

## A COMPARISON OF CLOZAPINE AND HALOPERIDOL IN HOSPITALIZED PATIENTS WITH REFRACTORY SCHIZOPHRENIA

ROBERT ROSENHECK, M.D., JOYCE CRAMER, B.S., WEICHUN XU, PH.D., JONATHAN THOMAS, M.S.,  
WILLIAM HENDERSON, PH.D., LINDA FRISMAN, PH.D., CAROL FYE, R.PH., M.S., AND DENNIS CHARNEY, M.D.,  
FOR THE DEPARTMENT OF VETERANS AFFAIRS COOPERATIVE STUDY GROUP ON CLOZAPINE IN REFRACTORY SCHIZOPHRENIA\*

### ABSTRACT

**Background** Clozapine, a relatively expensive antipsychotic drug, is widely used to treat patients with refractory schizophrenia. It has a low incidence of extrapyramidal side effects but may cause agranulocytosis. There have been no long-term assessments of its effect on symptoms, social functioning, and the use and cost of health care.

**Methods** We conducted a randomized, one-year, double-blind comparative study of clozapine (in 205 patients) and haloperidol (in 218 patients) at 15 Veterans Affairs medical centers. All participants had refractory schizophrenia and had been hospitalized for the disease for 30 to 364 days in the previous year. All patients received case-management and social-rehabilitation services, as clinically indicated.

**Results** In the clozapine group, 117 patients (57 percent) continued their assigned treatment for the entire year, as compared with 61 (28 percent) of the patients in the haloperidol group ( $P < 0.001$ ). As judged according to the Positive and Negative Syndrome Scale of Schizophrenia, patients in the clozapine group had 5.4 percent lower symptom levels than those in the haloperidol group at all follow-up evaluations (mean score, 79.1 vs. 83.6;  $P = 0.02$ ). The differences on a quality-of-life scale were not significant in the intention-to-treat analysis, but they were significant among patients who did not cross over to the other treatment ( $P = 0.003$ ). Over a one-year period, patients assigned to clozapine had fewer mean days of hospitalization for psychiatric reasons than patients assigned to haloperidol (143.8 vs. 168.1 days,  $P = 0.03$ ) and used more outpatient services (133.6 vs. 97.9 units of service,  $P = 0.03$ ). The total per capita costs to society were high — \$58,151 in the clozapine group and \$60,885 in the haloperidol group ( $P = 0.41$ ). The per capita costs of antipsychotic drugs were \$3,199 in the clozapine group and \$367 in the haloperidol group ( $P < 0.001$ ). Patients assigned to clozapine had less tardive dyskinesia and fewer extrapyramidal side effects. Agranulocytosis developed in three patients in the clozapine group; all recovered fully.

**Conclusions** For patients with refractory schizophrenia and high levels of hospital use, clozapine was somewhat more effective than haloperidol and had fewer side effects and similar overall costs. (*N Engl J Med* 1997;337:809-15.)

©1997, Massachusetts Medical Society.

**S**CHIZOPHRENIA is a chronic, disabling mental illness that affects approximately 1 percent of the U.S. population and costs \$33 billion per year.<sup>1,2</sup> Although conventional antipsychotic drugs have been the mainstay of treatment since the mid-1950s, only 70 percent of patients respond to these agents.<sup>3</sup> Recently, clozapine was found to be more efficacious than standard drugs in patients with schizophrenia that was refractory to treatment.<sup>4-7</sup> Although studies have shown that clozapine reduces “positive” symptoms, such as hallucinations and delusions,<sup>8</sup> its efficacy as compared with that of traditional antipsychotic agents is unclear for “negative” symptoms, such as blunted affect and lack of motivation, and for social functioning.<sup>9-12</sup> As compared with other drugs for schizophrenia, clozapine is associated with a far lower incidence of extrapyramidal and related adverse effects.<sup>13</sup>

Unfortunately, clozapine is associated with potentially fatal agranulocytosis in about 1 percent of patients.<sup>14,15</sup> Since this blood dyscrasia can be reversed by discontinuing the drug, safety can be monitored with weekly white-cell testing.<sup>15</sup>

Clozapine is more expensive than most other antipsychotic drugs (although it is not more expensive than many treatments for severe medical illnesses). The estimated yearly cost of clozapine for a typical patient receiving 300 to 400 mg per day is \$4,500, plus an additional \$1,000 for blood monitoring — 11 times the typical annual cost of conventional antipsychotic drugs.<sup>16</sup> Several nonexperimental studies have suggested that the additional cost of clozapine treatment may be more than offset by the consequent reduction in hospital costs,<sup>17-19</sup> and one controlled trial showed reduced rates of readmission and fewer days in the hospital with clozapine.<sup>20</sup>

If the use of clozapine rather than conventional drugs resulted in significant cost savings or was neu-

---

From the Veterans Affairs Connecticut Healthcare System, West Haven, and the Department of Psychiatry, Yale School of Medicine, New Haven, Conn. (R.R., J.C., L.F., D.C.); the Center for Cooperative Studies in Health Services, Hines Veterans Affairs Medical Center, Hines, Ill. (W.X., J.T., W.H.); and the Veterans Affairs Cooperative Studies Program Clinical Research Pharmacy Coordinating Center, Albuquerque, N.M. (C.F.). Address reprint requests to Dr. Rosenheck at the Northeast Program Evaluation Center (182), VA Connecticut Healthcare System, 950 Campbell Ave., West Haven, CT 06516.

\*Members of the study group are listed in the Appendix.

tral with respect to cost, the additional expenditure for the treatment would be worthwhile. If clozapine resulted in greater costs than conventional therapy, widespread use of clozapine would have to be weighed against its benefits. We compared the long-term effectiveness and cost of clozapine with those of haloperidol, a widely used conventional treatment. The primary outcomes measured were symptoms of schizophrenia, quality of life, days in the hospital for psychiatric reasons, and costs.

## METHODS

Between March 1993 and April 1995, patients hospitalized at 15 Veterans Affairs medical centers were randomly assigned to receive clozapine (Clozaril) or haloperidol (Haldol) for 12 months. The protocol was approved by the human-rights committee at each participating medical center, and all patients gave written informed consent.

### Entry Criteria

The study targeted patients with schizophrenia refractory to treatment and a history of a high level of use of inpatient services, defined as 30 to 364 days of hospitalization for schizophrenia during the previous year. Nationwide, 43 percent of all inpatients in Veterans Affairs hospitals with a primary diagnosis of schizophrenia meet these utilization criteria, and these patients account for 73 percent of all treatment days for schizophrenia in Veterans Affairs hospitals. Clinical eligibility criteria consisted of a diagnosis of schizophrenia, as defined in the *Diagnostic and Statistical Manual of Mental Disorders* (third edition, revised) (DSM-III-R),<sup>21</sup> on the basis of the results of the Structured Clinical Interview for DSM-III-R<sup>22</sup>; refractoriness, defined as persisting psychotic symptoms despite adequate treatment trials of two or more antipsychotic drugs at 1000-mg chlorpromazine equivalents unless limited by adverse effects; severe symptoms, indicated by scores on the Brief Psychiatric Rating Scale<sup>23</sup> and the Clinical Global Impressions Scale<sup>24</sup>; and serious social dysfunction for the previous two years.

Patients were excluded if they were unable to give informed consent, had been treated previously with clozapine, had a current myeloproliferative disorder, or were pregnant. Virtually all patients screened for the study were accepted.

### Pharmacotherapy

After base-line assessments had been completed, the patients were randomly assigned, within centers, to treatment with clozapine (100 to 900 mg per day) or haloperidol (5 to 30 mg per day). The dose was adjusted as clinically indicated; 12 fixed dosage levels were used. The patients receiving haloperidol also received benztropine mesylate (2 to 10 mg per day) for extrapyramidal side effects, and the patients receiving clozapine received a matching benztropine placebo. To maintain blinding, the patients receiving haloperidol also had weekly blood counts taken, as is required for patients treated with clozapine.

### Psychosocial Treatment

To assess the potential effectiveness of clozapine in typical clinical practice, a predefined program of locally available adjunctive psychotherapeutic and rehabilitative treatment was offered to the patients through a structured process of treatment planning.

### Assessment of Outcome and Reliability of Ratings

Symptom outcome was assessed with the Structured Clinical Interview for the Positive and Negative Syndrome Scale, in which high scores indicate worse symptoms and a 20 percent reduction is considered to represent clinically important improvement (range

of possible scores, 30 to 210).<sup>25</sup> Social functioning and quality of life were evaluated with the Heinrichs-Carpenter Quality-of-Life Scale, a scale in which the clinician rates social functioning and severe behavioral deficits and a 20 percent increase indicates clinically important improvement (range of possible scores, 0 to 126).<sup>26</sup> The side effects of the medications were assessed with scales in which higher scores uniformly indicate more serious problems: the Barnes Akathisia Scale for restlessness<sup>27</sup> (range of possible scores, 0 to 14), the Abnormal Involuntary Movement Scale for tardive dyskinesia (range of possible scores, 0 to 40),<sup>28</sup> the Simpson-Angus Scale for extrapyramidal syndromes (range of possible scores, 0 to 40),<sup>29</sup> and a weekly checklist of adverse reactions (e.g., hypotension, hypersalivation, and sedation).

All interviewers were trained and received annual reassessments of interrater reliability based on videotaped demonstration interviews. A statistical method was developed to assess the reliability of multiple assessments of a single patient or taped interview on the basis of biostatistical and clinical criteria that determine whether the ratings of any given examiner are appreciably higher or lower than the group average.<sup>30</sup> Agreement was excellent for both the Positive and Negative Syndrome Scale (96 percent agreement; range, 94 to 96 percent across subscales) and the Heinrichs-Carpenter Quality-of-Life Scale (95 percent agreement; range, 90 to 98 percent across subscales).

### Assessment of Costs

#### Health Care Costs

Health care costs were estimated by multiplying the number of units of service (e.g., inpatient days or outpatient visits) for each patient by the estimated unit costs, according to cost data for fiscal year 1994. To estimate the unit costs at each center for general psychiatric and substance-abuse care of inpatients and outpatients, including group treatment and day hospital care, the total expenditures for each service were divided by the total number of units of service provided at the center.<sup>31-33</sup> The costs of Veterans Affairs medical, surgical, domiciliary, and nursing home care and of outpatient treatment for non-mental problems were estimated from national average costs. Non-Veterans Affairs health care costs were minimal (less than 2 percent of all costs) and were estimated on the basis of a recent study that compared Veterans Affairs and non-Veterans Affairs medical costs in various communities.<sup>34</sup>

#### Use of Services

Data on the use of Veterans Affairs health services were derived from national automated Veterans Affairs data systems. Use of non-Veterans Affairs services was evaluated by monthly interviews with patients and validated by reviews of treatment records from non-Veterans Affairs providers.

#### Clozapine-Related Treatment Costs

The costs of the medications used in the study were estimated on the basis of Veterans Affairs pharmacy costs of \$2.13 per 100 mg for clozapine and \$0.02 per 5 mg for haloperidol. The costs of drawing blood, performing white-cell counts, and additional pharmacy processing were added to the weekly cost of clozapine (\$14 per week). Since the double-blind design artificially inflated the cost of haloperidol treatment by requiring weekly clinic visits and blood counts, the costs of outpatient care for patients receiving haloperidol — but not the outpatient utilization data — were decreased to 73 percent of their actual value, on the basis of an analysis of use of outpatient services before study entry.

#### Non-Health Care Costs

Interview data were used to estimate the use of services other than health care. The costs of these services were derived from interview data and published literature.<sup>35-38</sup> These costs included the costs of the criminal-justice system (such as police contacts and arrests),<sup>36,37</sup> loss of productivity (estimated on the basis of

earnings from employment, included as negative costs), family burden (days lost by family members from work and from unpaid domestic activity because of caring for the patient, valued at twice the minimum wage),<sup>39</sup> and the administrative costs of transfer payments — that is, of programs that provide public support such as welfare and disability payments to patients.<sup>35,36</sup> For transfer payments, only administrative costs were included, because only they represent the consumption of society's resources.<sup>35</sup> Although the full value of transfer payments may have a substantial impact on governmental budgets, we did not analyze the data from the governmental perspective.

### Summary Costs

Cost data were summarized and analyzed from two perspectives: that of the entire health care system (Veterans Affairs and non-Veterans Affairs) and that of society (health care and non-health care costs).

### Statistical Analysis

The primary analyses for this study are based on intention-to-treat principles that include all subjects randomized. Chi-square tests were used to evaluate differences in the proportion of patients in each group who had significant clinical improvement.

To maximize statistical power for testing hypotheses involving longitudinal data, we analyzed the primary outcomes with random-effects regression models,<sup>40</sup> using the PROC MIXED program from the statistical computer package SAS, version 6.12. These models accommodate correlations among repeated observations and therefore allow the inclusion of subjects with missing observations. The significance of differences between treatment groups was tested by the likelihood-ratio chi-square test. Specifically, we compared a model that included the effects of time, time squared, and treatment group with a model that added interactions of group and time. The interaction of group and time is the hypothesis of interest.

A number of patients discontinued the assigned study medication because of lack of efficacy, adverse effects, or non-drug-related reasons and received open-label clozapine, haloperidol, or another standard medication on the basis of individual needs. The treatment groups were compared both as randomized (according to intention to treat) and with crossover cases excluded. All statistical tests were two-sided.

## RESULTS

### Study Sample and Treatment

Table 1 shows that the patients randomly assigned to receive clozapine (n = 205) and those assigned to receive haloperidol (n = 218) had similar sociodemographic and clinical characteristics at base line. At the midpoint of the trial (26 weeks), the average ( $\pm$ SD) dose of clozapine was 552 $\pm$ 229 mg per day, and the average dose of haloperidol was 28 $\pm$ 5.3 mg per day.

### Compliance

Survival analysis showed a significantly longer period of compliance with the study protocol among the patients assigned to clozapine. Among the patients assigned to clozapine, 117 (57 percent) continued the randomized, blinded treatment for the entire year, as compared with 61 of the patients assigned to haloperidol (28 percent,  $P < 0.001$ ). The primary reasons for discontinuation differed between the groups. Fifty-one percent of the patients who

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

CHARACTERISTIC	CLOZAPINE (N=205)	HALOPERIDOL (N=218)
Age — yr	43.2 $\pm$ 7.7	43.9 $\pm$ 8.3
Male sex — no. (%)	202 (99.0)	211 (96.8)
Race or ethnic group — no. (%)		
White	135 (66.2)	145 (66.5)
Black	60 (29.4)	65 (29.8)
Hispanic	8 (3.9)	8 (3.7)
Other	1 (0.5)	0 (0.0)
Marital status — no. (%)		
Married	17 (8.3)	13 (6.0)
Never married	119 (58.3)	125 (57.3)
Separated or divorced	65 (31.9)	73 (33.5)
Widowed	3 (1.5)	7 (3.2)
Education — yr	12.4 $\pm$ 1.7	12.3 $\pm$ 1.5
Receiving disability payments — no. (%)	199 (97.1)	208 (95.4)
Employed in past 3 yr — no. (%)	29 (14.1)	28 (12.8)
Lifetime comorbidity — no. (%)		
Major depression	27 (13.2)	27 (12.4)
Alcohol abuse	144 (70.6)	133 (61.0)
Any drug abuse	97 (47.5)	104 (47.7)
Cocaine	48 (23.5)	61 (28.0)
Age at onset of schizophrenia — yr	22.2 $\pm$ 5.8	22.4 $\pm$ 4.9
Quality-of-life and symptom-severity scores†		
Heinrichs-Carpenter Scale	39.9 $\pm$ 17.3	37.6 $\pm$ 16.8
PANSS	91.0 $\pm$ 14.9	92.2 $\pm$ 14.5
AIMS	5.9 $\pm$ 5.9	5.8 $\pm$ 6.2
Simpson-Angus Scale	5.2 $\pm$ 4.5	5.1 $\pm$ 4.7
Barnes Akathisia Scale	3.6 $\pm$ 3.4	3.1 $\pm$ 3.4
Days of hospitalization for schizophrenia in past yr — no. (%)		
1-30	33 (16.3)	45 (20.9)
31-70	85 (42.1)	79 (36.7)
71-180	55 (27.2)	65 (30.2)
>180	29 (14.4)	26 (12.1)
Health care costs in past 6 mo	\$26,460 $\pm$ \$18,698	\$26,753 $\pm$ \$16,208

\*Plus-minus values are means  $\pm$ SD. Some data were missing on up to three patients in the clozapine group and three in the haloperidol group.

†Quality of life was measured with the Heinrichs-Carpenter Quality-of-Life Scale<sup>26</sup> (range, 0 to 126) and symptoms with the Positive and Negative Syndrome Scale (PANSS) for Schizophrenia (range, 30 to 210). The Abnormal Involuntary Movement Scale (AIMS) (range, 0 to 40) is a measure of symptoms of tardive dyskinesia. The Simpson-Angus Scale of Extrapyramidal Effects (range, 0 to 40) and the Barnes Akathisia Scale (range, 0 to 14) assess drug side effects. On all of these scales except the Quality-of-Life Scale, higher scores indicate more severe symptoms and poorer clinical status.

discontinued haloperidol treatment, but only 15 percent of those who discontinued clozapine treatment, stopped taking the medication because of lack of efficacy or worsening of symptoms ( $P < 0.001$ ). The primary reasons for discontinuing clozapine treatment were side effects (30 percent of those who discontinued clozapine treatment vs. 17 percent of those who discontinued haloperidol treatment) or non-drug-related reasons, such as not wanting to continue the trial (55 percent of those who discontinued clozapine treatment vs. 32 percent of those who discontinued haloperidol treatment).

## Outcomes

Altogether, 82 percent of the planned outcome assessments were completed. Analysis of the patients as randomized (intention-to-treat analysis) showed 5.4 percent lower symptom levels (i.e., greater clinical improvement) in all follow-up periods for the patients assigned to clozapine (mean score on the Positive and Negative Syndrome Scale, 79.1 for clozapine vs. 83.6 for haloperidol;  $P=0.02$ ). Superior improvement in the clozapine group was observed for both positive symptoms, such as hallucinations and delusions (mean score, 19.5 vs. 21.2;  $P=0.04$ ) and negative symptoms, such as blunted affect and withdrawal (20.9 vs. 21.2,  $P=0.02$ ), although the differences were small. Table 2 shows the symptom scores for the two groups according to the length of treatment. After six weeks and six months of treatment, significantly more patients assigned to clozapine had a clinically important improvement (at least 20 percent) in symptoms than those assigned to haloperidol. The differences between the groups were not significant at other times.

Although the group means for all follow-up points for the patients assigned to clozapine were 8.6 percent higher (44.4 vs. 40.9) on the Quality-of-Life Scale (in which higher scores reflect better quality of life), improvement over time was not significantly different between groups ( $P=0.17$ ), and there were no significant differences in the proportion of patients with clinically significant improvement (at least 20 percent) at the times examined (Table 2).

Clozapine was associated with markedly greater reductions on the tardive-dyskinesia scale over time, with mean scores for all follow-up points of 3.6 for clozapine and 5.2 for haloperidol ( $P=0.005$ ), as compared with 5.9 and 5.8, respectively, at base line. Clozapine also was associated with a marked reduction in akathisia (mean score, 2.6, vs. 4.0 for haloperidol;  $P<0.001$ ) and in extrapyramidal symptoms (2.6 vs. 4.0,  $P<0.001$ ).

As compared with patients assigned to haloperidol, those assigned to clozapine had, on the average, 24.3 fewer days in the hospital for psychiatric reasons in a year (143.8 vs. 168.1,  $P=0.03$ ) and 35.7 more units of outpatient service (133.6 vs. 97.9,  $P=0.03$ ), a difference predominantly reflecting additional visits for professional services (Table 3). The total per capita cost of health care was high: \$57,785 in the clozapine group and \$60,226 in the haloperidol group ( $P=0.39$ ). The total per capita costs to society were similar to the health care costs: \$58,151 in the clozapine group and \$60,885 in the haloperidol group ( $P=0.41$ ). Outpatient treatment was substantially more costly for patients assigned to clozapine than for patients assigned to haloperidol (\$8,473 vs. \$3,474 per capita,  $P<0.001$ ). The per capita cost of antipsychotic drugs was \$3,199 in the clozapine group and \$367 in the haloperidol group

**TABLE 2. NUMBER OF PATIENTS WITH CLINICALLY IMPORTANT IMPROVEMENT AT VARIOUS TIMES AFTER THE INITIATION OF TREATMENT.**

VARIABLE	CLOZAPINE		HALOPERIDOL		P VALUE*
	NO. IN SAMPLE	NO. IMPROVED (%)	NO. IN SAMPLE	NO. IMPROVED (%)	
<b>Intention to treat</b>					
Symptoms†					
6 wk	186	44 (24)	198	26 (13)	0.008
3 mo	176	55 (31)	190	47 (25)	0.16
6 mo	170	44 (26)	177	22 (12)	0.001
9 mo	165	62 (38)	158	49 (31)	0.21
1 yr	163	61 (37)	159	51 (32)	0.31
Quality of life‡					
6 wk	184	52 (28)	198	56 (28)	1.00
3 mo	173	68 (39)	190	57 (30)	0.06
6 mo	169	72 (43)	176	65 (37)	0.28
9 mo	164	66 (40)	158	67 (42)	0.69
1 yr	162	77 (48)	157	71 (45)	0.68
<b>Crossover cases excluded§</b>					
Symptoms†					
6 wk	120	36 (30)	153	21 (14)	0.001
3 mo	121	44 (36)	144	43 (30)	0.26
6 mo	121	36 (30)	131	18 (14)	0.002
9 mo	120	54 (45)	112	35 (31)	0.03
1 yr	122	51 (42)	113	35 (31)	0.09
Quality of life‡					
6 wk	119	35 (29)	152	43 (28)	0.84
3 mo	119	51 (43)	144	41 (28)	0.02
6 mo	121	55 (45)	130	45 (35)	0.08
9 mo	121	53 (44)	112	46 (41)	0.67
1 yr	121	64 (53)	111	41 (37)	0.02

\*P values were determined by the chi-square test.

†Symptoms were assessed with the Positive and Negative Syndrome Scale<sup>25</sup> (range, 30 to 210), a specific measure of symptoms of schizophrenia. Clinically important improvement in symptoms is indicated by a 20 percent decline in the symptom score as compared with the base-line value.

‡Quality of life was measured with the Heinrichs-Carpenter Quality-of-Life Scale<sup>26</sup> (range, 0 to 126). Clinically important improvement in quality of life is indicated by a 20 percent increase in the score over the base-line value.

§Patients assigned to haloperidol who discontinued the study medication but continued unblinded treatment with any standard antipsychotic medications were considered to have continued on a "standard treatment."

( $P<0.001$ ). However, this difference was offset by the decrease in the cost of inpatient hospital days for psychiatric care in the clozapine group (\$45,247 vs. \$53,931,  $P=0.01$ ). Non-health care costs were much smaller than health care costs, because few of these severely disabled patients worked for pay, few were involved with the criminal-justice system, and only the administrative costs related to transfer payments were counted as costs.

## Crossovers

During the study, some patients stopped taking the assigned medication because of lack of efficacy, adverse effects, or other reasons. Eighty-three patients assigned to clozapine (40 percent) switched to haloperidol or other standard antipsychotic drugs during the follow-up period, and 49 patients as-

**TABLE 3.** ONE-YEAR USE AND COST DATA ACCORDING TO TREATMENT ASSIGNMENT.

VARIABLE	CLOZAPINE (N=205)	HALOPERIDOL (N=218)	P VALUE
	mean		
<b>Use</b>			
Inpatient or residential care (days)	158.7	179.8	0.07
Psychiatric	143.8	168.1	0.03
Medical, surgical, or other	14.9	11.7	0.50
Inpatient psychiatric readmissions	1.7	1.5	0.22
Outpatient services (units)*	133.6	97.9	0.03
<b>Cost (\$)</b>			
<b>Health care</b>			
Inpatient or residential	49,311	56,752	0.03
Psychiatric	45,247	53,931	0.01
Medical, surgical, or other	4,064	2,821	0.20
Outpatient	8,473	3,474	<0.001
Patient care†	5,274	3,107	<0.001
Antipsychotic medication	3,199	367	<0.001
Total health care costs	57,785	60,226	0.39
<b>Non-health care</b>			
Productivity‡	-83	-5	0.02
Criminal justice	106	258	0.08
Family burden (lost income)	78	153	0.16
Transfer payments§	265	253	0.61
Total non-health care costs	366	659	0.008
Total cost to society	58,151	60,885	0.41

\*Outpatient services included professional services and laboratory visits, such as those required by the study protocol.

†Costs of outpatient care for the haloperidol group have been adjusted to 73 percent of their actual value to account for services required exclusively by the study protocol.

‡Productivity was estimated on the basis of the patients' earnings from employment and is included as a negative cost.

§Only administrative costs of transfer payments are included (see the Methods section).<sup>35</sup>

signed to haloperidol (22 percent) received clozapine for four weeks or more. Since the inclusion of these crossover patients in our analyses might have caused us to underestimate the effectiveness of clozapine, secondary analyses were conducted in which these crossover cases were excluded. Of the 157 patients assigned to haloperidol who interrupted the blinded treatment, all but the 49 who crossed over to clozapine continued to receive conventional antipsychotic medication (including open-label haloperidol) and were therefore classified as having completed haloperidol treatment for the purposes of the secondary analyses.

Patients who crossed over to another drug and those who completed the year of therapy with their assigned drugs differed significantly in only one baseline measure, quality of life ( $P=0.01$ ). There were no significant differences in baseline measures between treatment groups among patients who completed their assigned treatments.

Longitudinal symptom ratings (total scores on the Positive and Negative Syndrome Scale) are shown according to crossover status in Figure 1. Among patients who completed their assigned treatment,

those who received clozapine had a substantially greater reduction in symptoms than those who received haloperidol or another conventional medication ( $P=0.005$ ). Among patients who crossed over, those assigned to clozapine who later switched to haloperidol or another conventional antipsychotic medication had an initial decrease in symptoms (while receiving clozapine) but then had increased symptoms (after the crossover). Patients assigned to haloperidol who switched to clozapine had fewer symptoms after the crossover.

Similar data for the Quality-of-Life Scale are presented in Figure 2. Among patients who completed their assigned treatment, there was a significant benefit from clozapine ( $P=0.003$ ). The numbers of patients with greater than 20 percent improvement in symptoms and quality of life are shown in Table 2.

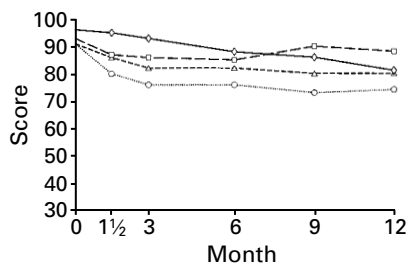
#### Leukopenia and Agranulocytosis

Leukopenia (white-cell count, less than 3000 per cubic millimeter) developed in four patients while they were taking clozapine and in two patients while they were taking haloperidol. Neutropenia (granulocyte count, less than 1500 per cubic millimeter) developed in eight patients while they were taking clozapine and nine patients while they were taking haloperidol. Agranulocytosis developed in three patients while they were taking clozapine, all of whom recovered fully after they stopped taking the drug.

#### DISCUSSION

We found that clozapine was somewhat more effective than haloperidol for the treatment of symptoms associated with refractory schizophrenia; clozapine was associated with fewer extrapyramidal effects than haloperidol, and the greater cost of clozapine was offset by reductions in the number of days spent in the hospital. Although our analysis of patients as randomized showed no effect of clozapine on the quality of life, this analysis probably underestimated the effectiveness of the drug, because of crossovers. When crossovers were excluded, clozapine was found to have a marked effect on both symptoms and the quality of life.

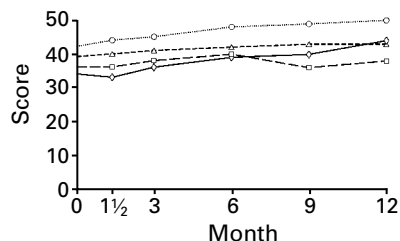
The clinical benefits and cost savings associated with clozapine were less pronounced than in previous studies. In a multicenter trial of 248 patients, Kane et al.<sup>4</sup> found that after six weeks, 38 percent of the patients taking clozapine showed clinically important improvement, as compared with only 5 percent of controls taking chlorpromazine. Other investigators have also reported improvement in 30 to 60 percent of patients with refractory schizophrenia taking clozapine.<sup>5-7</sup> Among the patients taking clozapine in the current study, clinically important improvement occurred in 24 percent after six weeks and in 37 percent after one year. However, clinically important improvement also occurred in 13 percent



○ Completed clozapine	122	120	121	121	120	122
△ Completed haloperidol	169	153	144	131	112	113
□ Crossed over to haloperidol	83	66	55	49	45	41
◇ Crossed over to clozapine	49	46	46	46	46	46

**Figure 1.** Symptom Outcomes (Total Scores on the Positive and Negative Syndrome Scale) among Patients Assigned to Clozapine or Haloperidol, According to Whether They Completed Treatment or Crossed Over to the Other Treatment.

Crossovers were defined retrospectively at the end of the study. Among those who completed their assigned treatment, patients assigned to clozapine had significantly reduced symptoms ( $P=0.005$ ). Crossovers from clozapine to another standard treatment occurred an average of  $4.1\pm 3.3$  months after the trial began (median, 3.3). Crossovers from haloperidol to clozapine occurred an average of  $5.5\pm 3.0$  months after the trial began (median, 4.8). The numbers at the bottom of the figure show the numbers of patients in each category who were evaluated at each follow-up period.



○ Completed clozapine	122	119	119	121	121	121
△ Completed haloperidol	169	152	144	130	112	111
□ Crossed over to haloperidol	83	65	54	48	43	41
◇ Crossed over to clozapine	49	46	46	46	46	46

**Figure 2.** Quality-of-Life Outcomes (Total Scores on the Heinrichs-Carpenter Scale) among Patients Assigned to Clozapine or Haloperidol, According to Whether They Completed Treatment or Crossed Over to the Other Treatment.

Crossovers were defined retrospectively at the end of the study. Among those who completed their assigned treatment, patients assigned to clozapine had significantly better quality of life ( $P=0.003$ ). Crossovers from clozapine to another standard treatment occurred an average of  $4.1\pm 3.3$  months after the trial began (median, 3.3). Crossovers from haloperidol to clozapine occurred an average of  $5.5\pm 3.0$  months after the trial began (median, 4.8). The numbers at the bottom of the figure show the numbers of patients in each category who were evaluated at each follow-up period.

of the patients taking haloperidol or another standard medication after six weeks and in 32 percent of these patients after one year.

Differences in patients' characteristics (our patients were older male veterans) and treatment settings (all treatment in our study was provided at Veterans Affairs facilities) are two possible reasons we did not replicate the findings of other studies. However, age has not been identified as a predictor of response to clozapine, and in one study men benefited more than women.<sup>6</sup> The institutional context does not seem to provide an explanation, since a large proportion of the subjects in the study by Kane et al.<sup>4</sup> were also treated in Veterans Affairs hospitals.

It is notable that a recent two-year randomized trial of clozapine in long-term patients in state hospitals<sup>20</sup> found no effect of the medication on either symptoms or quality of life. The patients in that study were less severely ill than in other studies, with base-line symptom scores on the Brief Psychiatric Rating Scale of only 43, as compared with mean scores of 52 in our study and 61 in the study by Kane et al.<sup>4</sup> This comparison suggests that the beneficial effect of clozapine may be less strong among patients with less severe symptoms according to the Brief Psychiatric Rating Scale.

The contrast between our finding of a limited effect of clozapine on quality of life and costs and the results of previous studies is easier to explain. Most earlier studies did not include randomly assigned control groups, typically enrolled patients after serious relapses, and used pretreatment status for comparison.<sup>10,13,17-19</sup> Like others,<sup>11</sup> we observed a steady increase in the quality of life among patients treated with clozapine, but improvement was also seen in patients treated with haloperidol and other standard medications.

We confirmed previous reports of far lower rates of extrapyramidal side effects with clozapine than with conventional antipsychotic medications. Its lower rate of side effects and its greater effectiveness are probably the principal reasons for the better compliance of patients assigned to clozapine in this study than among those assigned to haloperidol.

As in previous studies, there were few instances of agranulocytosis. These were readily identified by white-cell monitoring and resolved after clozapine was discontinued. The costs of treating agranulocytosis were limited to the cost of three to seven additional hospital days.

We conclude that among patients with refractory schizophrenia and high levels of hospital use, clozapine was somewhat more effective than standard treatments, had fewer side effects, and did not increase the total cost of care. Although patients receiving clozapine had higher costs for medication and outpatient care, they spent fewer days in the hospital and therefore had lower inpatient costs.

Supported by the Department of Veterans Affairs Health Services Research and Development Service. Clozapine and matching placebos were provided by Sandoz Pharmaceuticals, a division of Novartis Corporation.

*We are indebted to John Feussner, M.D., Daniel Deykin, M.D., Shirley Meehan, Ph.D., Charles Welch, Ph.D., Joseph Gough, Janet Gold, and Ping Huang, Ph.D., of the Department of Veterans Affairs Research Office for their support; to Lois Ucas, J. Cabill, and D. Thompson of the Chairman's Office; to Amy Smith, Jeff Parker, Michael Kelley, and Shenglin Wang of the Cooperative Studies in Health Services Coordinating Center; to Bill Gagne, Loretta Guidarelli, and Mike Sather of the Pharmacy Coordinating Center; and to David Garver, M.D., Gary Ripper, and Stephanie Todd of the National Veterans Affairs Clozapine Coordinating Center.*

## APPENDIX

The following investigators were responsible for the conduct of the study at their respective Veterans Affairs facilities: J. Grabowski (principal investigator), L. Alphas, A. Pizzuti, and R. Wancha, Allen Park, Mich.; D. Evans (principal investigator), P.Y. Puczkowski, J. Martin, and M. Brandsma, Augusta, Ga.; L. Herz (principal investigator), M. Avtges, R. Smith, T. Phillips, and J. Di Vicenzo, Bedford, Mass.; G. Jurjus (principal investigator), K.Y. Kwon (co-investigator), C. Faust, K. Brown, and M. Manuel, Brecksville, Ohio; S. Chang (principal investigator), J.D. Wojcik, and C.D. Kohberger, Brockton, Mass.; L. Dunn (principal investigator), M. Evans, A. Bush, and S. Bennett, Durham, N.C.; J.C. Crayton (principal investigator), K.F. Foley, S. Neafsey, and S. Sideman, Hines, Ill.; W.B. Lawson (principal investigator), P. Arnold, M. Edmison, and M.M. Storey, Little Rock, Ark.; Y. Choe (principal investigator), D. Broad, E. Waterbury, and E. Cabezon, Lyons, N.J.; R. Douyon (principal investigator), M. Miller, J. Hamel, S. Kerr, and D. Feenane, Miami; E. Allen (principal investigator), K. Wainwright, and D. Widmer, Montrose, N.Y.; J. Lauriello (principal investigator), S. Whistance, J. Breen, and M. Getty, Palo Alto, Calif.; M. Peszke (principal investigator), M. Castiglione, and J. Frock, Perry Point, Md.; J.L. Peters (principal investigator), N. Snyder, D. Stefanik, and K. Henry, Pittsburgh; J. Tekell (principal investigator), B. Tobey, D. Hall, and E. Kyle, San Antonio, Tex.; and J. Erdos (principal investigator), D. Miles, A. Genovese, and D. Soliwoda, West Haven, Conn. The members of the Data Monitoring Board were A. Breier, H. Goldman, J. Klett, and D. Pickar. The members of the Executive Committee were B. Astrachan and W. Hargreaves, as well as the authors. D. Hedeker provided statistical review.

## REFERENCES

- Bromet EJ, Dew MA, Eaton W. Epidemiology of psychosis with special reference to schizophrenia. In: Tsuang MT, Tohen M, Zahner GEP, eds. *Textbook in psychiatric epidemiology*. New York: John Wiley, 1996:283-300.
- Rupp A, Keith SJ. The costs of schizophrenia: assessing the burden. *Psychiatr Clin North Am* 1993;16:413-23.
- Kane JM, Marder SR. Psychopharmacologic treatment of schizophrenia. *Schizophr Bull* 1993;19:287-302.
- Kane JM, Honigfeld G, Singer J, Meltzer HY, Clozaril Collaborative Study Group. Clozapine for the treatment-resistant schizophrenic: a double-blind comparison with chlorpromazine. *Arch Gen Psychiatry* 1988;45:789-96.
- Breier A, Buchanan RW, Kirkpatrick B, et al. Effects of clozapine on positive and negative symptoms in outpatients with schizophrenia. *Am J Psychiatry* 1994;151:20-6.
- Lieberman JA, Safferman AZ, Pollack S, et al. Clinical effects of clozapine in chronic schizophrenia: response to treatment and predictors of outcome. *Am J Psychiatry* 1994;151:1744-52.
- Pickar D, Ownen RR, Litman RE, Konicki E, Gutierrez R, Rapaport MH. Clinical and biologic response to clozapine in patients with schizophrenia: crossover comparison with fluphenazine. *Arch Gen Psychiatry* 1992;49:345-53.
- Buchanan RW. Clozapine: efficacy and safety. *Schizophr Bull* 1995;21:579-91.
- Carpenter WT Jr, Conley RR, Buchanan RW, Breier A, Tamminga CA. Patient response and resource management: another view of clozapine treatment of schizophrenia. *Am J Psychiatry* 1995;152:827-32.
- Breier A, Buchanan RW, Irish D, Carpenter WT Jr. Clozapine treatment of outpatients with schizophrenia: outcome and long-term response patterns. *Hosp Community Psychiatry* 1993;44:1145-9.
- Meltzer HY, Burnett S, Bastani B, Ramirez LF. Effects of six months of clozapine treatment on the quality of life of chronic schizophrenic patients. *Hosp Community Psychiatry* 1990;41:892-7.
- Meltzer HY. Clozapine: is another view valid? *Am J Psychiatry* 1995;152:821-5.
- Marder SR. Adverse effects of clozapine. *J Clin Psychiatry Monogr Ser* 1996;14:11-2.
- Griffith RW, Saameli J. Clozapine and agranulocytosis. *Lancet* 1975;2:657.
- Alvir JMJ, Lieberman JA, Safferman AZ, Schwimmer JL, Schaff JA. Clozapine-induced agranulocytosis: incidence and risk factors in the United States. *N Engl J Med* 1993;329:162-7.
- Meltzer HY, Cola PA. The pharmacoeconomics of clozapine: a review. *J Clin Psychiatry* 1994;55:Suppl B:161-5.
- Revicki DA, Luce BR, Weschler JM, Brown RE, Adler MA. Cost-effectiveness of clozapine for treatment-resistant schizophrenic patients. *Hosp Community Psychiatry* 1990;41:850-4.
- Meltzer HY, Cola P, Way L, et al. Cost effectiveness of clozapine in neuroleptic-resistant schizophrenia. *Am J Psychiatry* 1993;150:1630-8.
- Reid WH, Mason M, Toprac M. Savings in hospital bed-days related to treatment with clozapine. *Hosp Community Psychiatry* 1994;45:261-4.
- Essock SM, Hargreaves WA, Covell NH, Goethe J. Clozapine's effectiveness for patients in state hospitals: results from a randomized trial. *Psychopharmacol Bull* 1996;32:683-97.
- Diagnostic and statistical manual of mental disorders: DSM-III-R. 3rd ed., rev. Washington, D.C.: American Psychiatric Press, 1987.
- Spitzer RS, Williams JBW, Gibbon M, First MB. User's guide for the Structured Clinical Interview for DSM-III-R: SCID. Washington, D.C.: American Psychiatric Press, 1990.
- Overall JE, Gorham DR. The Brief Psychiatric Rating Scale. *Psychol Rep* 1962;10:799-812.
- Guy W. Clinical global impression. In: Guy W, ed. *ECDEU assessment manual for psychopharmacology*. Rockville, Md.: National Institute of Mental Health, 1976:218-21. (DHEW publication no. ADM 76-338.)
- Kay SR, Fiszbein A, Opler LA. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. *Schizophr Bull* 1987;13:261-76.
- Heinrichs DW, Hanlon ET, Carpenter WT Jr. The Quality of Life Scale: an instrument for rating the schizophrenic deficit syndrome. *Schizophr Bull* 1984;10:388-98.
- Barnes TRE. A rating scale for drug-induced akathisia. *Br J Psychiatry* 1989;154:672-6.
- Guy W. Abnormal involuntary movements. In: Guy W, ed. *ECDEU assessment manual for psychopharmacology*. Rockville, Md.: National Institute of Mental Health, 1976. (DHEW publication no. ADM 76-338.)
- Simpson GM, Angus JWS. A rating scale for extrapyramidal side effects. *Acta Psychiatr Scand Suppl* 1970;212:11-9.
- Cicchetti DV, Showalter D, Rosenheck RA. A new method for assessing interexaminer agreement when multiple ratings are made on a single subject: applications to the assessment of neuropsychiatric symptomatology. *Psychiatry Res* (in press).
- Rosenheck RA, Neale M, Leaf P, Milstein R, Frisman L. Multisite experimental cost study of intensive psychiatric community care. *Schizophr Bull* 1995;21:129-40.
- Rosenheck R, Frisman L, Neale M. Estimating the capital component of mental health care costs in the public sector. *Admin Policy Mental Health* 1994;21:493-509.
- Rosenheck RA, Neale M, Frisman L. Issues in estimating the cost of innovative mental health programs. *Psychiatr Q* 1995;66:9-31.
- Comparison of costs and outcomes of matched pairs of VAMCs and their university affiliates. Washington, D.C.: Office of the Inspector General, 1992.
- Frisman LK, Rosenheck RA. How transfer payments are treated in cost-effectiveness and cost-benefit analysis. *Adm Policy Mental Health* 1996;23:533-46.
- Schobel BD. Administrative expenses under OASDI. *Soc Secur Bull* 1981;44:21-8.
- Department of Justice Office of Justice Programs, Bureau of Justice Statistics. *Justice expenditures and employment in the United States, 1988*. Washington, D.C.: Government Printing Office, 1991. (Publication no. NCJ-125619.)
- Department of Justice Office of Justice Programs, Bureau of Justice Statistics. *Sourcebook of criminal justice statistics — 1990*. Washington, D.C.: Government Printing Office, 1991. (Publication no. NCJ-130580.)
- Tessler R, Gamache G. Continuity of care, residence and family burden in Ohio. *Milbank Q* 1994;72:149-69.
- Gibbons RD, Hedeker D, Elkin I, et al. Some conceptual and statistical issues in analysis of longitudinal psychiatric data: application to the NIMH Treatment of Depression Collaborative Research Program dataset. *Arch Gen Psychiatry* 1993;50:739-50.