

## LOW-DOSE CLOZAPINE FOR THE TREATMENT OF DRUG-INDUCED PSYCHOSIS IN PARKINSON'S DISEASE

THE PARKINSON STUDY GROUP\*

**ABSTRACT**

**Background** Drug-induced psychosis is a difficult problem to manage in patients with Parkinson's disease. Multiple open-label studies have reported that treatment with clozapine at low doses ameliorates psychosis without worsening parkinsonism.

**Methods** We conducted a randomized, double-blind, placebo-controlled trial of low doses of clozapine (6.25 to 50 mg per day) in 60 patients at six sites over a period of 14 months. The patients (mean age, 72 years) had idiopathic Parkinson's disease and drug-induced psychosis of at least four weeks' duration. All the patients continued to receive fixed doses of antiparkinsonian drugs during the four weeks of the trial. Blood counts were monitored weekly in all the patients.

**Results** The mean dose of clozapine was 24.7 mg per day. The patients in the clozapine group had significantly more improvement than those in the placebo group in all three of the measures used to determine the severity of psychosis. The mean ( $\pm$ SE) scores on the Clinical Global Impression Scale improved by  $1.6\pm 0.3$  points for the patients receiving clozapine, as compared with  $0.5\pm 0.2$  point for those receiving placebo ( $P<0.001$ ). The score on the Brief Psychiatric Rating Scale improved by  $9.3\pm 1.5$  points for the patients receiving clozapine, as compared with  $2.6\pm 1.3$  points for those receiving placebo ( $P=0.002$ ). The score on the Scale for the Assessment of Positive Symptoms improved by  $11.8\pm 2.0$  points for the patients receiving clozapine, as compared with  $3.8\pm 1.9$  points for those receiving placebo ( $P=0.01$ ). Seven patients treated with clozapine had an improvement of at least three points on the seven-point Clinical Global Impression Scale, as compared with only one patient given placebo. Clozapine treatment improved tremor and had no deleterious effect on the severity of parkinsonism. In one patient, clozapine was discontinued because of leukopenia.

**Conclusions** Clozapine, at daily doses of 50 mg or less, is safe and significantly improves drug-induced psychosis without worsening parkinsonism. (N Engl J Med 1999;340:757-63.)

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**D**RUG-INDUCED psychosis in patients with Parkinson's disease is a difficult problem to manage.<sup>1,2</sup> It is the single most important factor leading to the placement of such patients in nursing homes,<sup>3</sup> and it causes more stress for care givers than does motor dysfunction.<sup>4</sup> Estimates of the frequency of drug-induced psychosis are as high as 22 percent.<sup>2,5,6</sup> Until recently, the treat-

ment of drug-induced psychosis was limited to reducing the dose of antiparkinsonian medication, adding a neuroleptic drug, discontinuing drug therapy for a period,<sup>7-10</sup> or using electroconvulsive therapy.<sup>11</sup>

The introduction of the "atypical" antipsychotic drugs — those with few or no extrapyramidal side effects<sup>12</sup> — raised the possibility of treating drug-induced psychosis without reducing motor function in patients with Parkinson's disease. Clozapine is virtually free of extrapyramidal side effects.<sup>13</sup> It causes potentially fatal agranulocytosis<sup>14</sup> in 1 to 2 percent of those exposed, however, and the Food and Drug Administration has mandated weekly blood-count monitoring of patients taking this drug. Such monitoring has made fatal agranulocytosis a rare event.<sup>15</sup> Since the first report of the successful use of clozapine in treating drug-induced psychosis in patients with Parkinson's disease,<sup>16</sup> there have been confirmatory reports of its effectiveness, but all such reports were from open-label studies.<sup>17-39</sup> These studies, involving a total of more than 400 patients, reported significant benefit in approximately 85 percent of patients using  $\frac{1}{10}$  or less of the usual dosage of clozapine prescribed for schizophrenia. Open-label studies of the newer atypical antipsychotic drugs risperidone and olanzapine in patients with Parkinson's disease have yielded conflicting results,<sup>40-45</sup> with clear worsening of motor signs in some patients.<sup>40,41,43,44</sup> We report the results of a multicenter, randomized, placebo-controlled, double-blind study of clozapine for the treatment of drug-induced psychosis in patients with Parkinson's disease.

**METHODS****Patients**

Patients were candidates for the study if they had idiopathic Parkinson's disease and psychosis induced by antiparkinsonian drugs. Parkinson's disease was diagnosed when at least three of the four cardinal features were present (tremor at rest, rigidity, hypokinesia, and problems with posture and balance typical of Parkinson's disease) and there were no alternative explanations for the findings. Psychosis was defined as a major psychiatric illness in which reality testing was impaired, typically by the presence of hallucinations or delusions, leading to substantial communication and social problems.<sup>46</sup> Neither age nor the severity of motor dysfunction was a factor in the selection of patients. Special attempts

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\*The members of the Parkinson Study Group who participated in the study are listed in the Appendix.

were made to recruit women and members of minority groups. The protocol was approved by the institutional review board at each participating site.

Before entering the study, each patient was treated as deemed most appropriate by the enrolling investigator but without an antipsychotic drug. Patients were excluded if they had taken clozapine or a neuroleptic drug within three months before the start of the study. The doses of antiparkinsonian medications were generally reduced to the lowest level that was considered tolerable for motor function. To prevent the enrollment of patients whose improvement was the result of an adjustment of their antiparkinsonian medication, all the patients had to have been taking a fixed dose of medication for at least seven days before enrollment. The criteria for study entry were psychosis severe enough to have warranted treatment with a standard neuroleptic drug if the patient had not had Parkinson's disease and a score of 3 (indicating mild psychosis) or higher on the Clinical Global Impression Scale<sup>47</sup> for the severity of psychosis.

To be included in the study, each patient had to have a documented history of psychosis of at least four weeks' duration before enrollment and had to have a reliable care giver who could accurately report the patient's daily level of function, accompany the patient to each visit, and administer the study drug.

Criteria for exclusion were a history of leukopenia; the presence of any systemic factor that might contribute to a behavioral disorder; therapy with any dopamine-blocking drug within the three months before the study began; therapy with neuroleptic drugs administered in depot form within the year before the study; a change in antidepressant or anxiolytic drugs within the month before the study; previous therapy with clozapine for the treatment of psychosis; the presence of symptomatic orthostatic hypotension, uncontrolled seizures, uncontrolled angina, the acquired immunodeficiency syndrome or another illness that would make the use of clozapine potentially hazardous, or narrow-angle glaucoma; myocardial infarction during the three months before the study; treatment with chemotherapeutic drugs that lower white-cell counts; an inability to tolerate a fixed dose of antiparkinsonian drugs for one month; an inability to tolerate the current level of psychosis for one month; or the presence of dementia severe enough to preclude assessment on the psychiatric-test battery. Women of childbearing potential who were not using reliable forms of contraception were also excluded.

### Design of the Study

The study was designed to determine whether clozapine, administered at low doses, is an effective treatment for drug-induced psychosis in patients with Parkinson's disease and to determine its effect on motor function in such patients. The primary outcome measures were the scores on the Clinical Global Impression Scale<sup>47</sup> for psychosis and the Unified Parkinson's Disease Rating Scale for parkinsonism.<sup>48</sup>

If the screening laboratory tests revealed no clinically significant abnormality, the patient or his or her legal guardian was asked to give written informed consent. The patient was then enrolled in the Clozaril Patient Monitoring System administered by Sandoz Pharmaceuticals (now Novartis Pharmaceuticals, Hanover, N.J.) and enrolled in the study. The random assignment of the patients to the clozapine group or the placebo group was stratified according to the site and the age of the patient (under 70 years vs. 70 or older).

The double-blind evaluation lasted four weeks. At base line, a physical examination was conducted and the Mini-Mental State Examination<sup>49</sup> was administered. Three measures of psychosis were used: the Clinical Global Impression Scale,<sup>47</sup> which rates the severity of psychotic symptoms on a scale from 0 (no symptoms) to 7 (the most severe symptoms); the Scale for the Assessment of Positive Symptoms, in which the score for the severity of symptoms ranges from 0 (no symptoms) to 176<sup>50</sup>; and the Brief Psychiatric Rating Scale, in which scores can range from 18 to 126, with higher scores indicating more severe psychosis.<sup>51</sup> A modified

version of the Brief Psychiatric Rating Scale was also used in which the four items measuring tension, mannerisms, posturing, and motor retardation that we considered unreliable because of confounding with motor signs of Parkinson's disease were omitted.

All the patients were evaluated on the psychiatric scales by the site investigator (a neurologist or a psychiatrist). All the investigators were trained in the administration of the tests to patients with Parkinson's disease at a teaching session in which videotaped interviews were used, but no formal study of interrater reliability was performed. The severity of parkinsonism was assessed with the use of sections II and III of the Unified Parkinson's Disease Rating Scale (possible range of scores, 0 to 160),<sup>48</sup> including the Step-Seconds Test, the Hoehn-Yahr staging system (stage I indicates newly diagnosed disease, and stages IV and V advanced disease),<sup>52</sup> and the Schwab and England Activities of Daily Living scale (range of scores, 0 to 100, with lower scores indicating more severe dysfunction).<sup>53</sup> The scores for tremor on the Unified Parkinson's Disease Rating Scale were analyzed in isolation because of reports that clozapine decreases tremor in Parkinson's disease.<sup>54-58</sup> Adverse events and changes in sleep patterns were evaluated in detailed questionnaires.

Clozapine (Clozaril) was obtained in bulk from Sandoz Pharmaceuticals. It was ground into powder form and repackaged in 6.25-mg capsules along with matching placebo at the University of Rhode Island School of Pharmacy. At the time of study entry, the patients received a 10-day supply of the assigned medication and started taking one capsule each night. On day 3 or 4, the study coordinator or investigator spoke with the patients' care givers to determine, on the basis of an unstructured conversation carried out over the telephone, the response to treatment. The dose could then be increased or decreased. If there were adverse events before the scheduled phone call, the care givers were asked to contact the study coordinator or investigator. The patients were evaluated weekly in the office, where vital signs (pulse, blood pressure, and temperature), weight, adverse events, and compliance (measured by pill counts) were assessed. Telephone calls to the care givers were made mid-week. The investigators assessed the level of psychosis weekly.

Possible daily doses were as follows: 6.25, 12.5, 18.75, 25, 37.5, and 50 mg. All daily doses started at 6.25 mg and could be raised one level depending on the patient's clinical response; if the patient's daily dose had been increased from the initial 6.25-mg level, it could also be lowered one level. The dose could be changed once between weekly office visits or at the visit. A dose could be increased even if the patient had not been able to tolerate that dose on a previous occasion. The dosage reached at the beginning of the final week was the maximal dose; it could not be increased further but could be decreased, if necessary, because of side effects. Thus, at the final assessment, when all base-line measures were repeated, the patient had been receiving a stable or declining dose of study medicine for at least seven days.

During the study, all the patients had a complete blood count performed weekly. The results were reported to a monitor who was not aware of the patients' treatment assignments. Monitoring guidelines were the same as those for all patients in the Clozaril Patient Monitoring System. Since a request for an additional complete blood count if the white-cell count declined could reveal the treatment assignment to the participants, additional blood tests were also randomly performed. Thus, some patients had additional blood drawn even if the standard weekly complete blood count was normal. The results were available only to the monitor, who remained unaware of the treatment assignments. The study participants were not told whether the additional blood test was triggered by a decline in the white-cell count or was randomly ordered. At the end of the fourth week, all base-line tests were repeated.

### Safety

A safety monitoring committee, composed of two physicians and a statistician who did not otherwise participate in the study, met quarterly. This committee reviewed all laboratory data and

reports of adverse events; its members had full access to treatment assignments.

**Statistical Analysis**

Data were sent to the Clinical Trials Coordination Center (Rochester, N.Y.). Forms were reviewed for completeness and accuracy before the data were entered into the data base. The protocol required a sample of 60 subjects in order to have the power to demonstrate that clozapine did not worsen motor function in patients with Parkinson's disease. Unpublished data on drug-induced psychosis in patients with Parkinson's disease that were obtained with use of the Brief Psychiatric Rating Scale indicated that fewer patients would be required in order to demonstrate that clozapine improved drug-induced psychosis. Assuming a standard deviation of six units for the change from base line in the scores on the Unified Parkinson's Disease Rating Scale (items II and III) and a drop-out rate of 10 percent, we estimated that a sample of 30 patients per treatment group would give the study a 90 percent power to detect a worsening of five points on the Unified Parkinson's Disease Rating Scale in the group assigned to clozapine (P=0.05 by a two-sided test),<sup>59</sup> a decline thought to be clinically significant.

The base-line characteristics of the patients in the two groups were compared by chi-square tests or t-tests, as appropriate. The effect of treatment on each outcome measure was assessed by analysis of covariance, with adjustments made for the base-line value and the investigator. Consistency with respect to possible investigator bias was examined by the inclusion of terms for investigator-treatment interactions.

The intention-to-treat analysis called for in the protocol was modified to account for one patient who was randomly assigned to receive placebo but actually received clozapine. When this error was discovered midway through the trial, we opted to keep giving the patient the active drug. Very similar results with respect to efficacy were obtained regardless of whether this patient was excluded from or included in the group to which she had been randomly assigned. The analyses reported here are based on the treatment the patients received, not on the intention-to-treat analysis, and include data only for those who completed evaluations at base line and four weeks.

**RESULTS**

**Base-Line Characteristics**

Sixty patients were enrolled between April 1995 and October 1996, with the numbers recruited varying from 9 to 12 patients per site. All had had hallucinations or delusions. There were some significant imbalances at base line between the groups in the intention-to-treat analysis (the patients receiving clozapine had slightly less severe psychosis than those receiving placebo), but not between the groups in the analysis based on the treatment the patients actually received (Table 1). Fifty-four patients completed the trial.

The mean score at base line was 3.0 (indicating mild psychosis) or higher for the following individual items on the Brief Psychiatric Rating Scale only: anxiety, suspiciousness, and hallucinations. There were no significant differences in the use of antiparkinsonian or psychotropic drugs between the two groups (Table 2). All 60 patients were taking levodopa.

**Safety**

Three patients receiving placebo and three receiving clozapine withdrew from the study. The psychi-

**TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS ACCORDING TO TREATMENT ACTUALLY RECEIVED.\***

CHARACTERISTIC	PLACEBO (N=30)	CLOZAPINE (N=30)	P VALUE
Female sex (no.)	10	16	0.12
White race (no.)	30	28	0.15
Weight (kg)	68.4±11.9	65.1±11.6	0.29
Hours of sleep per 24 hr	6.3±2.1	6.3±1.6	0.87
Age (yr)	71.9±8.1	70.8±8.6	0.62
Years of education	13.0±3.1	13.7±3.4	0.42
Duration of Parkinson's disease (yr)	10.4±7.5	10.8±6.1	0.84
Step-Seconds Test	0.8±0.2	0.8±0.3	0.80
Hoehn-Yahr stage of disease	2.8±0.8	2.6±0.9	0.33
Activities of Daily Living Score†			
"On" period	68.8±18.3	68.5±19.4	0.95
"Off" period	54.5±14.3	47.6±16.4	0.17
UPDRS score‡			
Motor	37.1±13.0	32.8±11.3	0.19
Total	61.3±20.3	52.0±17.3	0.07
MMSE score§	21.7±5.2	23.8±4.8	0.11
BPRS score¶			
Modified	40.6±12.1	38.6±12.1	0.52
Unmodified	35.0±10.7	33.1±9.9	0.47
SAPS score	22.4±12.3	20.9±13.0	0.64
CGIS score**	4.4±1.0	4.4±0.8	0.89

\*Plus-minus values are means ±SD.

†The maximal score is 100, with lower scores indicating more severe impairment. "On" period denotes the period when antiparkinsonian medication ameliorates symptoms. "Off" period denotes the period when antiparkinsonian medication does not ameliorate symptoms.

‡UPDRS denotes Unified Parkinson's Disease Rating Scale. The range of possible scores is 0 to 160 for the total scale and 0 to 44 for the motor section, with higher scores indicating more severe impairment.

§MMSE denotes Mini-Mental State Examination. The range of possible scores is 0 to 30, with lower scores indicating more severe impairment.

¶BPRS denotes Brief Psychiatric Rating Scale. The range of possible scores is 18 to 126 for the unmodified version and 14 to 98 for the modified version, with higher scores indicating more severe psychosis.

||SAPS denotes Scale for the Assessment of Positive Symptoms. The range of possible scores is 0 to 176, with higher scores indicating more severe psychosis.

\*\*CGIS denotes Clinical Global Impression Scale. The range of possible scores is 0 to 7, with higher scores indicating more severe psychosis.

atric condition of two of the three patients receiving placebo worsened. One patient required psychiatric hospitalization, and the other discarded her medications, declaring herself "cured." The third patient was hospitalized for pneumonia. Of the three patients in the clozapine group who withdrew from the study, one discontinued the drug because of leukopenia (white-cell count, 2900 per cubic millimeter), one because of myocardial infarction, and one because of sedation.

There were no significant changes in the mean neutrophil or white-cell counts in either group. There were no significant differences between groups in changes in orthostatic blood pressure, but there was a small but statistically significant increase from base

**TABLE 2. PSYCHOACTIVE DRUGS TAKEN DURING THE STUDY, ACCORDING TO TREATMENT GROUP.\***

TYPE AND NAME OF MEDICATION	PLACEBO GROUP		CLOZAPINE GROUP	
	NO. OF PATIENTS	MEAN DOSE mg/day	NO. OF PATIENTS	MEAN DOSE mg/day
<b>Antiparkinsonian drugs</b>				
Amantadine	6	217.0	1	200.0
Benzotropine	1	18.0	0	—
Bromocriptine	1	20.0	5	5.25
Pergolide	8	10.2	9	1.3
Selegiline	5	2.8	3	3.3
Trihexyphenidyl	2	6.0	1	2.0
<b>Antidepressant drugs</b>				
Amitriptyline	0	—	4	37.5
Bupropion	0	—	1	100.0
Desipramine	0	—	1	20.0
Fluoxetine	0	—	2	10.0
Maprotiline	0	—	1	25.0
Nortriptyline	1	10.0	1	30.0
Sertraline	4	62.5	3	56.7
Trazodone	1	50.0	0	—
<b>Anxiolytic and sedative drugs</b>				
Alprazolam	2	0.25	2	1.0
Bupirone	1	5.0	0	—
Clonazepam	2	0.63	0	—
Diazepam	1	1.0	1	2.0
Lorazepam	5	1.2	1	1.0
Meprobamate	0	—	1	400.0
Oxazepam	2	12.5	0	—
Zolpidem	1	5.0	0	—
<b>Stimulant drug</b>				
Methylphenidate	1	10.0	0	—

\*The dosages of these psychoactive drugs were kept fixed during the study and had been fixed for the month preceding study entry.

**TABLE 3. CHANGES IN SCORES FOR PRIMARY OUTCOME MEASURES FROM BASE LINE TO FOLLOW-UP.\***

PRIMARY OUTCOME MEASURE	PLACEBO GROUP (N=27)	CLOZAPINE GROUP (N=27)	P VALUE
change in score			
<b>Measures of parkinsonism†</b>			
UPDRS, total score	-3.8±1.5	-6.4±2.9	0.36
UPDRS, motor score	-1.8±1.2	-3.6±1.9	0.34
UPDRS, tremor score	-0.2±0.4	-1.5±0.5	0.02
<b>Psychiatric measures</b>			
BPRS score	-2.6±1.3	-9.3±1.5	0.002
BPRS-M score	-2.5±1.2	-8.6±1.3	0.003
CGIS score	-0.5±0.2	-1.6±0.3	<0.001
SAPS score	-3.8±1.9	-11.8±2.0	0.01
MMSE score	-0.1±0.4	0.0±0.5	0.90

\*This analysis was based on the actual treatment each patient received. UPDRS denotes Unified Parkinson's Disease Rating Scale, BPRS Brief Psychiatric Rating Scale, BPRS-M the modified BPRS, CGIS Clinical Global Impression Scale, SAPS Scale for the Assessment of Positive Symptoms, and MMSE Mini-Mental State Examination. Plus-minus values are means ±SE, and negative values indicate improvement.

†The scores for these items are based on 25 patients in each group.

**TABLE 4. CHANGES IN PSYCHOSIS SCORES FROM BASE LINE TO FOLLOW-UP, AS MEASURED BY THE CLINICAL GLOBAL IMPRESSION SCALE.\***

TREATMENT GROUP	CHANGE IN SCORE					
	-4	-3	-2	-1	0	+1
	no. of patients					
Placebo	0	1	4	4	16	2
Clozapine	3	4	8	5	6	1

\*A decrease in the score indicates improvement. P=0.002 by test for trend.

line, of 3.9 beats per minute, in the mean resting heart rate of the patients receiving clozapine as compared with no increase in that of the patients receiving placebo (P=0.046). Weight increased by 0.7 kg (1.6 lb) in the patients receiving clozapine and 0.1 kg (0.27 lb) in those receiving placebo (P=0.005). There were no significant differences between the groups in the severity of drooling, memory impairment, constipation, orthostatic lightheadedness, urinary hesitancy, confusion, headaches, fatigue, or daytime sedation.

Analyses were repeated with the use of the intention-to-treat method, the last-observation-carried-forward method, or both methods; the results of all analyses were similar.

**Efficacy**

The mean daily dose of clozapine prescribed at the end of the study was 24.7 mg (range, 6.25 to 50). The mean daily dose of placebo was equivalent to 35.2 mg (range, 6.25 to 50).

Improvements were seen in all measures of psychosis in the clozapine group, including the Clinical Global Impression Scale, the Brief Psychiatric Rating Scale (original and modified versions), and the Scale for the Assessment of Positive Symptoms (Table 3). In 13 patients in the clozapine group but in only 3 patients in the placebo group the severity of psychosis decreased to a level that, if present at base line, would have made them ineligible for the study. Table 4 shows the distribution of changes in the scores on the Clinical Global Impression Scale. Hallucinations (almost entirely visual) improved by 1.9 points for the patients receiving clozapine and 0.7 point for those receiving placebo (P=0.002) on the Brief Psychiatric Rating Scale. There were no significant differences between the groups with respect to any of the five items on our sleep questionnaire.

There was no worsening of motor symptoms in either group according to the measures of parkinsonism (Table 3). There was a statistically significant beneficial effect of clozapine on tremor, and there were no significant differences between the

two groups with respect to the other measures of parkinsonism.

There were no statistically significant investigator-treatment interactions in any of the outcome measures, indicating consistency of results among investigators. Compliance, as measured by pill counts, was 96 percent in the placebo group and 98 percent in the clozapine group.

### DISCUSSION

In this double-blind study, clozapine ameliorated psychosis despite the fact that the patients continued taking antiparkinsonian drugs. Moreover, clozapine did not worsen motor function and actually decreased tremor.

Several aspects of our study design require explanation. We excluded patients whose psychosis had lasted for less than four weeks so as to avoid confounding between improvement due to clozapine and that due to a delayed response to a reduction in the dose of antiparkinsonian medication. Because there are no validated instruments for measuring psychosis in Parkinson's disease, we chose four separate measures of psychotic symptoms. The Clinical Global Impression Scale was the primary tool we used to measure the severity of psychosis. The Brief Psychiatric Rating Scale rates both positive (e.g., presence of hallucinations) and negative (e.g., absence of emotion) symptoms and is valid for assessing the severity of schizophrenia. We also used the Scale for the Assessment of Positive Symptoms, on the basis of numerous reports of drug-induced psychosis consisting of positive symptoms.<sup>60-64</sup> We used these measures in combination to buttress the reliability of our results.

The patients in this study were fairly typical of those encountered in clinical practice, although we excluded those with the most severe psychosis because of our concern that four weeks of placebo therapy might jeopardize the patients' safety. We defined improvement of psychosis according to three separate clinical measures, and our results demonstrated both clinically and statistically significant improvement. These results held true in the analysis of the patients according to actual treatment as well as in the intention-to-treat analysis. The improvements were greater than those reported in most trials of antipsychotic drugs in schizophrenia.<sup>65,66</sup> The finding that parkinsonism did not worsen in our study confirms the results of open-label studies. The improvement in tremor is commensurate with that in previous studies.<sup>54-58</sup> Our results contrast markedly with those of the one previous placebo-controlled trial, which had only six subjects.<sup>67</sup> The most obvious explanation for the difference in outcomes is the fact that higher doses were used in that study.

The reduction in the number of white cells in the patients receiving clozapine, necessitating discontinuation of the drug in one patient, is within the range

expected on the basis of much larger samples. The complete blood count returned to normal once clozapine was discontinued. In more than 400 patients with Parkinson's disease who were treated with clozapine, there have been only 3 cases of leukopenia, a percentage somewhat smaller than that found in our study.<sup>37</sup> Our results covered a period of four weeks, and the greatest risk of agranulocytosis extends through the first four months of treatment. Thus, clozapine can be safely given to elderly patients with Parkinson's disease for at least four weeks, with weekly monitoring of the white-cell count.

Although weekly visits could have revealed adverse effects that might have made the investigator aware of the treatment assignments, the nature and frequency of side effects were similar in the clozapine and placebo groups. Although clozapine has anticholinergic activity in the brain,<sup>68</sup> we found that it did not impair memory or cognitive function as measured on the Mini-Mental State Examination. There were no anticholinergic effects, such as urinary retention, dry mouth, blurred vision, or constipation. Somnolence was as frequent in the placebo group as in the clozapine group, and there were no differences between the groups in any of the measures of sleep patterns — namely, the amount of time spent sleeping, the amount of time needed to fall asleep, and the duration of naps during the day.

Other adverse events associated with clozapine in our study were weight gain and an increase in the pulse rate. To our knowledge, weight gain in patients with drug-induced psychosis has not been noted before, although it has occurred in patients with Parkinson's disease who were treated with higher doses of clozapine for tremor.<sup>55</sup> Weight gain is not necessarily a problem, since patients with Parkinson's disease commonly lose weight during the course of their illness. Tachycardia was asymptomatic in the patients in our study and was not of clinical importance. Whether this could be a problem for patients with unstable angina needs to be considered. Fever did not occur in our patients.

At the end of the double-blind trial, all the patients were offered treatment for three months with clozapine, provided free of charge. Fifty-three patients were enrolled in this open-label extension of the study. During the three-month extension, the white-cell count dropped to 3000 per cubic millimeter in one patient, who was then withdrawn from the study, after which the count returned to normal. Six patients died, three of whom had been living in nursing homes. Two of these three had advanced directives limiting intervention; one died of a stroke and the other of bronchitis. The third nursing home resident died in her sleep of unknown causes. Two other patients died of pneumonia. The sixth patient died of cardiac arrest shortly after the three-month extension of the study ended. No deaths were asso-

ciated with a low white-cell count. The site investigators did not believe clozapine was related to death in any of the patients. Other drugs were changed (the doses were either increased or decreased, or the drugs were discontinued, or new drugs were started) during this extension phase. We believe the deaths were due to complications of disease in patients who had generally requested that no aggressive interventions should be used to save their lives. Such a high death rate has not been reported before in studies of clozapine, but increased mortality and hallucinations have been reported in patients with Parkinson's disease in nursing homes.<sup>69</sup>

In summary, we found that clozapine at doses ranging from 6.25 to 50 mg per day, which are far lower than the doses of 300 to 900 mg required for the treatment of schizophrenia, reduced the severity of drug-induced psychosis in patients with Parkinson's disease. Although the most feared adverse effect is agranulocytosis, the incidence of which is reported to increase with age, it did not occur in our study. Leukopenia developed in one patient during the four weeks of clozapine therapy, but it resolved after clozapine was stopped. The fact that the three-month extension of the study had an open-label design makes it difficult to interpret the relation between clozapine and morbidity, since other drugs were changed during this period, but continued study of the morbidity and mortality associated with clozapine is appropriate.

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## APPENDIX

The following persons participated in the study: *Investigators* — J. Friedman and M. Lannon, Memorial Hospital of Rhode Island, Pawtucket, and Brown University School of Medicine, Providence; C. Comella, Rush-Presbyterian—St. Luke's Medical Center and Rush School of Medicine, Chicago; S. Factor, Albany College of Medicine, Albany, N.Y.; R. Kurlan and I. Richard, University of Rochester, Rochester, N.Y.; M. Parsa, Case Western University School of Medicine, Cleveland; R. Pfeiffer, University of Tennessee Medical Center, Memphis; *Study Coordinators* — R. Davies, Memorial Hospital of Rhode Island, Pawtucket, and Brown University School of Medicine, Providence; K. Janko, Rush-Presbyterian—St. Luke's Medical Center, Chicago; D. Brown, Albany College of Medicine, Albany, N.Y.; I. Gardner and N. Pearson, University of Rochester, Rochester, N.Y.; K. Large, Case Western University School of Medicine, Cleveland; S. Rast, University of Tennessee Medical Center, Memphis; *Steering Committee* — D. Oakes, University of Rochester, Rochester, N.Y.; C. Goetz, Rush-Presbyterian—St. Luke's Medical Center, Chicago; G. Paulson, Ohio State University, Columbus; F. Marshall, K. Kiebertz, and A. Rudolph, University of Rochester, Rochester, N.Y.; *Clinical Trials Coordination Center* — K. Bourgeois, C. Casacelli, A. Freimuth, B. Guthrie, R. Pelusio, and A. Watts, University of Rochester, Rochester, N.Y.; *Safety Monitoring Committee* — P. Tariot and R. Raubertas, University of Rochester, Rochester, N.Y.; and T. Greenamyre, Emory University, Atlanta.

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