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Pramipexole versus sertraline in the treatment of depression in Parkinson's disease

A national multicenter parallel-group randomized study

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■ **Abstract** In addition to treating the motor symptoms of Parkinson's disease, the dopamine agonist pramipexole has shown an antidepressant effect. The trials, however, included patients with motor complications, raising the question of whether the antidepressant benefit represented only a treatment-related motor improvement. To address this issue, we have conducted a 14-week randomized trial comparing pramipexole with an established antidepressant in patients without motor complications. At

seven Italian centers, 67 Parkinsonian outpatients with major depression but no history of motor fluctuations and/or dyskinesia received open-label pramipexole (at 1.5 to 4.5 mg/day) or sertraline (at 50 mg/day). In both groups, the Hamilton Depression Rating Scale (HAM-D) score decreased throughout 12 weeks of treatment, but in the pramipexole group the proportion of patients who recovered, as defined by a final HAM-D score ≤ 8 , was significantly higher, at 60.6% versus 27.3% ($p = 0.006$). Patients' self-ratings improved in both groups. All adverse events were mild or moderate, but five patients (14.7%) withdrew from the sertraline group. Despite the absence of motor complications, the pramipexole recipients showed improvement on the Unified Parkinson's Disease Rating Scale (UPDRS) motor subscore. We conclude that dopamine agonists may be an alternative to antidepressants in Parkinson's disease.

■ **Key words** Parkinson's disease · depression · pramipexole · sertraline

Introduction

Depression is a common complication of Parkinson's disease (PD), and its impact is often severe: in a recent survey of PD patients, it accounted for approximately 40% of the variability in quality-of-life scores [8]. Nevertheless, there is little evidence concerning the efficacy and safety of antidepressant therapies. A recent meta-analysis [26] describes a large effect size, but no larger than that of placebo, and less benefit than in elderly patients without PD. The uncertainties are heightened by conflicting evidence of a potential of selective serotonin reuptake inhibitors (SSRIs) to exacerbate parkinsonism [2, 21, 24].

Pramipexole is a non-ergoline dopamine receptor agonist with high binding specificity for the D3 receptor subtype [13]. Clinical trials have shown it to be effective in treating motor symptoms of PD [15, 17, 22]. In addition, an antidepressant effect has recently been documented in major depressive disorder [3, 23] and in bipolar depression [9, 27]. An antidepressant effect has also been identified in PD [14, 19]. In a prospective randomized study, pramipexole was compared with the ergoline D2 dopamine receptor agonist pergolide [19]. Both agonists exhibited an antidepressant effect, as measured by the Zung self-rating depression scale, but only pramipexole showed a significant decrease in the average score on the Montgomery-Åsberg Depression Rating Scale. In another study, a prospective observational trial in 657 PD outpatients, pramipexole significantly reduced anhedonia, a core symptom of depression [14].

In both studies, pramipexole improved motor symptoms, raising the question of whether the benefit against depressive symptoms might be secondary to drug-related motor improvement instead of representing a specific antidepressant activity. In fact, PD patients were included in both studies regardless of motor complications such as fluctuations or dyskinesia, either of which might influence depressive symptoms [16] [18]. To address these issues, we have conducted a 14-week multicenter, randomized, parallel-group study designed to evaluate pramipexole compared with the SSRI sertraline for the management of depressive symptoms in PD patients without motor complications and under stable levodopa treatment.

Methods

Subjects

At seven centers in Italy, outpatients suffering from idiopathic PD according to the United Kingdom Parkinson's Disease Brain Bank criteria [7] were screened for major depression according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) [1]. Patients became eligible for the study if they met the following further criteria:

(1) a Hamilton Depression Rating Scale (HAM-D) [10] total score ≥ 16 on the instrument's 17-item scale; (2) stable treatment with levodopa, alone or in combination with other antiparkinsonian drugs, but not dopamine agonists; (3) no history of motor fluctuations and/or dyskinesia; and (4) a PD rating of 1.5 to 4 on the Modified Hoehn and Yahr scale [12].

Exclusion criteria were: (1) use of dopamine agonists, typical or atypical neuroleptics, alpha-methyl dopa, cinnarizine, flunarizine, or investigational drugs during the preceding three months; (2) use of antidepressants during the preceding month; (3) history of psychosis; (4) suicide attempts during the preceding 12 months, or a severe suicidal tendency (score ≥ 3 on HAM-D item 3, suicide); and (5) cardiovascular disease and/or symptomatic orthostatic hypotension.

After being informed of the study's nature, scope, and possible results, all patients gave written consent. The study was conducted in accordance with the principles of Good Clinical Practice, and at all participating centers, the study protocol was approved by the local ethics committees.

Study design

The trial was multicenter and comparative, and after randomization, parallel groups received open-label pramipexole or sertraline. All assessments were performed by a trained rater blinded to treatment assignments.

At study entry (Visit 1), informed consent was obtained, and each patient underwent clinical and neurological evaluation. Patients who qualified for the study then entered a two-week screening period, during which any antiparkinsonian treatment (anticholinergic agents, MAO-B or COMT inhibitors, amantadine) being combined with a patient's levodopa was discontinued. Patients continued to take levodopa at their previous dosage or at increased dosage, according to the investigator's judgment. The levodopa dosage was then kept fixed.

At two weeks (Visit 2), patients were evaluated to obtain baseline ratings and were randomized in a 1:1 ratio to receive pramipexole or sertraline. For pramipexole, therapy consisted of an initial seven weeks of dose titration and then a five-week maintenance period. During the first three weeks of titration, daily doses were started at 0.375 mg (0.125 mg t. i. d.) and were escalated to 1.5 mg/day (0.5 mg t. i. d.). During the next four weeks, the dose was kept flexible, within the bounds of 1.5 to 4.5 mg/day, so as to optimize each patient's clinical status. During the five-week maintenance period, the dosage was kept fixed until the final assessment of efficacy at the end of 12 weeks. For sertraline, daily doses were 25 mg during the first week and 50 mg during the following weeks until the final assessment after 12 weeks. Sertraline was administered once a day, in the morning.

The study drugs were commercially available. Levodopa preparations provided levodopa in combination with either carbidopa or benserazide. To reduce risk of adverse events, use of the antiemetic domperidone (20 mg t. i. d.) was permitted.

Clinical assessments of safety and efficacy were performed at entry (Visit 1), at baseline (Visit 2), during the seven-week titration period (Visits 3 and 4, at the end of the third and seventh week), and at the end of the study, corresponding to the end of the 12-week treatment period (Visit 5). Efficacy assessments included the 17-item HAM-D rating scale [10], the Zung self-rating depression scale [28], the Short-Form health survey (SF-36) total score [25], and the Unified Parkinson's Disease Rating Scale subscores for activities of daily living and for motor function (UPDRS Parts II and III) [6]. Safety and tolerability were assessed by recording adverse events and by measuring vital signs. Routine laboratory measurements were performed at entry (Visit 1) and at the end of the 12-week therapy period (Visit 5).

The primary outcome measure was change in the HAM-D total score, expressed as the difference between the baseline (Visit 2) and final (Visit 5) scores for each of the two treatment groups. Secondary measures were changes from baseline to endpoint in UPDRS Parts II

and III, the Zung self-rating depression scale total score, and the SF-36 total score. Responders were defined as having at least a 50% reduction in HAM-D total score, and full recovery was defined as a final HAM-D total score ≤ 8 .

Data analysis

All efficacy analyses were of the study's intent-to-treat (ITT) population, defined as comprising all randomized patients who received at least one dose of trial medication and for whom a baseline and at least one post-baseline assessment were available. A Shapiro-Wilk test was employed to verify the normal distribution of both primary and secondary variables. In case of non-normality, a rank transformation of the original data was applied. For the primary variable, differences between the treatment groups were analyzed by an ANCOVA model. The center effect was not considered because the center size was not representative.

For the secondary variables, descriptive statistics and frequency tables were calculated. The endpoint total score of the Zung scale and UPDRS Part II and III were analyzed by the ANCOVA model, using baseline total score as covariate. The two components of the SF-36 (standardized physical component, or PCS, and standardized mental component, or MCS) were analyzed by means of the Wilcoxon test between treatments. The relationship between HAM-D total score and UPDRS Part II and III subscore was calculated as a Spearman rank correlation coefficient.

Results

Demographics

Of the 71 patients who were screened, 67 were randomized, 33 to receive pramipexole and 34 to receive sertraline. Demographic characteristics including age and sex were similar between the two treatment groups. The groups were also homogeneous for PD severity and for depression severity at baseline (Table 1). Among the 67, all but nine (six in the pramipexole group and three in the sertraline group) had been taking stable doses of levodopa alone. The adjunctive agents had been amantadine (four patients), biperidene (three patients), and entacapone (two patients), all of which were withdrawn during the two-week period preceding randomization and baseline evaluation (Visit 2). During the same period, the daily levodopa dosage was slightly adjusted in both groups (see Table 1).

The trial profile and allocation of patients are depicted in Fig. 1. Eight patients discontinued the trial prematurely: one in the pramipexole group (who was lost to follow-up) and seven in the sertraline group (including five due to adverse events, one due to protocol violation, and one lost to follow-up).

At the study's end, the mean (\pm SD) daily doses of pramipexole and sertraline in the ITT population were 3.24 ± 1.3 mg and 48.1 ± 5.9 mg, respectively.

Table 1 Demographic Characteristics*

	Pramipexole (N = 33)	Sertraline (N = 34)
Mean age \pm SD, years	64.8 \pm 8.3	68.1 \pm 6.5
Men/Women, %	51.5/48.5	52.9/47.1
Hoehn & Yahr stage, median	2	2.5
HAM-D total score, mean \pm SD	19.7 \pm 3.5	21.33 \pm 4.4
UPDRS Part II, activities of daily living subscore, mean \pm SD	12.6 \pm 6.5	12.2 \pm 5.7
UPDRS Part III, motor subscore, mean \pm SD	26.5 \pm 11.2	28.2 \pm 10.4
Levodopa daily dose, mg, mean \pm SD		
At screening	427.7 \pm 198.2	429.4 \pm 181.4
At baseline	487.8 \pm 218.7	456.2 \pm 199.6
Other antiparkinsonian treatments** at screening, patients (%)		
Amantadine	3 (9.1)	1 (2.9)
Biperidene	2 (6.1)	1 (2.9)
Entacapone	1 (3.0)	1 (2.9)

* Values are for the baseline visit unless otherwise indicated

** During the two-week screening period, all patients discontinued all antiparkinsonian treatments adjunctive to levodopa, including anticholinergic agents, MAO-B inhibitors, COMT inhibitors, and amantadine

Efficacy

In both the pramipexole and the sertraline group, the total HAM-D score decreased progressively. The overall difference was -10.76 ± 5.74 for the pramipexole group and -9.03 ± 7.28 for the sertraline group (Fig. 2). A between-time statistical analysis by Student's test for paired data was highly significant ($p < 0.001$) for both groups. By ANCOVA analysis, the difference between the two treatments showed a trend toward statistical significance ($p = 0.055$).

In the pramipexole group, 20 patients, or 60.6%, recovered (as defined by a total HAM-D score ≤ 8 at endpoint), a percentage significantly higher ($p = 0.006$) than that for the sertraline group (9 patients, 27.3%). Twenty-three patients, or 69.7%, responded to pramipexole (as defined by at least a 50% reduction in HAM-D total score), compared with 16 (48.5%) who responded to sertraline, but by Chi-square test this difference was not significant ($p = 0.08$). Applied to the difference between baseline and endpoint scores for single items on the HAM-D scale, the ANCOVA model showed a significant difference between treatment groups for only one item (genital symptoms).

The total score on the Zung self-rating scale also decreased significantly in both treatment groups, from 48.1 ± 7.4 at baseline to 35.5 ± 10.5 at endpoint for pramipexole ($p < 0.0001$, Wilcoxon test) and from 49.8 ± 7.7 to 39.3 ± 8.8 for sertraline ($p < 0.0001$, Wilcoxon test). By ANCOVA analysis, the difference be-

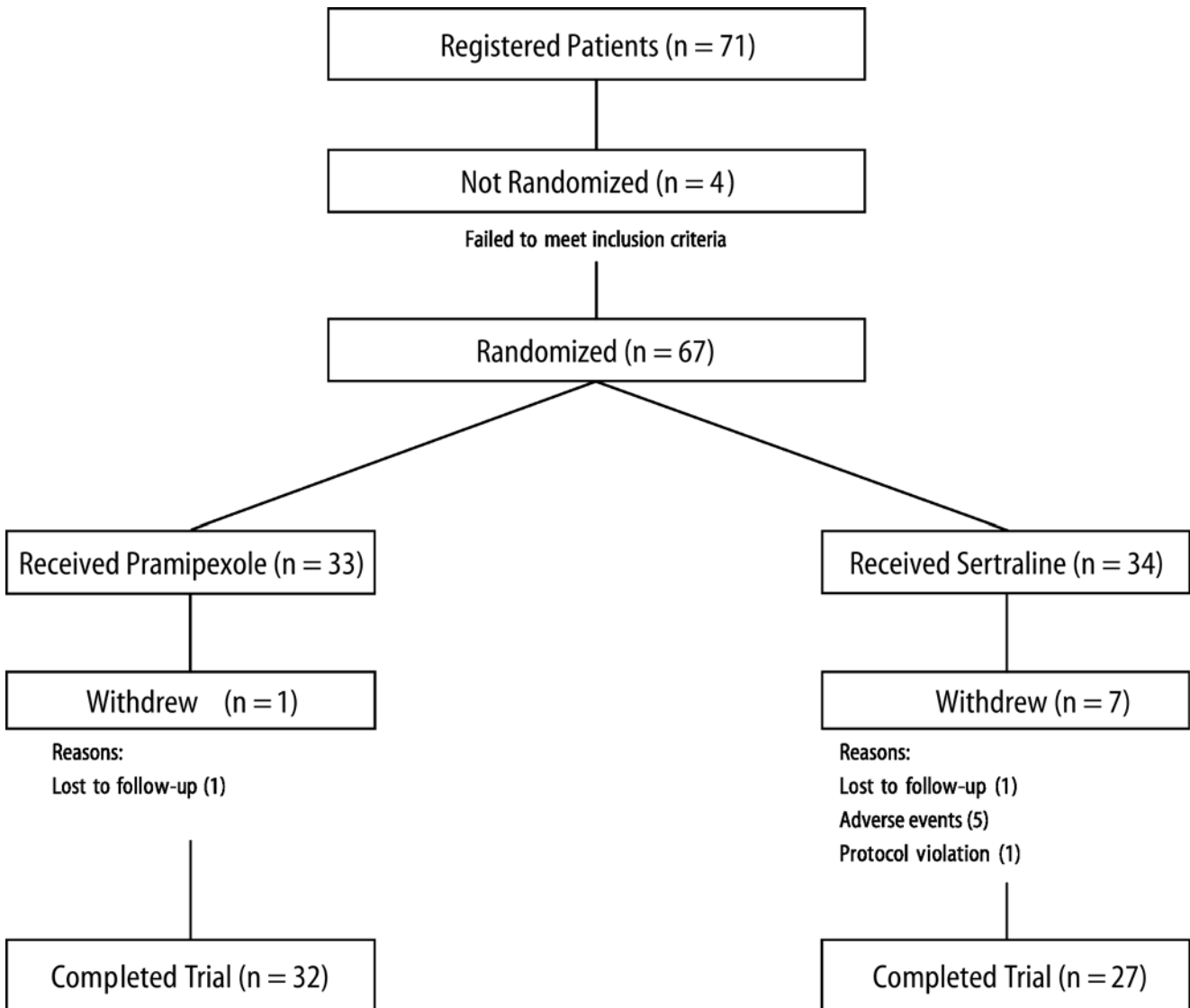


Fig. 1 Trial profile. Flow diagram summarizes participants, number of randomizations, and withdrawals

tween treatments was not significant ($F = 0.56$; $p = 0.4586$). A Spearman correlation analysis revealed a high, significant correlation between HAM-D and Zung endpoint total scores, and also between the changes in the two scales' total scores ($p < 0.0001$).

In both groups, the patients' evaluations of their own health, as quantified by the SF-36 questionnaire, showed a general improvement. For the standardized physical component (PCS), the difference between baseline and endpoint was 4.6 ± 7.4 in the pramipexole group ($p = 0.0001$, Wilcoxon test for paired data) and 2.9 ± 6.7 in the sertraline group ($p < 0.05$). The difference between the two treatments was not significant (Fig. 3A). For the standardized mental component (MCS), the difference between baseline and endpoint was 14.5 ± 11.9

in the pramipexole group ($p < 0.0001$, Wilcoxon test for paired data) and 9.7 ± 15.2 in the sertraline group ($p = 0.0008$). Again, the difference between the groups was not significant (Fig. 3B).

Spearman analysis revealed a significant correlation between HAM-D and SF-36 endpoint scores for both PCS and MCS components. For endpoint-baseline differences, the correlation between HAM-D and SF-36 was significant for both PCS and MCS in the pramipexole group (PCS: $p < 0.0075$; MCS: $p < 0.0001$) and for MCS ($p < 0.0001$) but not PCS in the sertraline group.

In both groups, the UPDRS Part II subscore improved, by a mean of 2.8 ± 3.5 for the pramipexole group and 1.8 ± 4.3 for the sertraline group. The change was statistically significant only for the pramipexole group

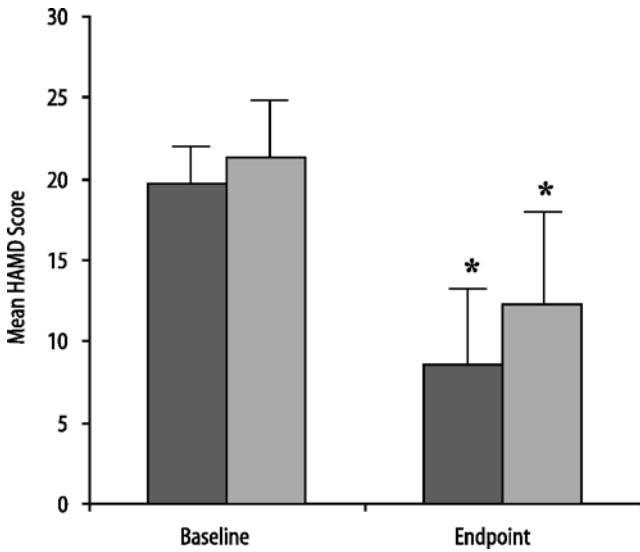


Fig. 2 Mean Hamilton Depression Rating Scale (HAM-D) score at baseline (left bars) and endpoint (right bars) for recipients of pramipexole (solid bars) or sertraline (shaded bars). Error bars represent standard deviations (SDs). Asterisks mark significant changes ($P < 0.001$) from baseline to endpoint

($p < 0.05$, Wilcoxon test). By ANCOVA analysis, the difference between the groups was not significant. In both groups, the UPDRS Part III subscore also improved, by 5.7 ± 8.5 for the pramipexole group and 0.9 ± 7.2 for the sertraline group (Fig. 4). Again, the change was significant only for the pramipexole group ($p < 0.05$, Wilcoxon

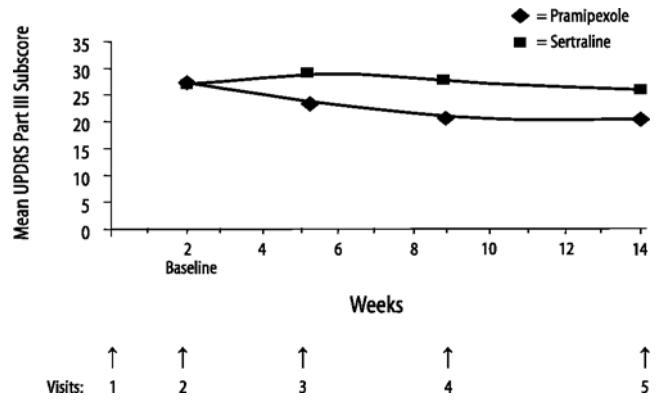


Fig. 4 Trends for mean Unified Parkinson's Disease Rating Scale (UPDRS) Part III (motor) subscores through 12 weeks of treatment with either pramipexole (diamonds) or sertraline (squares). For the pramipexole group, the change from baseline to endpoint was statistically significant ($P < 0.05$, Wilcoxon test), as was the difference between treatment groups ($F = 5.82$; $P = 0.0187$, ANCOVA analysis)

test). By ANCOVA analysis, this difference between the groups did have statistical significance ($F = 5.82$; $p = 0.0187$). Spearman analysis showed no relationship between HAM-D total score and UPDRS Part II ($p = 0.1260$) or Part III ($p = 0.2661$) subscores.

Safety and tolerability

Overall, 11 patients reported at least one adverse event. Of these patients, three were in the pramipexole group

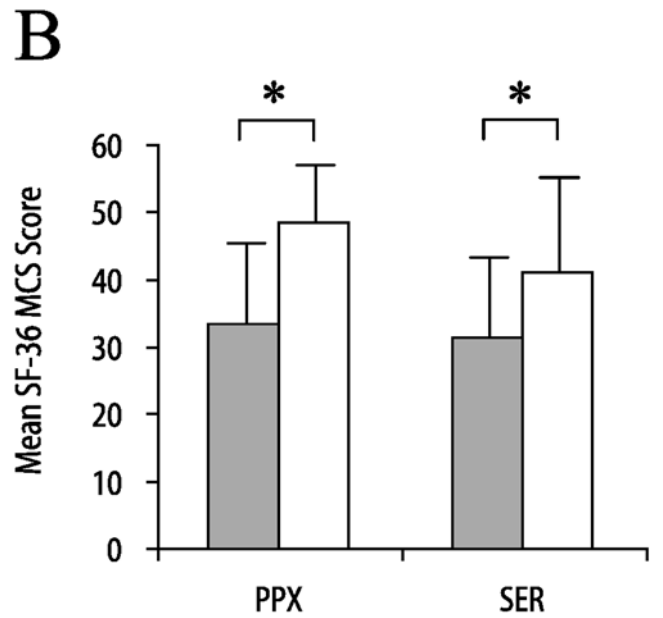
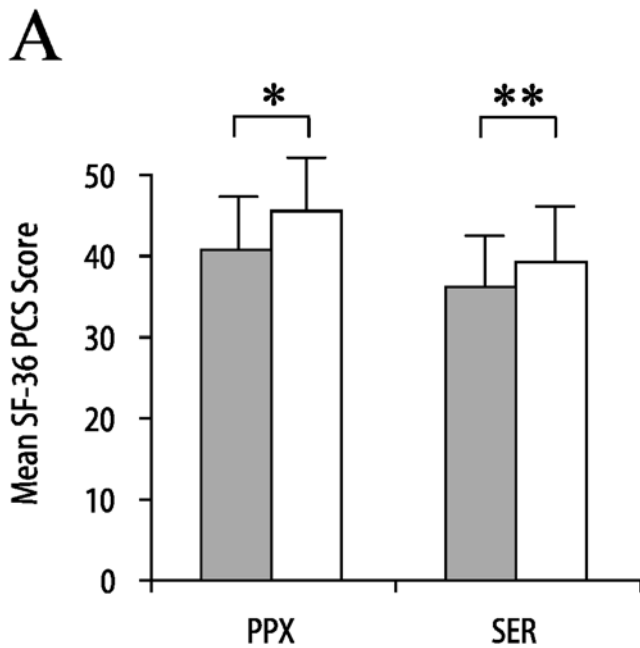


Fig. 3 Mean scores for the standardized physical component (A) and standardized mental component (B) of the Short-Form health survey (SF-36), as measured at baseline (grey bars) and endpoint (white bars) among recipients of pramipexole (PPX) or sertraline (SER). Error bars represent SDs. Asterisks mark significant differences (* $P < 0.0001$; ** $P < 0.05$) in changes from baseline to endpoint

(9.1%; 4 adverse events), and the other eight in the sertraline group (24.2%; 11 adverse events). Among pramipexole recipients, the reported events were one case each of dyskinesia, nausea, abdominal pain, and hypothyroidism. Among sertraline recipients, the events were two cases of vertigo, two of nausea, and one each of anxiety, abdominal pain, diarrhea, asthenia, palpitation, influenza, and tremor. All events were rated as mild (five events in the sertraline group) or moderate (four events in the pramipexole and six in the sertraline group).

No patients withdrew from pramipexole treatment, but five withdrew from sertraline. The reported reasons included nausea (two cases), vertigo, anxiety, and abdominal pain. Neither treatment produced clinically significant abnormalities in any vital signs or laboratory tests.

Discussion

The present trial is the first randomized, parallel-group study to compare the dopamine agonist pramipexole with an established antidepressant, in this instance sertraline, for treating depression in PD. Both pramipexole and sertraline ameliorated depressive symptoms, as indicated by a significant reduction ($p < 0.001$) in HAM-D total score between baseline and endpoint evaluations. The antidepressant activity of each drug was confirmed by a secondary analysis of responders, defined as patients with a 50% decrease in total HAM-D score. In another secondary analysis—the percentage of recovered patients, defined as those with a total HAM-D score of ≤ 8 at the endpoint—pramipexole was significantly more effective than sertraline. By a different assessment of depression, the Zung self-rating score, both drugs again showed antidepressant efficacy, with no difference between the two treatments. Similarly, the patients' general health status, as evaluated by SF-36 score, improved on both treatments and exhibited correlation with HAM-D score.

By the end of the study, the mean dosage of pramipexole was 3.24 mg/day, a level consonant with the investigators' efforts to achieve optimum benefit. For its part, the sertraline dosage was chosen on the basis of previous observations that 50 mg/day improves depression in PD with good tolerability [5]. As the study progressed, pramipexole was well tolerated, and adverse events never led to discontinuation. On the other hand, five of the 34 sertraline-treated patients (14.7%) discontinued their treatment.

Few previous studies have explored the utility of pramipexole as an antidepressant in PD. A randomized, open-label comparative trial reported a significant decrease in Zung depression score after eight months of either pramipexole or pergolide; improvement on the Montgomery-Åsberg Depression Rating Scale was seen

only among the pramipexole recipients [19]. Another, observational study involving 657 PD outpatients found that pramipexole improved anhedonia, as evaluated by the Snaith-Hamilton Pleasure Scale [14]. Both studies included PD patients with motor complications such as fluctuations and dyskinesia. Because depression may be related to the alternation of on- and off-time [16, 18], the reported improvement of depressive symptoms may have depended not on direct antidepressant activity but on the amelioration of parkinsonism achieved by the administration of a dopamine agonist. In both studies, pramipexole indeed improved motor symptoms and motor complications, as indicated by reduction in UPDRS Part III and IV subscores.

The present study met more rigorous design criteria. In addition to the overall design (using randomized, parallel groups), the exclusion of patients with any history of motor complications helped to limit the risk that motor fluctuations might affect depression. Despite the absence of fluctuations, we found an improvement in the UPDRS Part III, or motor, subscore, among the pramipexole but not the sertraline recipients, in line with an expectation that increasing the dopaminergic tone of patients already under stable levodopa treatment might yield an added improvement in motor symptoms. At the same time, no statistical correlation was found between motor improvement and relief of depressive symptoms, suggesting that pramipexole might exert an antidepressant activity independent of its effect on motor symptoms.

The results of the present study are also consistent with earlier clinical findings that SSRIs might be useful for treating depression in PD [5, 11]. To our knowledge, the present study is the largest to have explored the use of sertraline for depression in PD. Although the antidepressant efficacy of sertraline was found to be similar to that of pramipexole, the sertraline recipients experienced more adverse events, which in five cases (among 34 patients) were responsible for treatment discontinuation. In several anecdotal reports, sertraline, like other SSRIs, has been associated with the induction of a reversible parkinsonism, mainly in elderly persons [21]. In the present study, no significant worsening of parkinsonism was observed in the sertraline group.

Because the present trial was designed to compare pramipexole (at doses appropriate to manage the motor symptoms of PD) with an antidepressant (at doses appropriate for depression), the design did not include a placebo arm. Taken together, recent antidepressant trials suggest a substantial placebo effect [26], but recent evidence also suggests that the effect may be unavoidable, representing the activity of dopaminergic reward mechanisms triggered by a patient's expectation of clinical benefit [4]. In this regard, it is pertinent that sertraline, like other SSRIs, may promote release of dopamine in the frontal cortex [20].

Although we cannot exclude a placebo effect, we found that with sertraline as the comparative standard, pramipexole ameliorated depression in PD, with slight differences in efficacy in favor of pramipexole. The implication is that dopamine agonists, at the same doses utilized to manage motor symptoms, may be an alterna-

tive to antidepressant drugs for treating depression in PD. The ancillary benefits of this approach would include an agonist-related improvement of motor symptoms without antidepressant-related risks of adverse events.

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