1 (37.3%) under pramipexole versus 5.9 (13.1%) under placebo. The reduction of UPDRS total score to the end of maintenance period shows a significant difference between treatment and placebo. The consequent adaptation of each stratum in both treatment groups. The mean levodopa dose at baseline was 537.5 (SD 314.4) mg/day in the pramipexole group and 592.6 (SD 264.0) mg/day in the placebo group.

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**Table 2  Reduction of UPDRS scores and significances (Wilcoxon-Mann-Whitney) for the ITT population (LOCF)**

<table>
<thead>
<tr>
<th></th>
<th>Pramipexole (n=33)</th>
<th>Placebo (n=44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean change (SD)</td>
<td>20.1 (16.0)</td>
<td>5.9 (12.8)</td>
</tr>
<tr>
<td>Mean % change</td>
<td>37.3</td>
<td>13.1</td>
</tr>
<tr>
<td>Median change</td>
<td>20.0</td>
<td>5.25</td>
</tr>
<tr>
<td>p Value</td>
<td>0.0002</td>
<td></td>
</tr>
</tbody>
</table>

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*V* test for categories “improved; unchanged; deteriorated”.

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![Graph Figure 1](http://jnnp.bmj.com/)  
**Figure 1** Median change in the UPDRS total score at each visit from baseline to the end of the maintenance period. In comparison with placebo, there is a significant decrease in the UPDRS total scores at each visit (p<0.05) beginning with week 1.

![Graph Figure 2](http://jnnp.bmj.com/)  
**Figure 2** Median change in the subscores of the UPDRS part II (activities of daily living) at each visit from baseline to the end of maintenance period.
Non-ergoline dopamine agonist pramipexole in advanced Parkinson’s disease

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The pramipexole group compared with 32% of

cacy was judged as good or fair in 76% of

Y

ever, based on the global clinical assessment,

1.7 more hours of “on” time each day. More-

“time, which resulted in about

reduction of “o

34.6%. The pramipexole group had a 12.3%

V

periods from 32.7% to

an increase in “o

20.7%, whereas patients on placebo reported

all decrease in average daily percentage of “off”

that patients on pramipexole reported an over-

3.70 to 2.77 in the placebo group. In addition,

the mean dyskinesia score dropped from 2.70

administration. At the end of the maintenance period,

placebo. However, no significant e

compared with 0.4 (SD 2.1) in those on

about 1.8(SD 2.6) in the pramipexole group

versus 27%.

18%; in the “o

“on” period in 54% of patients

in the “off” period in 54% of patients

versus 27%.

Furthermore, pramipexole led to a signifi-

cant decrease in UPDRS part IV subscore, by

about 1.8(SD 2.6) in the pramipexole group

compared with 0.4 (SD 2.1) in those on placebo. However, no significant effect on dys-

kinesia was found due to pramipexole admin-

istration. At the end of the maintenance period, the mean dyskinesia score dropped from 2.70
to 2.12 in the pramipexole group and from 3.70 to 2.77 in the placebo group. In addition, the
evaluation of the patients’ diaries disclosed that patients on pramipexole reported an over-

al decrease in average daily percentage of “off”

periods during waking hours, from 33.0% to

20.7%, whereas patients on placebo reported an increase in “off” periods from 32.7% to

34.6%. The pramipexole group had a 12.3% reduction of “off” time, which resulted in about

1.7 more hours of “on” time each day. More-

over, based on the global clinical assessment,
efficacy was judged as good or fair in 76% of

the pramipexole group compared with 32% of

the placebo group.

SAFETY AND TOLERABILITY

Adverse events were reported by 27 of 34

patients (79%) in the pramipexole group and by

32 of 44 patients (73%) in the placebo

group, whereas they were classified as drug

related in 17 patients (50%) treated with

pramipexole and in 20 patients (45%) treated

with placebo. Moreover, 15 patients (44%) in

the pramipexole group and 16 patients (36%) in

the placebo group required drug therapy due
to adverse events. With respect to the two

treatment groups 14 (41%) patients treated

with pramipexole versus seven (16%) patients

treated with placebo reported psychiatric

adverse events (mainly vivid dreams and visual

hallucinations) and 13 patients (38%) treated

with pramipexole versus 11 (25%) general dis-

orders (such as fatigue and malaise); whereas

in the placebo group relatively more patients—
namely, 21 (48%) versus 11 (32%)—had

adverse events of the central and peripheral

nervous system (mainly dizziness and head-

ache) and musculoskeletal disorders (back

pain, myalgia, arthralgia). Gastrointestinal sys-

tem disorders did not differ between treatment

groups.

For the most common adverse events—that

is, occurring in at least three patients (8.8% for

the pramipexole group)—a difference in inci-
dence of more than 5% of pramipexole over

placebo was found for fatigue, dyskinesia,

insomnia, agitation, postural hypotension,

visual hallucinations, vivid dreams, abnormal

lacrimation, nocturia, and renal calculus. Diz-

ziness, headache, and aggravated parkinsonism

appeared more often in the placebo group

(table 3).

Eight patients, three (9%) on pramipexole and

five (11%) on placebo had to be withdrawn

from the study due to adverse events. Reasons

for discontinuation in the pramipexole group

were (1) sedation and tiredness, (2) drowsiness

and myoclonia, and (3) hypotension with collapse

and confusion. In the placebo group patients

were withdrawn due to (1) nausea, dizziness,

and absence, (2) restlessness, (3) influenza,

drowsiness, and dizziness, (4) arte-

rial hypertension and headache, and (5) right

bundle branch block (ECG recording). No

deaths or fatal adverse events were reported.

During the trial, 14% of the patients had

clinically relevant abnormal values in the labo-

ratory evaluation, 24% in the pramipexole

group, 11% in the placebo group. The abnormalities comprised bacteriuria, raised

plasma

Table 3  Incidence (%) of most commonly reported

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treatment emergent adverse events (occurring with an

treatment emergent adverse events (occurring with an

incidence of at least 8% or a difference >5% between

treatment groups)

Pramipexole (n=34)  Placebo (n=44)

Fatigue  29.4  4.5

Dyskinesia  14.7  4.5

Insomnia  4.7  9.1

Agitation  11.8  6.8

Vivid dreams  11.8  8.0

Visual hallucinations  8.8  2.3

Cramps  8.8  4.5

Hypotension  8.8  4.5

Ataxia  8.8  4.5

Nausea  8.8  6.8

Increased sweating  8.8  6.8

Headache  5.9  18.2

Visual hallucinations  5.9  0.0

Abnormal lacrimation  5.9  0.0

Renal calculus  5.9  0.0

Nocturia  5.9  0.0

Somnolence  5.9  9.1

Dizziness  2.9  27.3

Aggravated parkinsonism  2.9  13.4

Back pain  0.0  6.8

Figure 3  Median change in the subscores of the UPDRS

part III (motor scores) at each visit from baseline to the end

of maintenance period.

placebo) the baseline and the end of mainte-
nance assessments were identical.

For the Schwab and England scale the

following was seen in the pramipexole group:
in the “on” period 17 patients (52%) improved,
16 (48%) remained unchanged, and none

worsened, and in the “off” period 18 patients

(54%) improved, 10 (30%) remained un-

changed, four (12%) deteriorated, and one

patient had missing data in the “off” period. In

the placebo group, in the “on” period eight

(18%) patients improved, 32 (73%) remained

unchanged, and four (9%) worsened, whereas

in the “off” period 12 (27%) patients im-

proved, 27 (62%) remained unchanged, and five

(11%) deteriorated. Based on the results

tained with the Schwab and England scale, it

is evident that pramipexole treatment was

superior compared with placebo; improvement

in the “on” period in 52% of patients versus

18%; in the “off” period in 54% of patients

versus 27%.

Furthermore, pramipexole led to a signifi-
cant decrease in UPDRS part IV subscore, by

about 1.8(SD 2.6) in the pramipexole group

compared with 0.4 (SD 2.1) in those on placebo. However, no significant effect on dys-
kinesia was found due to pramipexole admin-
istration. At the end of the maintenance period, the mean dyskinesia score dropped from 2.70
to 2.12 in the pramipexole group and from 3.70 to 2.77 in the placebo group. In addition, the

evaluation of the patients’ diaries disclosed that patients on pramipexole reported an over-
al decrease in average daily percentage of “off”

periods during waking hours, from 33.0% to

20.7%, whereas patients on placebo reported an increase in “off” periods from 32.7% to

34.6%. The pramipexole group had a 12.3% reduction of “off” time, which resulted in about

1.7 more hours of “on” time each day. More-

over, based on the global clinical assessment,
efficacy was judged as good or fair in 76% of

the pramipexole group compared with 32% of

the placebo group.

SAFETY AND TOLERABILITY

Adverse events were reported by 27 of 34

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32 of 44 patients (73%) in the placebo

group, whereas they were classified as drug

related in 17 patients (50%) treated with

pramipexole and in 20 patients (45%) treated

with placebo. Moreover, 15 patients (44%) in
potassium concentrations, increased blood
creatinine kinase, anaemia, and increased eryth-
ocyte sedimentation rate in the pramipexole
group, and anaemia, raised white blood cell
count, increased erythrocyte sedimentation
rate, and glucosuria in the placebo group. None
of these values were linked to the study drug
treatment by the investigators and all were
found to be normalised during follow up. For
the vital signs, pramipexole affected neither
blood pressure nor pulse rate. ECG deviations
were comparable in frequency under prami-
pexole and placebo.

Discussion
The results of this multicentre, double blind,
placebo controlled trial with pramipexole up to
5 mg/day in patients with advanced Parkinson’s
disease disclosed an efficacy to improve
parkinsonian signs and to decrease disabilities
in daily activities as assessed by clinical rating
scales. There was a highly significant reduction
in the UPDRS total scores and a significant
improvement in the activities of daily living
(ADL - UPDRS II), as well as in motor
function (UPDRS III) under pramipexole in
comparison with placebo. This beneficial treat-
ment effect was prolonged, lasting through the
whole maintenance period. Efficacy data as
assessed by UPDRS were confirmed by the
investigators’ global clinical assessment at the
end of the trial, which also showed superiority
of pramipexole compared with placebo. At first
sight, this result is surprising, as an adjunct
therapy in the best “on” period should not lead
to an improvement of clinical scales. In the
present study, however, patients were not
assessed during their best “on” period, but in a
defined “on” period—that is, 2 hours after
their last medication. Therefore, the improve-
ment of UPDRS due to pramipexole indicates
a more stable and prolonged “on” period com-
pared with placebo.

According to previously published studies on
pramipexole in patients with early Parkinson’s
disease, the beneficial effect on activities of
daily living is greater than the improvement in
motor function.1 However, another study in
early Parkinson’s disease found evidence that
the treatment effects of pramipexole on motor
function compared with placebo were more
pronounced in patients with worse UPDRS
scores at baseline.7,8 Findings of the present
study are similar to those seen in other double
blind, placebo controlled trials of pramipexole
in patients with advanced Parkinson’s disease.
9,10 Although all studies in advanced
disease showed a significant change in UPDRS
activities of daily living (22%-27%) and
UPDRS motor scores (25–35%) compared with
placebo, the present study discloses a
larger improvement induced by pramipexole in
the aforementioned scores (32.2% in activities
of daily living, 39.4% in motor score).

Furthermore pramipexole compared with
placebo led to a small but significant reduction
in therapy related complications such as motor
fluctuations or abnormal involuntary move-
ments (UPDRS IV) and to a reduction in “off”
time, which is in agreement with other studies,
although the extent of improvement differed
between the reports. Nevertheless in the only
study comparing pramipexole with another
dopamine agonist (bromocriptine), there was
indeed a significant reduction in “off” time
only under pramipexole and not under bromocriptine.15 This additional favourable
effect might be due to the pharmacological
properties of pramipexole with its rather long
elimination half life of around 12 hours.5

Dopaminergic drugs currently available often
cause severe and intolerable side effects—for
example, hypotension or gastrointestinal
disturbances—or other, albeit rare, adverse
events such as erythromelalgia, retropitoneal
fibrosis, or pleuropulmonary complications,
most likely associated with ergot structure and
function of dopamine agonists.15–17 Pramipex-
ole showed a low side effect profile, was well
tolerated and safe, with fatigue, vivid dreams,
and dyskinesia as the most prominent adverse
events. Visual hallucinations were experienced
by two patients (5.9%), which compares
favourably with the results gained elsewhere.7,9
In particular, gastrointestinal tolerability was
good in this study, as the incidence of these
symptoms did not differ significantly between
pramipexole and placebo groups. However, in
early Parkinson’s disease gastrointestinal symp-
toms were more pronounced under
pramipexole.7

Postural hypotension was only slightly more
frequent in the pramipexole group; this is in
accordance with the early Parkinson’s disease
studies, in which there were also no major dif-
ferences between the treatment groups with
respect to postural hypotension.5,7

The higher incidence of dyskinesia, which is
indeed a major problem of long term therapy of
Parkinson’s disease, is most likely to be due to
the introduction of pramipexole as an add on
therapy. As patients were not asked to change
their previously stabilised antiparkinson-
nian medication (including levodopa), the
higher incidence of dyskinesias compared with
placebo might be related to a dopaminergic
overstimulation under pramipexole when
added to levodopa. Nevertheless, a preliminary
study of pramipexole in patients with advanced
Parkinson’s disease showed that these dyskine-
sias could be controlled by lowering the level of
levodopa medication.5

In conclusion, pramipexole is an effective
and well tolerated add on therapy in advanced
Parkinson’s disease with motor fluctuations.

Pramipexole improved motor functions, activi-
ties of daily living, and reduced “off” time
during the waking day which resulted in more
hours of “on” time each day.

The following investigators and coinvestigators were involved in
the multicentre design of this study: C Albani, Zuerich, Switzerland;
B Conrad, Munich, Germany; W Gehlen, Bochum, Germany;
Mierau J, Bechtel WD. SND 919 inhibits dopamine release
1 Mierau J, Schneider FJ, Ensinger H, et al. Pramipexole
binding and activation of cloned and expressed dopamine
2 Mierau J, Bechtel WD. SND 919 inhibits dopamine release


Efficacy, safety, and tolerance of the non-ergoline dopamine agonist pramipexole in the treatment of advanced Parkinson’s disease: a double blind, placebo controlled, randomised, multicentre study

M M Pinter, O Pogarell and W H Oertel

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