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Brief Report

# Risperidone in the Treatment of Dopamine-Induced Psychosis in Parkinson's Disease: An Open Pilot Trial

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**Summary**

PURPOSE: To evaluate the safety and efficacy of risperidone in patients with Parkinson's disease (PD) who are experiencing significant dopamine-induced psychosis.

PATIENTS AND METHODS: Seventeen patients (median age, 72 yrs) participated in this 12-week, open pilot study receiving 0.5 to 3 mg oral risperidone per day. Maintenance antiparkinsonian medication was continued throughout, although psychotropic medication was discontinued.

EFFICACY RESULTS: Risperidone produced a substantial improvement in psychotic symptoms, shown on the mean total positive subscale score on the Positive and Negative Syndrome Scale (PANSS) by a 30% improvement (−3.1 decrease) after 1 week and a 66% improvement (−6.8 decrease) at end point. This improvement was most evident in the items delusions, hallucinatory behavior, and suspiciousness/persecution. Risperidone also achieved significant improvement from baseline in Clinical Global Impression (CGI)-severity and CGI-improvement ($p < 0.001$, Page test). Risperidone treatment did not adversely affect symptoms specific to Parkinson's disease, as assessed by the Unified Parkinson's Disease Rating Scale (UPDRS).

SAFETY RESULTS: Sixteen patients reported at least one adverse event, but only two patients withdrew as a result of adverse events. No significant changes or clinically relevant abnormalities were observed in laboratory parameters or vital signs.

CONCLUSION: Short-term use of risperidone (mean dosage, 1.1 mg per day) improves the psychopathology of patients with PD who have dopamine-induced psychosis without adversely affecting the symptoms of PD. Higher doses and long-term use were not addressed in this study and may be precluded by extrapyramidal side effects.

**Key Words:** Risperidone—Parkinson's disease—Psychosis—Extrapyramidal symptoms.

Parkinson's disease (PD) is a progressive neurodegenerative disease that causes serious disability. Patients experience increasing motor dysfunction with the typical associated symptoms inducing rigidity, tremor, akinesia, and bradykinesia.[1–4] Such symptoms arise as a result of neuronal degeneration in the basal ganglia, which creates a deficiency in nigrostriatal dopamine. Thus, the mainstay of current treatment of this illness are drugs that enhance dopaminergic transmission, most commonly levodopa.

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While dopamine replacement therapy has proven useful in alleviating motor symptoms in most patients with PD, after long-term use significant numbers of patients may develop psychotic features. Notably, the incidence of treatment-related psychoses in patients with PD increases with increasing dose and duration of treatment[5,6] and is also more common when there is a history of psychiatric illness in the patient or in a first-degree relative.[7]

Management of dopamine-induced psychoses with neuroleptics or by a reduction in dosage of dopaminomimetic therapy generally results in a worsening of parkinsonian symptoms.[6,8–10] Most conventional neuroleptics induce extrapyramidal symptoms (EPS), such as dystonia, akathisia, and dyskinesia. Clozapine, an atypical antipsychotic, has proven effective in treating patients

with PD who have drug-induced psychosis.[11–13] It causes few or no EPS[14,15]; however, the risk for agranulocytosis has prompted clinical trials with newer antipsychotics such as risperidone and olanzapine.[10,16,17]

Risperidone is an atypical antipsychotic and combines serotonin 5-$HT_2$ and dopamine-$D_2$ antagonists. When used in appropriate doses, induction of EPS tends to be minimal, but is ultimately dose-dependent.[18] Drug-induced EPS have been shown to decrease in patients with schizophrenia who were treated with risperidone.[19–22] Moreover, the efficacy of risperidone as an antipsychotic has been established in patients with schizophrenia, in both preliminary open studies[23–27] and subsequent double-blind, controlled trials.[19–21,28–32] The pharmacologic profile of risperidone and its low incidence of EPS suggests that it could be useful in the treatment of elderly patients,[18] especially those with PD and dopamine-induced psychosis. Indeed, a number of small-scale studies have indicated that risperidone is safe and effective in this population.[16,33–37]

To further evaluate the tolerability, safety, and efficacy of risperidone in patients with PD who are experiencing significant dopamine-induced psychosis, an open pilot study was undertaken.

## METHODS

### Study Design

This was a 12-week, open pilot study to evaluate the safety, tolerability, and efficacy of risperidone in patients with PD who had dopamine-induced psychosis.

Patients were recruited from hospitals in Canada (one center) and Belgium (two centers). Male or female patients, aged 40 to 80 years, were included. The primary clinical presentation was consistent with idiopathic PD, and patients showed signs and symptoms of psychosis primarily related to their antiparkinsonian medication. All patients demonstrated significant psychosis (defined by a score of $\geq$4 on at least one item of delusions, hallucinations, or suspiciousness/persecution in the Positive and Negative Syndrome Scale [PANSS]).

Patients had been treated with dopamine-enhancing agents for a minimum of 24 consecutive months. Patients were typically on levodopa–carbidopa in doses ranging from 300 mg to 1000 mg of levodopa with an average of 500 mg. Approximately one third of patients included in the study also received agonist therapy with bromocriptine. Doses for the latter ranged from 10 mg to 20 mg. No anticholinergics or MAO-B inhibitors were used. The attending neurologist attempted to optimize the therapeutic index of antiparkinsonian medication relative to psychosis before entry of patients into the current study. Attempts were made to simplify antiparkinsonian drug therapy by eliminating those agents most likely to aggravate psychotic symptoms before study entry. The approach used is described in an algorithm published by Mendis et al.[38] Antiparkinsonian drug treatment remained stable for a period of 1 month before study entry.

Patients had to discontinue current antipsychotic medication 1 week before study entry and all other psychotropic medications $\geq$2 weeks before study entry. An exception to this rule was the use of antidepressants which were permitted throughout the study. Anticholinergic medication prescribed for the treatment of parkinsonian symptoms was also allowed. Patients were asked not to begin vitamin B6 therapy during the study; if the patient was taking vitamin B6 at enrollment, dose and frequency had to remain stable throughout the trial.

Excluded from the study were patients with a current diagnosis (according to DSM-IV) of substance abuse or dependence, anxiety disorder, major depression, or schizophrenia; patients with a clinically relevant, serious, or unstable illness other than PD; those with clinically relevant cardiovascular disease, hepatic/renal disease, abnormal electrocardiographic findings or laboratory abnormalities at study entry, a history of hematologic abnormality, hypersensitivity to neuroleptic treatment, or neuroleptic malignant syndrome; patients presenting with tardive dyskinesia; those who had received an investigational drug in the 4 weeks before the study and those who, in the opinion of the investigator, were likely to be uncooperative or unable to comply with the requirements of the study. In addition, women of reproductive potential were excluded if their contraception was considered inadequate or if they were pregnant or lactating.

Oral risperidone at a dosage of 1 mg/mL, 0.5 to 3 mg per day, was administered for 12 weeks. The starting dose was 0.25 mg per day and this was increased, at the discretion of the investigator, in increments of 0.25 mg per week according to the patient's response. The maximum daily dose of risperidone was 3 mg. If necessary, dosage could be titrated downward at any time during the study in decrements of 0.25 mg per day, to a minimum dosage of 0.5 mg per day.

Compliance was assessed by measurement of risperidone plasma concentration, measuring all unused medication returned at the end of the study, as well as questioning by the investigator.

### Efficacy

Efficacy was assessed at weekly visits from week 1 to week 12; however, visits at weeks 7, 9, 10, and 11 were

optional. End point was defined as the last evaluable visit and all patients were included in the analysis.

### Primary Efficacy Variable

At each visit, patients were rated on the positive subscale of the PANSS.[39] This subscale comprises those seven items of the 30-item PANSS which assess the dopamine-induced psychotic symptoms experienced by the parkinsonian patient (delusions, conceptual disorganization, hallucinatory behavior, excitement, grandiosity, suspiciousness, hostility). Each of the seven items was evaluated based on a 7-point rating scale. The negative and general psychopathology subscales were omitted because many of the items categorized under these subscales are inherent to the parkinsonian disease state.

### Secondary Efficacy Variables

At each visit, the overall severity of psychosis (CGI-severity) and the overall change versus baseline (CGI-improvement) were assessed using the Clinical Global Impression (CGI) scale.[40] In addition, patients were rated at each visit on the Unified Parkinson's Disease Rating Scale (UPDRS).[41] The UPDRS is the accepted scale for assessing motor and functional status in the PD population, and was therefore used in this study, instead of the other traditional EPS scales. Organized in six subscales, the UPDRS rates a variety of clinical variables: (I) mentation, behavior, and mood; (II) activities of daily living; (III) motor examination; (IV) complications of therapy; (V) modified Hoehn and Yahr staging; and (VI) Schwab and England activities of daily living scale. This scale provided an overall assessment of the patients in terms of their self-reported disability (activities of daily living) and clinical examination of motor ability. Items within the motor examination section evaluated the presence of and changes in motor symptoms associated with PD.

**TABLE 1.** *Demographic data*

| | |
|---|---|
| Gender | |
| Female | 7 (41.2%) |
| Male | 10 (58.8%) |
| Mean age in years (SE) | 71.2 (1.29) |
| Mean weight in kg (SE) | 67.5 (3.52) |
| Mean height in cm (SE) | 160.6 (2.68) |
| Family history of PD | |
| No | 14 (82.4%) |
| Yes | 3 (17.6%) |
| Mean age at onset of PD in years (SE) | 57.1 (1.81) |
| Previous treatment with antipsychotic medication | |
| No | 11 (64.7%) |
| Yes | 6 (35.3%) |
| Mean duration of present dopamine-induced psychosis in years (SE) | 2.8 (0.68) |

SE, standard error; PD, Parkinson's disease.

### Variables to Assess Tolerability

A routine physical and neurologic examination was performed at visits 1 (selection, week 0) and 13 (end of study, week 12). This included measurements of body weight and an electrocardiogram. In addition, blood pressure (systolic and diastolic) and heart rate were measured at visits 1, 7, and 13. Adverse events were recorded at each visit.

Routine laboratory analyses (hematology, blood biochemistry, and urinalysis) were performed at visits 1, 7, and 13. At visits 1, 12, and 13 a Mini-Mental State Examination (MMSE) was completed.

### Statistical Methods*

Based on the assumption of a mean score change from baseline to end point of 6 (standard deviation 8) on the positive subscale of the PANSS rating scale (range, 7–49), 19 patients were planned for completion of the study to establish this change with a Wilcoxon signed rank test with 90% power at the 5% significance level (two-tailed).

There were two primary efficacy outcomes. The first was the change from baseline score of the positive PANSS subscale total score (P1 to P7); the second was the change from baseline score for the key PANSS subscale total score (P1 + P3 + P6). Both parameters were analyzed by means of the Wilcoxon signed rank test.

Secondary outcomes were CGI-severity, CGI-improvement, total UPDRS, and clusters of UPDRS. The two CGI ratings were analyzed using the Page test, whereas the change from baseline of the UPDRS score was assessed using the Wilcoxon signed rank test.

### Ethics

Written informed consent was obtained from the patient or from the legal representative or legal guardian, if appropriate. The study was conducted in accordance with the Declaration of Helsinki and its subsequent revisions. The trial protocol and amendments were reviewed by the local independent ethics committee/institutional review board.

## RESULTS

### Patients

Seventeen patients (10 men) with a median age of 72 years (range, 57–79 yrs) were enrolled in the study. The median age at onset of PD was 60 years (range, 41–67 yrs) and the median duration of the current dopamine-induced psychosis was 1.6 years (range, 0.1–9.0 yrs). Demographic and clinical parameters at baseline are shown in Table 1. Three patients withdrew from the trial

*NCSS (Number Cruncher Statistical System) PASS (Power Analysis and Sample Size) version 1, 1991.

before completion because of lack of efficacy (n = 1) and adverse events (n = 2).

### Dose

The mean daily risperidone dose at end point was 1.05 mg per day. Furthermore, the mean optimal daily dose, based on the clinical judgment of the investigators, was 1.13 mg per day (median, 1 mg per day).

### Efficacy

#### Primary Efficacy Variable

At baseline, the mean total score on the PANSS positive subscale was 17.3 (Table 2). By the end of the first week of treatment, the PANSS positive total score had decreased by 30.1% (−3.1), demonstrating a rapid improvement in psychopathology. This improvement continued throughout the study until, at end point, there was a mean reduction of 66% (−6.8) from baseline in the PANSS positive total score ($p < 0.001$; Fig. 1). This reduction in the PANSS positive subscale mainly comprised a reduction (−4.2; $p < 0.001$) in the PANSS cluster of key items 1, 3, and 6 measuring psychosis, that is, delusions, hallucinatory behavior, and suspiciousness/persecution.

#### Secondary Efficacy Variables

The CGI-severity data show that there was a significant improvement in the severity of psychosis during the trial ($p < 0.001$, Page test). Indeed, the mean severity score decreased from 4.2 ("moderate–marked") at baseline to 2.5 ("very mild–mild") at end point (Fig. 2). Similarly, there was a significant improvement in the CGI scores over the 12-week study period indicating a significant overall improvement in psychotic symptoms ($p < 0.001$, Page test; Fig. 2). At end point, 16 patients had improved and one had remained unchanged.

UPDRS results are shown in Table 3. It can be seen that the orientation, behavior, and mood cluster gradually improved in the course of the 12-week trial. The mean shift from baseline was −2.5 (range, −9, +1) at end point, an improvement of 36.2% versus baseline ($p < 0.001$).

### Safety

Sixteen of 17 patients reported adverse events during the trial; adverse events (reported in three patients) are shown in Table 4.

Two patients withdrew from the trial because of adverse events. One patient withdrew as a result of hypokinesia, anxiety, impaired concentration, and abnormal gait; all these adverse events were considered to be possibly drug-related in the opinion of the investigator. Another patient experienced leucopenia and thrombocytopenia on day 25 and was withdrawn. However, 2 years after the trial, these abnormalities were still present. According to the consultant hematologist, these were not related to risperidone and were diagnosed as "idiopathic leucopenia and thrombocytopenia." With the exception of the latter, all reported adverse events were either mild or moderate.

The mean UPDRS total score and all UPDRS subcales (except orientation, behavior, and mood) showed no significant change during treatment (Table 3). Of particular importance was the motor examination subscale and activities of daily living subscale, which was used to assess the presence of and changes in the EPS associated with PD. As seen in Figure 3, risperidone treatment did not appear to adversely affect EPS as measured on the motor examination subscale.

The Mini-Mental State Examination showed a median score of 22.5 (range, 15–29) at baseline and virtually no change at week 12 and at end point, when the median score was 23. The mean shift from baseline was +0.3 at week 12 and +0.1 at end point.

No consistent, or clinically relevant, changes in blood chemistry or hematology were reported. There were no clinically relevant changes in blood pressure or heart rate

**TABLE 2.** *Summary of results on the PANSS positive subscale*

| Cluster item | Mean score at baseline | Mean score at week 12 | Mean score at end point | Mean shift from baseline at end point (SE) | p value (Wilcoxon test) |
|---|---|---|---|---|---|
| Total score PANSS-positive subscale | 17.3 | 9.4 | 10.5 | −6.8 (1.29) | <0.001 |
| Total score of the cluster with items 1, 3, and 6 | 9.8 | 4.9 | 5.6 | −4.2 (0.72) | <0.001 |
| Item score | | | | | |
| 1: Delusions | 2.5 | 1.4 | 1.6 | −0.9 (0.31) | 0.016 |
| 3: Hallucinatory behavior | 4.4 | 2.1 | 2.4 | −2.0 (0.36) | <0.001 |
| 6: Suspiciousness/persecution | 2.9 | 1.3 | 1.5 | −1.4 (0.39) | 0.008 |

PANSS, Positive and Negative Syndrome Scale; SE, standard error.

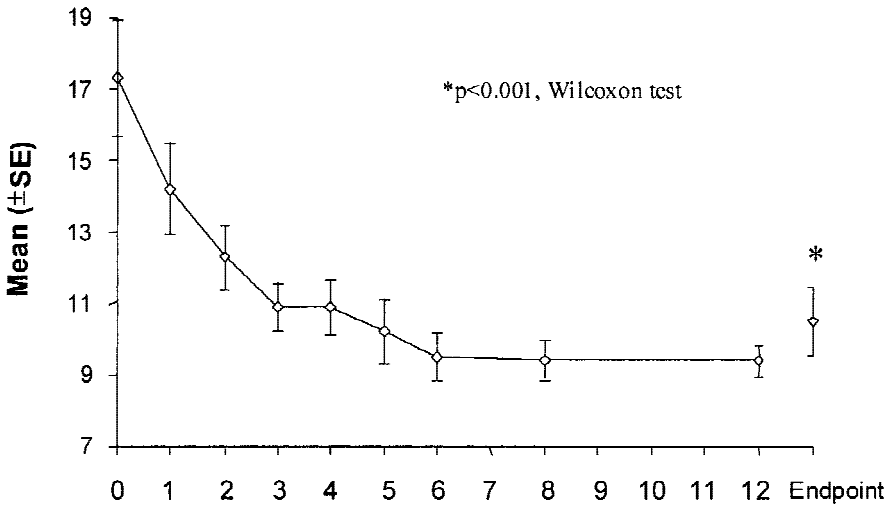


**FIG. 1.** Mean PANSS positive subscale score versus time.

during the course of treatment and no consistent trends were observed in any of the ECG parameters. In addition, no change was seen in the mean body weight of the patients after the 12-week treatment period.

## DISCUSSION

The treatment of dopamine-induced psychosis in PD has proven to be a difficult challenge for practitioners. Both a reduction in dopaminomimetic therapy and concomitant treatment with neuroleptics frequently worsen motor function.[10,42] Clozapine, an atypical antipsychotic, has been shown to improve psychosis without worsening motor disability in parkinsonian patients,[11,12] but has the disadvantages of causing sedation and conferring a risk of agranulocytosis.[43] Risperidone may offer an alternative treatment for such patients.

In the present study, a 66% improvement in the PANSS positive subscale score was reported at treatment end point. Moreover, risperidone showed a rapid onset of antipsychotic action, with a 30% improvement in this subscale after only 1 week of treatment. Because this early response was obtained while the risperidone dosage was still low (0.5 mg per day), it may be argued that the optimal dosage of risperidone might be lower than the 1.1 mg per day achieved at the end point of this trial.

PANSS data was supported by the CGI results, which showed significant improvement in psychosis, and by results from the UPDRS cluster of orientation, behavior, and mood, which gradually improved throughout the trial. This UPDRS cluster provides a measurement of severity of PD similar to that provided by the PANSS positive subscale. In the current study, improvement in psychotic symptoms throughout the course of risperidone treatment did not coincide with a deterioration in parkinsonian symptoms.

The results of the current trial are consistent with those of a number of earlier studies in which risperidone was found to be effective and safe in the treatment of

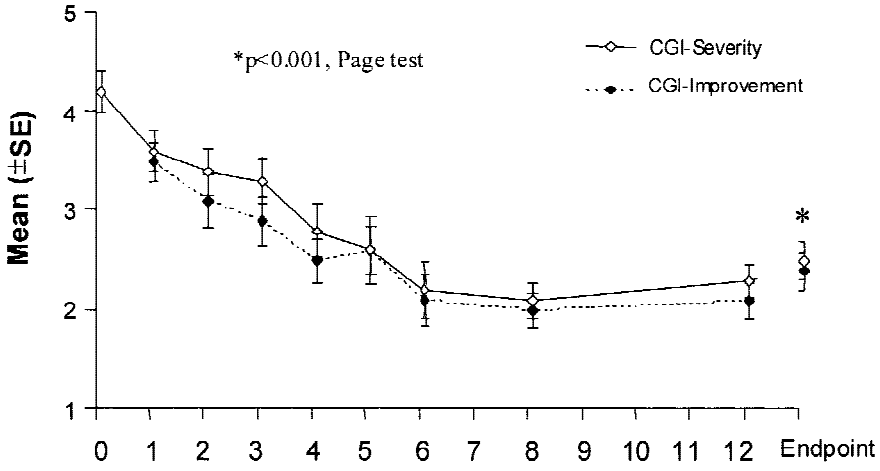


**FIG. 2.** Mean CGI-severity and CGI-improvement scores versus time.

**TABLE 3.** *Summary of results of the UPDRS*

| Cluster | Mean score at baseline | Mean score at week 12 | Mean score at end point | Mean shift from baseline at end point (SE) | p value (Wilcoxon test) |
|---|---|---|---|---|---|
| Orientation/behavior/mood | 6.9 | 4.2 | 4.4 | −2.5 (0.58) | <0.001 |
| Activities of daily living | | | | | |
| On | 17.9 | 17.6 | 16.8 | −1.1 (1.40) | 0.323 |
| Off | 28.6 | 27.5 | 26.6 | −0.5 (1.99) | 0.717 |
| Average on/off | 23.6 | 22.8 | 22.3 | −0.5 (1.45) | 0.740 |
| Motor examination | 25.6 | 28.5 | 27.2 | +1.6 (1.83) | 0.367 |
| Complications of therapy | 4.8 | 3.8 | 4.0 | −0.8 (0.60) | 0.218 |
| Hoehn & Yahr staging | 3.1 | 3.5 | 3.3 | +0.2 (0.16) | 0.406 |
| Schwab & England scale | 66.5 | 60.7 | 61.8 | −4.7 (2.73) | 0.158 |
| UPDRS total score | 58.0 | 56.8 | 55.5 | −0.5 (3.49) | 0.377 |

UPDRS, United Parkinson's Disease Rating Scale; SE, standard error.

dopamine-induced psychosis in patients with PD.[16,33–37] These studies involved 6 to 19 patients and assessed the safety and efficacy of risperidone over a range of doses from 0.125 to 2 mg per day. The length of treatment varied greatly between trials, for example, mean duration of the trial carried out by Meco et al.[35] was 34.8 weeks, compared with 16 months by Yuvarajan et al.[37]

By comparison, this present study examined the short-term effect of risperidone on dopamine-induced psychosis in patients with PD. Indeed, a significant response to the drug has been demonstrated within 12 weeks of treatment. The significance of these results was based on the inclusion of 19 patients into the trial; however, only 17 patients were recruited. Retrospective power calculations indicated a power of 80% was nonetheless maintained.

As a result of the short duration of this trial and the open design, it was not possible to determine whether the antipsychotic effect of risperidone was the result of a possible placebo or early treatment effect. However, previous long-term studies have shown risperidone to be efficacious and well-tolerated over periods of 1 to 2 years.[33,34,37]

A number of currently treated patients also evidenced dementia. In addition, depression can affect cognitive status, a confound which was not systematically assessed. However, many patients with PD who develop psychosis while being treated with anti-PD medications also have some degree of cognitive impairment. Future studies should therefore seek to differentiate psychotic symptoms related to dementia and depression.

Previous studies suggest that higher dosages of risperidone (1.5–4 mg per day) can worsen motor function in some patients with PD.[35,44,45] Therefore, it is suggested that risperidone treatment in patients with PD should be started with a low dose, and that this should be slowly titrated upward on an individualized basis. Although the mean dose at end point was 1.1 mg per day in this study, for some parkinsonian patients the optimal dose may be even lower.

Because the current study was not powered sufficiently to definitively answer the issue of motor worsening, larger studies will ultimately be required.

However, in the current trial risperidone achieved its antipsychotic effect without appearing to adversely affect the existing motor symptoms or daily functioning, as assessed by the UPDRS. In addition, safety data indicated that risperidone was relatively well tolerated in patients with PD. While other agents with the potential to treat dopamine-induced psychosis have been investigated, their possible efficacy is less well understood. In particular, olanzapine and quetiapine,[46] both new atypical antipsychotic agents, have been used to treat drug-induced psychosis in PD, as has ondansetron, a 5HT3 receptor agonist.[47,48] However, they have not been adequately assessed in controlled trials.[49]

It is also worthy of note that risperidone has a similar effect to typical neuroleptics in higher doses and may result in elevated prolactin levels and acute dystonia.[50] Tardive dyskinesia may occur with prolonged use. In the doses used, acute dystonia was not observed.

**TABLE 4.** *Most common adverse events (reported by ≥3 patients)*

| Adverse event (AE) | No. of patients reporting AE |
|---|---|
| Hypokinesia | 10 |
| Somnolence | 7 |
| Saliva increased | 7 |
| Fall | 6 |
| Dizziness | 6 |
| Constipation | 4 |
| Confusion | 4 |
| Fatigue | 3 |
| Leg cramps | 3 |
| Gait abnormal* | 3* |
| Depression | 3 |

* These three patients also had hypokinesia.

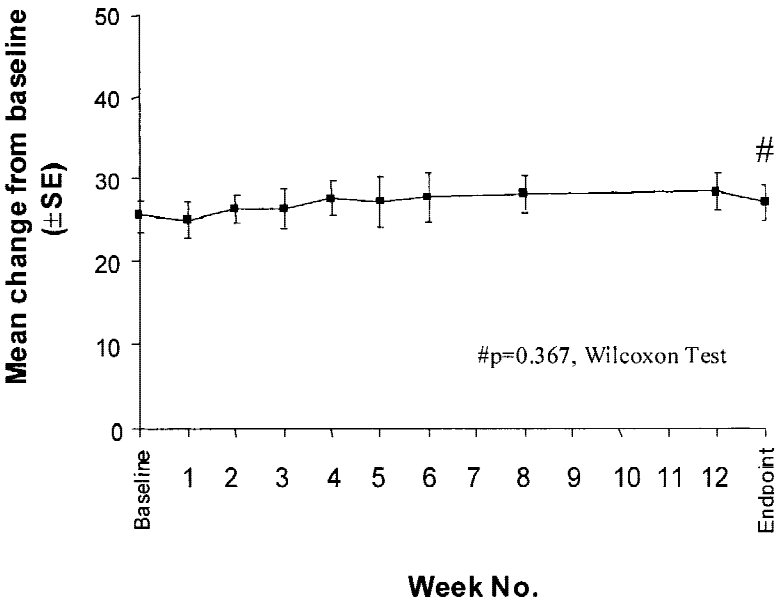


**FIG. 3.** Change in mean UPDRS motor examination scale with time.

In conclusion, the results of the trial indicate that 1 mg risperidone per day effectively reduces the psychopathology of patients with PD who have dopamine-induced psychosis, without adversely affecting the symptoms of PD and the patients' daily functioning, as measured by UPDRS. While these results suggest that risperidone in low doses has a therapeutic role, high doses and long-term use should be avoided because of the potential of long-term extrapyramidal side effects, an issue not addressed in the current investigation. Further, large controlled trials are required to confirm these promising preliminary results.

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## REFERENCES

1. Barbosa ER, Limongi JCP, Cummings JL. Parkinson's disease. *Psychiatr Clin North Am* 1997;20:769–790.
2. Hagan JJ, Middlemiss DN, Sharpe PC, Poste GH. Parkinson's disease: prospects for improved drug therapy. *Trends Pharmacol Sci* 1997;18:156–163.
3. Marsden CD. Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1994;57:672–681.
4. Playfer JR. Parkinson's disease. *Postgrad Med J* 1997;73:257–264.
5. Banjeree AK, Falkai PG, Savidge M. Visual hallucinations in the elderly associated with the use of levodopa. *Postgrad Med J* 1989; 65:358–361.
6. Weiner WJ, Koller WC, Perlik ST, Nausieda PA, Klawans HL. Drug holiday and management of Parkinson's disease. *Neurology* 1980;30:1257–1261.
7. Damasio AR, Antunes JL, Macedo C. Psychiatric aspects in parkinsonism treated with L-dopa. *J Neurol Neurosurg Psychiatry* 1971;34:502–507.
8. Fischer P, Danielczyk W, Simanyi M, Streifler MB. Dopaminergic psychosis in advanced Parkinson's disease. *Adv Neurol* 1990;53: 391–397.
9. Pfeiffer R. Optimization of levodopa therapy. *Neurology* 1992;42 (suppl 1):39–43, 57–60.
10. Young BK, Camicioli R, Ganzini L. Neuropsychiatric adverse effects of antiparkinsonian drugs. Characteristics, evaluation and treatment. *Drugs Aging* 1997;10:367–383.
11. Factor SA, Brown D, Molho ES, Podskalny GD. Clozapine: a 2-year open trial in Parkinson's disease patients with psychosis. *Neurology* 1994;44:544–546.
12. Friedman JH, Lannon MC. Clozapine in the treatment of psychosis in Parkinson's disease. *Neurology* 1989;39:1219–1221.
13. Trosch RM, Friedman JH, Lannon MC, et al. Clozapine use in Parkinson's disease: a retrospective analysis of a large multicentered clinical experience. *Mov Disord* 1998;13:377–382.
14. Casey DE. Clozapine: neuroleptic-induced EPS and tardive dyskinesia. *Psychopharmacology* 1989;99:S47–53.
15. Kane J, Honigfeld G, Singer J, Meltzer H. Clozapine for the treatment-resistant schizophrenic. A double-blind comparison with chlorpromazine. *Arch Gen Psychiatry* 1988;45:789–796.
16. Meco G, Alessandri A, Bonifati V, Giustini P. Risperidone for hallucinations in levodopa-treated Parkinson's disease patients [Letter]. *Lancet* 1994;343:1370–1371.
17. Mendis T, Mohr E, George A, Rusk IN, Gray P, Grimes JD. Symptomatic relief from treatment-induced psychosis in Parkinson's disease: an open-label pilot study with remoxipride. *Mov Disord* 1994;9:197–200.
18. Livingston MG. Risperidone. *Lancet* 1994;343:457–460.
19. Borison RL, Pathiraja AP, Diamond BI, Meibach RC. Risperidone: clinical safety and efficacy in schizophrenia. *Psychopharmacol Bull* 1992;28:213–218.
20. Chouinard G, Jones B, Remington G, et al. A Canadian multicenter placebo-controlled study of fixed doses of risperidone and haloperidol in the treatment of chronic schizophrenic patients. *J Clin Psychopharmacol* 1993;13:25–40.
21. Claus A, Bollen J, De Cuyper H, et al. Risperidone versus haloperidol in the treatment of chronic schizophrenic inpatients; a multicentre, double-blind comparative study. *Acta Psychiatr Scand* 1992;85:295–305.
22. Peuskens J, Heylen S. *Risperidone in the treatment of chronic schizophrenic patients: an international multicentre double-blind,*

*parallel group comparative study versus haloperidol.* Internal Clinical Research Report. Janssen Research Foundation. November 1, 1991.
23. Bersani G, Bressa GM, Meco G, Marini S, Pozzi F. Combined serotonin 5-HT2 and dopamine-D2 antagonism in schizophrenia: clinical, extrapyramidal and neuroendocrine response in a preliminary trial with risperidone (R64 766). *Human Psychopharmacology* 1990;5:225–231.
24. Castelão JF, Ferreira L, Gelders YG, Heylen SL. The efficacy of the D2 and 5HT antagonist risperidone in the treatment of chronic psychosis: an open dose-finding trial. *Schizophr Res* 1989;2:411–415.
25. Gelders YG, Heylen SLE, Vanden Bussche G, Reyntjens AJ, Janssen PA. Pilot clinical investigation of risperidone in the treatment of psychotic subjects. *Pharmacopsychiatry* 1990;23:206–211.
26. Meco G, Bedini L, Bonifati V, Sonsini U. Risperidone in the treatment of chronic schizophrenia with tardive dyskinesia: a single-blind cross-over trial versus placebo. *Curr Ther Res* 1989; 46:876–883.
27. Roose K, Gelders Y, Heylemn S. Risperidone (R64 766) in psychotic subjects: a first clinical therapeutic exploration. *Acta Psychiatr Belg* 1988;88:233–241.
28. Hoyberg OJ, Fensbo C, Remvig J, Lingjaerde O, Sloth-Nielson M, Salvesen I. Risperidone versus perphenazine in the treatment of chronic schizophrenic patients with acute exacerbations. *Acta Psychiatr Scand* 1993;88:395–402.
29. Marder SR, Meibach RC. Risperidone in the treatment of schizophrenia. *Am J Psychiatry* 1994;151:825–835.
30. Peuskens J. Risperidone in the treatment of patients with chronic schizophrenia: a multi-national, multi-centre, double-blind, parallel-group study versus haloperidol. Risperidone Study Group. *Br J Psychiatry* 1995;166:712–726; discussion 727–733.
31. Blin O, Azorin JM, Bouhours P. Antipsychotic and anxiolytic properties of risperidone, haloperidol and methotrimeprazine in schizophrenic patients. *J Clin Psychopharmacol* 1996;16:38–44.
32. Huttunen MO, Piepponen T, Rantanen H, Larmo I, Nyholm R, Raitasuo V. Risperidone versus zuclopenthixol in the treatment of acute schizophrenic episodes: a double-blind parallel-group trial. *Acta Psychiatr Scand* 1995;91:271–277.
33. Anguenot A, Gil R, Senon JL, Couderq C, Neau JP. Risperidone in the treatment of psychosis in Parkinson's disease. *Annales de Psychiatrie* 1998;13:41–47.
34. Meco G, Fabrizio E, Alessandri A, Vanacore N, Bonifati V. Risperidone in levodopa induced dyskineseae. *J Neurol Neurosurg Psychiatry* 1998;64:135–142.
35. Meco G, Alessandri A, Giustini P, Bonifati V. Risperidone in levodopa-induced psychosis in advanced Parkinson's disease: an open-label, long-term study. *Mov Disord* 1997;12:610–612.
36. Workman RH Jr, Orengo CA, Bakey AA, Molinari VA, Kunik ME. The use of risperidone for psychosis and agitation in demented patients with Parkinson's disease. *J Neuropsychiatry Clin Neurosci* 1997;9:594–597.
37. Yuvarajan R. *Risperidone for treatment of psychosis in patients with Parkinson's disease.* 8th Congress of the International Psychogeriatric Association; August 17–22, 1997; Jerusalem, Israel:p63.
38. Mendis T, Barclay CL, Mohr E. Drug-induced psychosis in Parkinson's disease: a review of management. *CNS Drugs* 1996;5: 166–174.
39. Kay SR, Fiszbein A, Opler LA. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. *Schizophr Bull* 1987;13: 261–276.
40. Guy W, ed. *ECDEU Assessment Manual for Psychopharmacology,* revised. DHEW Publication No. (ADM) 76-338. Rockville, MD: National Institute of Mental Health, 1976.
41. Fahn S, Elton RL, and members of the UPDRS Development Committee. Unified Parkinson's Disease Rating Scale. In: Fahn S, Marsden CD, Calne DB, Goldstein M, eds. *Recent Developments in Parkinson's Disease*, vol 2. Florham Park, NJ: Macmillan Health Care Information, 1987:153–164.
42. Factor SA, Molho ES, Podskalny GD, Brown D. Parkinson's disease: drug-induced psychiatric states. *Adv Neurol* 1995;65:115–138.
43. Greene P, Cote L, Fahn S. Treatment of drug-induced psychosis in Parkinson's disease with clozapine. *Adv Neurol* 1993;60:703–706.
44. Ford B, Lynch T, Greene P. Risperidone in Parkinson's disease [Letter]. *Lancet* 1994;344:681.
45. Rich SS, Friedman JH, Ott BR. Risperidone versus clozapine in the treatment of psychosis in six patients with Parkinson's disease and other akinetic-rigid syndromes. *J Clin Psychiatry* 1995;56:556–559.
46. Pars MA, Bastani B. Quetiapine (Seroquel) in the treatment of psychosis in patients with PD. *J Neuropsychiatry Clin Neurosci* 1998;10:216–219.
47. Zoldan J, Friedberg G, Livneh M, Melamed E. Psychosis in advanced Parkinson's disease: treatment with Ondansetron, a 5HT3 receptor agonist. *Neurology* 1995;45:1305–1308.
48. Zoldan J, Friedberg G, Goldberg-Stern H, Melamed E. Ondansetron for hallucinosis in advanced Parkinson's disease. *Lancet* 1993; 341:562–563.
49. Mendis T, Suchowersky O, Lang A, Gauthier S. Management of Parkinson's disease: a review of current and new therapies. *Can J Neurol Sci* 1999;26:89–103.
50. Rosebush PI, Mazurek MF. Neurologic side effects in neuroleptic-naive patients treated with haloperidol or risperidone. *Neurology* 1999;52:782–785.