Clozapine for the Treatment-Resistant Schizophrenic

A Double-blind Comparison With Chlorpromazine

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• **The treatment of schizophrenic patients who fail to respond to adequate trials of neuroleptics is a major challenge. Clozapine, an atypical antipsychotic drug, has long been of scientific interest, but its clinical development has been delayed because of an associated risk of agranulocytosis. This report describes a multicenter clinical trial to assess clozapine's efficacy in the treatment of patients who are refractory to neuroleptics. *DSM-III* schizophrenics who had failed to respond to at least three different neuroleptics underwent a prospective, single-blind trial of haloperidol (mean dosage, 61 ± 14 mg/d) for six weeks. Patients whose condition remained unimproved were then randomly assigned, in a double-blind manner, to clozapine (up to 900 mg/d) or chlorpromazine (up to 1800 mg/d) for six weeks. Two hundred sixty-eight patients were entered in the double-blind comparison. When a priori criteria were used, 30% of the clozapine-treated patients were categorized as responders compared with 4% of chlorpromazine-treated patients. Clozapine produced significantly greater improvement on the Brief Psychiatric Rating Scale, Clinical Global Impression Scale, and Nurses' Observation Scale for Inpatient Evaluation; this improvement included "negative" as well as positive symptom areas. Although no cases of agranulocytosis occurred during this relatively brief study, in our view, the apparently increased comparative risk requires that the use of clozapine be limited to selected treatment-resistant patients.**

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The efficacy of antipsychotic drugs in short-term and maintenance treatment of schizophrenia has been well established in numerous double-blind placebo controlled trials over the past 30 years.[1,2] However, despite the considerable magnitude of the medication effect in this condition, most controlled trials continue to find a subgroup of 10% to 20% of patients who derive little benefit from typical neuroleptic drug therapy.[1] The treatment of this refractory subgroup remains a major public health problem—these individuals require more intensive care and are subject to the persistent disabilities associated with chronic schizophrenia. In addition, the continued presence of psychotic signs and symptoms makes these patients less available to psychosocial and vocational rehabilitation.

It is estimated that about 1 million Americans suffer from schizophrenia. While there are no definitive data available on how many do not respond to neuroleptics, extrapolations from clinical trial data suggest that there may be 100 000 to 200 000 such patients.

Data from maintenance medication trials indicate that even among patients initially responsive to antipsychotic drugs, 20% to 30% may relapse during the first year or two of maintenance drug treatment.[3] A proportion of these patients contributes to the number in the subgroup of patients refractory to treatment. Since many of these patients remain ill, there is a cumulative increase in the number of people in the treatment-refractory category.

See also p 865.

The recognition that some patients do not benefit from typical neuroleptics has resulted in research along two fronts: (1) to identify phenomenologic, demographic, and/or biologic factors that may be associated with poor treatment response and (2) to explore alternative treatment strategies that might be beneficial to this subgroup. With regard to the former, there are no consistently replicated findings providing clues about why patients are refractory to treatment. There are countless reports of anecdotal or pilot study experiences with a variety of alternative treatments for poor responders. However, no particular strategy has been found to be more than occasionally useful; with controlled studies, the usual result is that the experimental treatment proves to be no more effective than conventional treatments.

Since the introduction of chlorpromazine, numerous other chemical classes and compounds with antipsychotic activity have been used. Despite considerable differences in chemical structures, these agents seem to share an ability to bind to dopamine receptors. When in vitro binding assays are used, antidopaminergic (specifically, dopamine D_2 receptor antagonism) action and therapeutic potency are highly correlated.[4] To a greater or lesser degree these are all "neuroleptics," ie, associated with short-term extrapyramidal side effects (including dystonias) and share the longer-term liability of inducing tardive dyskinesia. Despite numerous comparative trials, there are no consistent data suggesting that any specific antipsychotic drug or drug class is superior to any other in treating schizophrenia.[1,2]

Over the past decade, considerable effort has gone into the development and testing of potential antipsychotic compounds designated *atypical*. The concept of atypicality, however, is a working concept rather than a well-delineated

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and validated classification. In general, this term has been used to describe drugs that appear to have limited short-term extrapyramidal effects in animals or human subjects. Most are more selective in their dopamine D_2 antagonist properties (eg, sulpiride or raclopride) and/or more broadly active, with marked antiserotonergic, antinoradrenergic, or other effects as well (eg, clozapine).

Clozapine (8-chloro-11-(4-methyl-1-piperazinyl)-5*H*-dibenzo[*b*,*e*][1,4]diazepine) belongs to the chemical class of dibenzodiazepines, related chemically to the antipsychotic dibenzoxazepine drug loxapine. However, its pharmacologic characteristics are different from those of loxapine. Clozapine has serotonin (S_2), adrenergic (α_1), and histaminergic (H_1) blocking activity. It is also a potent muscarinic acetylcholine receptor antagonist.[5-7] Its binding to D_1 and D_2 receptors is relatively weak and more equivalent than that of most typical neuroleptics.[8] The relationship between these characteristics and clozapine's clinical effects remains highly speculative, and a full review of this topic is beyond the scope of this report.[9]

Unlike "typical" neuroleptics, clozapine produces only slight, transient elevations in serum prolactin levels in patients, even when moderate to high doses are given.[10,11] Its profile of extrapyramidal side effects appears to be very different from those of typical neuroleptics. In both US and foreign studies, it has been reported that clozapine does not induce dystonia when administered on a short-term basis, and although akinesia or akathisia develops in some patients, the incidence appears to be low.[12]

Thirteen cases of "dyskinesia" were reported from a sample of 12 000 patients in Europe, but the nature of these cases is not clear (unpublished results, P. Krupp, MD, and C. Monka, Sandoz Ltd, Basel, Switzerland, 1987). There has been one report of clozapine apparently exacerbating preexisting tardive dyskinesia.[13] One case of apparent neuroleptic malignant syndrome has been reported in a patient receiving clozapine and lithium.[14]

Previous controlled clinical trials have been conducted with clozapine. Claghorn et al[15] reported a six-center double-blind comparison of clozapine and chlorpromazine in 151 hospitalized schizophrenic patients who had experienced either extrapyramidal side effects or tardive dyskinesia with at least two different neuroleptics. Clozapine was significantly superior to chlorpromazine according to the major efficacy measures, and it produced fewer side effects. The dosage ratio of chlorpromazine to clozapine in this study was approximately 2:1. Fischer-Cornelssen and Ferner[16] conducted a five-center double-blind comparison of clozapine and chlorpromazine in 223 hospitalized schizophrenic patients; they found clozapine to be superior in efficacy, particularly among the more severely ill patients. In this study, however, the mean chlorpromazine dose at six weeks was only 360 mg compared with 310 mg of clozapine. In a similar two-center European study,[16] clozapine was compared with haloperidol in a sample of 79 schizophrenic inpatients. The average dosage of clozapine was 397 mg/d at day 40 compared with a dosage of 7.6 mg/d of haloperidol. Though clozapine was found to be more efficacious, the latter two comparisons could be criticized on the basis of inadequate dosing of the reference drug. The results of these clinical trials suggested that clozapine is an effective antipsychotic drug and also provided some suggestions of potential benefit in patients who are more severely ill or refractory to treatment.

However, in 1975, granulocytopenia developed in 16 patients in Finland, and agranulocytosis developed in 13 of these patients (eight fatalities resulted from secondary infection).[17,18] Worldwide experience now reveals over 100 cases of agranulocytosis in patients receiving clozapine. Because of this, the use of clozapine was curtailed in many countries, and the drug was withdrawn for a time from clinical research by its US sponsor. For humanitarian reasons, some countries (including the United States) allowed continued use of the drug for carefully selected patients who were resistant to treatment, sensitive to extrapyramidal side effects, or dyskinetic; these patients underwent intensive precautionary monitoring of white blood cell and differential counts. Since the introduction of restrictions in use and intensive hematologic monitoring, the overall incidence of agranulocytosis has declined, as has the lethal risk for patients in whom this reaction develops. Overall estimates continue to indicate that the risk of agranulocytosis with clozapine exceeds that associated with other antipsychotic drugs. In the United States, this problem developed in ten patients of 894 treated, and all of these patients recovered without any apparent long-term effect. Using the life-table method of calculating risk, data from the US experience indicate a 2% cumulative incidence after 52 weeks of clozapine treatment (95% confidence limits, 0.2% and 4%).[19] Based on US and worldwide experience, the risk of this adverse effect does not appear to be related to age, sex, or dose. The risk of "benign" neutropenia, however, does not appear to be any higher than with marketed neuroleptics.

Given clozapine's apparently greater risk and its promise of benefit for patients unresponsive to neuroleptics, the decision was made to initiate a controlled trial in carefully selected treatment-resistant patients. In considering the benefit-to-risk ratio of a therapeutic trial of clozapine, the time course of the development of agranulocytosis was also considered. The majority of agranulocytosis cases worldwide have occurred between the sixth and 18th weeks of clozapine treatment. Previous data also suggest that six weeks would provide a reasonably accurate test of the drug's therapeutic potential in individual patients. Exposure beyond that time was therefore limited in the present study to only those patients who had already shown significant therapeutic benefit from clozapine.

METHODS

Study Design

This study was designed to test the comparative efficacy of clozapine in schizophrenic inpatients who by history and prospective study would be considered to be resistant to treatment. Sixteen participating centers contributed data on a total of 319 patients. Patients had to meet *DSM-III*[20] criteria for schizophrenia. The criteria for being classified as refractory to treatment included the following: (1) at least three periods of treatment in the preceding five years with neuroleptic agents (from at least two different chemical classes) at dosages equivalent to or greater than 1000 mg/d of chlorpromazine for a period of six weeks, each without significant symptomatic relief, and (2) no period of good functioning within the preceding five years.

Subjects had to meet the following psychopathologic severity criteria: total Brief Psychiatric Rating Scale (BPRS) score of at least 45 (18-item version, in which 1 indicates absent and 7 indicates severe) plus a minimum Clinical Global Impressions (CGI) Scale rating of 4 (moderately ill). In addition, item scores of at least 4 (moderate) were required on two of the following four BPRS items: conceptual disorganization, suspiciousness, hallucinatory behavior, and unusual thought content.

All patients who met both the historical criteria for treatment resistance and the initial severity criteria and gave their informed consent entered a prospective period of treatment with haloperidol (up to 60 mg/d or higher) and benztropine mesylate (6 mg/d) for a period of six weeks to confirm the lack of drug responsiveness. Improvement in this context was defined a priori as a 20% decrease in the BPRS total score plus either a post-treatment CGI Scale

rating of mildly ill (≤3) or a post-treatment BPRS score of 35 or less. Any haloperidol responders (ie, those who met the improvement criteria) were dropped from further study.

Patients who met the multiple psychiatric symptom criteria were then randomly assigned to a six-week double-blind treatment trial with either clozapine (up to 900 mg/d) or chlorpromazine and benztropine mesylate (up to 1800 mg/d of chlorpromazine hydrochloride and up to 6 mg/d of benztropine mesylate). All medications were coded and administered under double-blind conditions; in addition to coded active antipsychotic medication in blue capsules, patients received either white benztropine tablets (chlorpromazine group) or identical white placebo tablets (clozapine group). The use of prophylactic benztropine mesylate (up to 6 mg/d) for all patients receiving chlorpromazine was designed to enhance the double-blind condition, in light of clozapine's previously established profile of reduced extrapyramidal side effects. In addition, this strategy was thought to minimize the potential for behaviorally manifest adverse effects to confound assessment of the relative clinical efficacy of the two drugs.

Before the start of the study, a priori criteria for supporting the superiority of clozapine in this patient population were determined. These criteria required proof of statistical superiority in *all* of three predetermined areas: the CGI Scale, changes in BPRS total score, and significant improvement in at least two of the following four BPRS items (or the cluster score derived from summing these four items): conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content.

Treatment

Patients entering the double-blind phase of the study were treated for six weeks. During the first two weeks, the dosage was titrated upward, if well tolerated, to dosage levels of either 500 mg/d of clozapine or 1000 mg/d of chlorpromazine (plus 6 mg/d of benztropine mesylate for chlorpromazine patients only). Dosing during the final four weeks was flexible, to maximum allowable dosages of 900 mg/d of clozapine and 1800 mg/d of chlorpromazine (plus up to 6 mg/d of benztropine mesylate). The number of patients entering each study period was as follows:

Period No.	Description	Duration, d	No. of Patients
1	Baseline placebo	≤14	319
2	Haloperidol	≤42	305
3	Placebo washout	≤7	272
4	Double-blind	≤42	268

Of the patients who entered period 4, 126 were randomized to clozapine, and 142 were randomized to chlorpromazine and benztropine mesylate.

Evaluation of Efficacy

Patients were interviewed by physicians or psychologists weekly during the course of double-blind treatment, and their assessments were recorded on the BPRS and on a seven-point CGI Scale (in which 1 indicates no mental illness and 7 indicates severe mental illness). In addition, patients were regularly evaluated in terms of ward behavior by the nursing staff, using the 30-item Nurses' Observation Scale for Inpatient Evaluation (NOSIE-30).[21]

Evaluation of Safety

Adverse reactions were evaluated by systematic patient query and observation by both medical and nursing personnel. Reactions were graded for severity and evaluated as to attribution to study drug, and the course of the reaction was documented. Regular clinical laboratory tests were performed, as were physical examinations, an electrocardiogram, and vital sign determinations. Systematic assessments of extrapyramidal symptoms and abnormal involuntary movements were made weekly using the Simpson-Angus Scale for Extrapyramidal Side Effects[22] and the Abnormal Involuntary Movements Scale (AIMS).[23]

SUBJECTS

Three hundred nineteen inpatients entered this study; their demographic and treatment history characteristics are summarized in Tables 1 and 2. Only 20% of the patients were female, largely due to the high proportion of Veterans Administration medical centers among the participating institutions and possibly also because women were less likely to have received 1000-mg chlorpromazine equivalents of three different neuroleptics.

Table 1.—Sex, Race, and Diagnosis of Patients Entering the Study (N=319)

Characteristic	No. (%) of Patients
Sex	
M	256 (80)
F	63 (20)
Race	
White	208 (65)
Black	74 (23)
Hispanic	31 (10)
Oriental	2 (1)
Other	4 (1)
Diagnosis (*DSM-III* schizophrenic subtypes)	
Undifferentiated	160 (50)
Paranoid	107 (34)
Disorganized	25 (8)
Residual	11 (3)
Unspecified	10 (3)
Catatonic	6 (2)

The typical patient was a 35-year-old male chronic undifferentiated schizophrenic first hospitalized for psychosis at age 20 years, after which seven or eight additional periods of hospitalization ensued. The median duration of the current hospitalization was about two years.

RESULTS

Over 80% of the patients completed the six-week prospective haloperidol phase of the study. A complete tabulation of patient outcomes after haloperidol treatment is provided in Table 3.

Of those patients who completed the full six weeks of haloperidol treatment (dosages up to 60 mg/d and greater; mean [SD], 61 [14] mg/d), 80% were nonresponders. Fewer than 2% were classified as haloperidol responders. In the balance of the patients, haloperidol was terminated early for a variety of reasons, the most prominent of which was intolerance to haloperidol. On average, haloperidol-treated patients showed no change during the course of six weeks of treatment in any areas of the BPRS or NOSIE-30. Twenty-two patients were unable to tolerate the complete haloperidol phase due to adverse effects, but since they met all retrospective criteria for treatment resistance, they were allowed to continue into the double-blind comparison. (Thirteen of these patients received chlorpromazine, and nine received clozapine. Efficacy analyses excluding these patients were also carried out and did not alter the results.)

Two hundred sixty-eight patients entered the critical clozapine vs chlorpromazine and benztropine double-blind phase. The diagnostic composition of each treatment subgroup in the double-blind phase was similar to that seen initially: approximately half of the patients in each treatment group were in the "undifferentiated" category and about one third were in the "paranoid" category. From the point of view of psychiatric history, the subgroups did not differ in any significant way in major characteristics of patient history and treatment, including age at first hospitalization for psychosis, number of hospitalizations, duration of illness, duration of current episode, and duration of present hospitalization.

Average daily doses of active antipsychotic medication received during double-blind treatment are shown by treatment week in Fig 1. Adequate dose levels of each drug were attained with mean peak dosages exceeding 1200 mg/d of chlorpromazine and 600 mg/d of clozapine. The decrease in average dosage for both treatment groups at week 6 reflects the mandated taper-down at the end of the treatment period for all patients, designed to avoid abrupt discontinuation.

Review of dispositions at the end of each patient's double-blind participation indicated high overall completion rates for both clozapine- and chlorpromazine-treated patients (88% and 87%, respectively). Early terminations occurred for the following reasons: adverse reactions (6%), illness not related to drugs (1%),

Table 2.—General Characteristics of Patients Entering the Study (N = 319)				
Characteristic	No. of Patients*	Median	Mean (SD)	Range
Age, y	318	35.0	35.7 (8.87)	20-59
Duration of current symptoms, wk	307	212.0	314.7 (316.76)	5-1976
Age at first hospitalization, y	294	20	20.4 (4.61)	8-40
No. of hospitalizations	245	7.0	9.2 (7.26)	1-50
Duration of current hospitalization, wk	304	104.0	215.9 (321.41)	0-1976

*The number of patients varies because of "missing" or "unknown" data elements.

Table 3.—Patient Classification After Treatment With Haloperidol and Benztropine	
Patient Classification	No. (%) of Patients (n = 305)
Haloperidol responder	5 (1.6)
Haloperidol nonresponder	248 (81.3)
Terminated early	52 (17.0)
Intolerant of haloperidol	22 (7.2)
Uncooperative	15 (4.9)
Protocol violated	4 (1.3)
Physical conditions not related to drug	5 (1.6)
Other (eg, seizure, electrocardiographic changes, withdrew consent)	6 (2.0)

uncooperativeness (2.9%), protocol violations (1%), symptom exacerbation (1%), and other causes (1%). Rates of early termination for all reasons were comparable for patients in both treatment groups.

Clinical Efficacy

Analyses of covariance of posttreatment change scores conducted for week 6 vs baseline (using pretreatment scores as covariates) were performed for all efficacy variables. An "intent to treat" analysis[24] was carried out for all patients who had a baseline assessment and at least one assessment following randomization, with the last observation carried forward, yielding essentially equal numbers of patients in each cell.

Figures 2 and 3 display findings for two of the predetermined critical variables, the two overall indexes of improvement: BPRS total score and the CGI Scale. The improvement in both the BPRS total score and the CGI Scale was approximately three times greater in the clozapine-treated patients. Differences favoring clozapine were statistically significant by the first week of treatment and continued to be present each week over the entire course of study. Similarly, four "positive" BPRS items determined a priori to be central to the assessment of therapeutic response (conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content) all demonstrated significant differences favoring clozapine over chlorpromazine and benztropine. These items were combined into a cluster score, which also yielded significant differences favoring clozapine (Fig 4). The mean scores at baseline and end point are presented in Table 4. Clozapine was superior to chlorpromazine in the treatment of negative signs and symptoms as well, as evidenced by statistically significant differences on the BPRS items of emotional withdrawal, blunted affect, psychomotor retardation, and disorientation. These items in combination form the BPRS "anergia" factor, displayed in Fig 5.

Analysis of variance and analysis of covariance results for all BPRS variables, including the a priori criteria, are shown in Table 5. Therapeutic response was assessed by the nursing staff as well, who rated patients' ward behavior on the NOSIE-30 (Table 5). For all six factors (social competence, social interest, personal neatness, irritability, manifest psychosis, and retardation), the nursing staff, blind to treatment assignment, judged clozapine effects superior to those of chlorpromazine and benztropine. Weekly

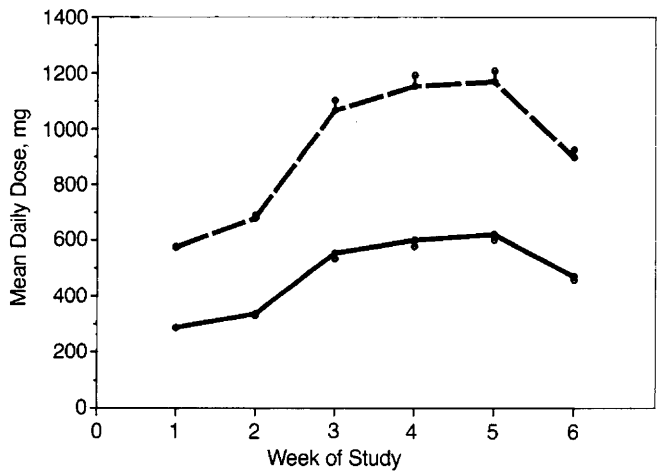

Fig 1.—Mean daily doses of clozapine (solid line) and chlorpromazine (broken line) during double-blind phase of study (period 4). For clozapine, at week 1, n = 126; week 2, n = 126; week 3, n = 122; week 4, n = 120; week 5, n = 119; and week 6, n = 116. For chlorpromazine, at week 1, n = 141; week 2, n = 140; week 3, n = 137; week 4, n = 133; week 5, n = 128; and week 6, n = 125.

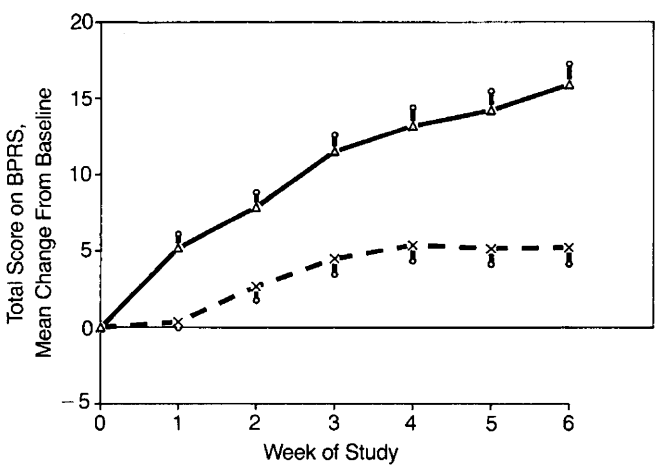

Fig 2.—Mean change from baseline in total score on Brief Psychiatric Rating Scale (BPRS) for patients treated with clozapine (solid line, n = 126) or chlorpromazine and benztropine mesylate (broken line, n = 139). $P<.001$ during each week of study.

changes on the composite score, "total patient assets," are presented in Fig 6.

Concerning the onset of therapeutic effects, Figs 2 to 6 indicated significant differences favoring clozapine over chlorpromazine as early as the first week. Analysis of variance of the comparative rates of improvement for these treatment groups (analysis of slopes) found that clozapine produced more rapid onset of activity

Table 4.—Comparative Drug Efficacy and Neurologic Ratings

Scale*	Drug	No. of Patients†	Score (Mean ± SD) Baseline	Score (Mean ± SD) End Point	Two-Tailed Analysis of Covariance, *P*
BPRS total score	Clozapine	126	61 ± 12	45 ± 13	<.001
	Chlorpromazine	139	61 ± 11	56 ± 12	
BPRS cluster of four key items	Clozapine	126	19 ± 4	14 ± 5	<.001
	Chlorpromazine	139	19 ± 4	17 ± 4	
CGI Scale	Clozapine	126	5.6 ± 0.7	4.4 ± 1.1	<.001
	Chlorpromazine	139	5.7 ± 0.7	5.3 ± 0.8	
AIMS total score	Clozapine	126	8.8 ± 6.8	5.1 ± 5.4	.09
	Chlorpromazine	139	6.5 ± 5.4	5.8 ± 5.5	
Simpson-Angus Scale for Extrapyramidal Side Effects	Clozapine	126	3.2 ± 3.6	1.8 ± 2.1	.03
	Chlorpromazine	139	3.3 ± 3.5	2.9 ± 3.2	

*BPRS indicates Brief Psychiatric Rating Scale; CGI, Clinical Global Impressions; and AIMS, Abnormal Involuntary Movements Scale.
†Three patients were excluded from these analyses. One patient did not undergo rating after randomization, and one study site had only two patients, both of whom received chlorpromazine.

Table 5.—Comparative Efficacy of Clozapine vs Chlorpromazine and Benztropine

Criterion Variable*	Drug(s) Proved Effective†	Drug Proved Superior/*P*‡	Week of Onset of Superior Drug Activity‡	Drug Proved Faster§
BPRS positive symptoms				
Conceptual disorganization	Clozapine and chlorpromazine	Clozapine/<.001	1	Clozapine
Mannerisms/posturing	Clozapine	Clozapine/<.001	1	Clozapine
Hostility	Clozapine and chlorpromazine	Clozapine/<.001	1	Clozapine
Suspiciousness	Clozapine and chlorpromazine	Clozapine/<.001	2	. . .
Hallucinatory behavior	Clozapine and chlorpromazine	Clozapine/<.001	2	. . .
Excitement	Clozapine and chlorpromazine	Clozapine/<.001	3	. . .
Unusual thought	Clozapine and chlorpromazine	Clozapine/<.001	1	Clozapine
Grandiosity	Clozapine	. . .	. . .	. . .
BPRS negative symptoms				
Emotional withdrawal	Clozapine	Clozapine/<.001	2	Clozapine
Uncooperativeness	Clozapine	Clozapine/<.001	1	Clozapine
Blunted affect	Clozapine	Clozapine/<.001	3	Clozapine
Disorientation	Clozapine	Clozapine/<.001	2	Clozapine
Motor retardation	. . .	Clozapine/<.05	6	. . .
BPRS general symptoms				
Somatic concern	Clozapine	Clozapine/<.01	6	Clozapine
Anxiety	Clozapine and chlorpromazine	. . .	. . .	. . .
Guilt	Clozapine and chlorpromazine	. . .	. . .	. . .
Tension	Clozapine and chlorpromazine	Clozapine/<.001	1	. . .
Depressed mood	Clozapine and chlorpromazine	. . .	. . .	. . .
BPRS total score	Clozapine and chlorpromazine	Clozapine/<.001	1	Clozapine
CGI Scale	Clozapine and chlorpromazine	Clozapine/<.001	1	Clozapine
NOSIE-30 factors				
Social competence	Clozapine and chlorpromazine	Clozapine/<.001	2	Clozapine
Social interest	Clozapine	Clozapine/<.001	1	Clozapine
Personal neatness	Clozapine	Clozapine/<.001	2	Clozapine
Irritability	Clozapine and chlorpromazine	Clozapine/<.01	2	. . .
Manifest psychosis	Clozapine and chlorpromazine	Clozapine/<.001	2	. . .
Motor retardation	. . .	Clozapine/<.05	2	Clozapine
NOSIE total assets	Clozapine and chlorpromazine	Clozapine/<.001	2	Clozapine

*BPRS indicates Brief Psychiatric Rating Scale; CGI, Clinical Global Impression; and NOSIE-30; 30-item Nurses' Observation Scale for Inpatient Evaluation.
†Significant pre-post change by within-group *t* tests.
‡Significant pre-post change by between-group analysis of covariance.
§Analysis of variance of rates of improvement.

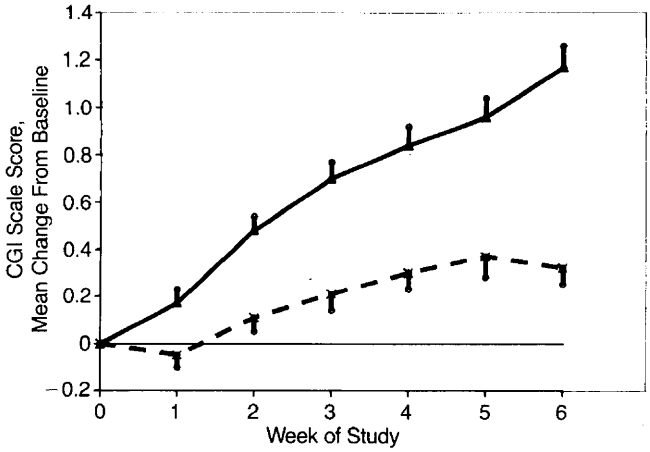

Fig 3.—Mean change from baseline in score on Clinical Global Impressions (CGI) Scale for patients treated with clozapine (solid line, n = 126) or chlorpromazine and benztropine mesylate (broken line, n = 139). For week 1, $P = .003$; weeks 2 through 6, $P < .001$.

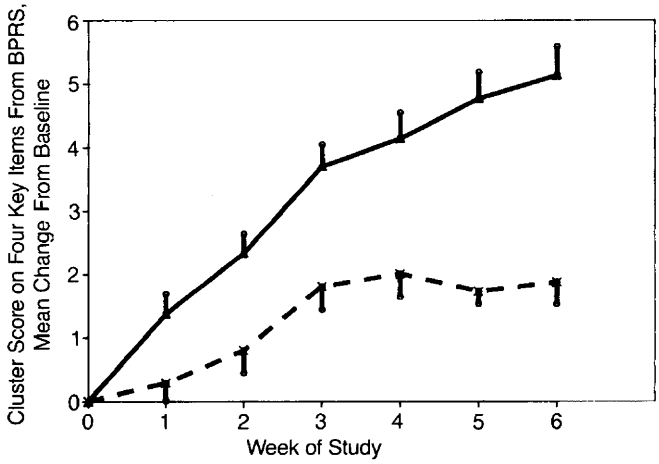

Fig 4.—Mean change from baseline in cluster score on four key items from Brief Psychiatric Rating Scale (BPRS) for patients treated with clozapine (solid line, n = 126) or chlorpromazine and benztropine mesylate (broken line, n = 139). For week 1, $P = .011$; week 2, $P = .001$; weeks 3 through 6, $P < .001$.

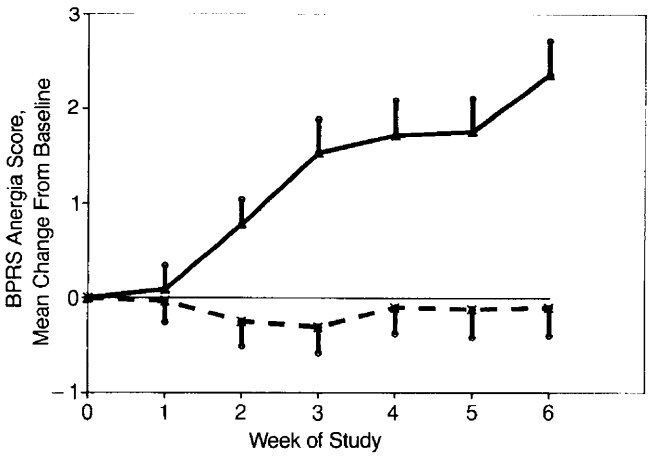

Fig 5.—Mean change from baseline in score on anergia item from Brief Psychiatric Rating Scale (BPRS) for patients treated with clozapine (solid line, n = 125) or chlorpromazine and benztropine mesylate (broken line, n = 139). For week 1, $P < .544$; week 2, $P = .002$; weeks 3 through 6, $P < .001$.

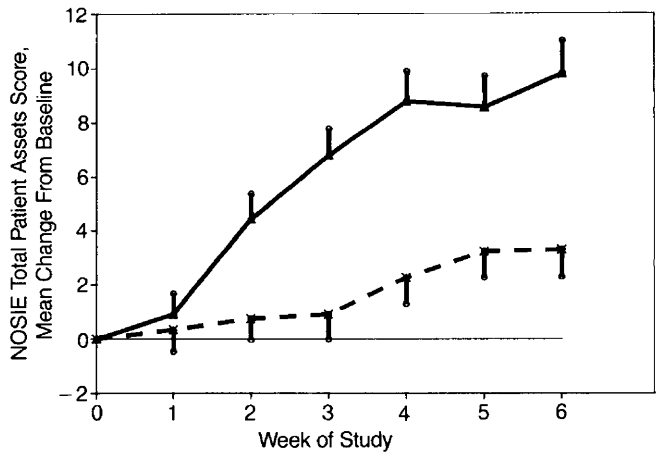

Fig 6.—Mean change from baseline in score on total patient assets item from Nurses' Observation Scale for Inpatient Evaluation (NOSIE) for patients treated with clozapine (solid line, n = 126) or chlorpromazine and benztropine mesylate (broken line, n = 139). For week 1, $P = .356$, weeks 2 through 6, $P < .001$.

in 16 of 27 tests performed; this was never true for chlorpromazine (Table 5).

To test for differential effects among centers, mean improvement scores (total BPRS) by treatment group were individually arrayed for each of the 16 centers. The data were homogeneous: in 14 of 16 centers, greater improvement was found for clozapine-treated patients.

The interpretations allowed by the parametric data are limited by the fact that clinically unimportant changes in rating-scale scores can be statistically significant if a large enough sample of patients is studied. The critical test from a clinical perspective is the extent to which a treatment produces a clinically meaningful response; ie, is the patient believed to have truly benefited from the medication? This issue underscores the importance of the a priori criteria for clinical improvement that provide the critical outcome measures in this investigation.

Patients were classified as having "improved" to a clinically significant extent or not over the course of double-blind treatment. The a priori criteria for defining a patient as improved included a reduction greater than 20% from baseline in the BPRS total score plus either a posttreatment CGI Scale score of 3 (mild) or less or a posttreatment BPRS total score of 35 or lower. When these criteria were applied to all patients who completed at least one week of the double-blind phase of treatment, it was found that only 4% of patients treated with chlorpromazine and benztropine had improved, while 30% of clozapine-treated patients had improved ($P < .001$) (Table 6). These results provide the most cogent evidence of clozapine's superiority.

Evaluation of Safety

Comparative incidences of adverse reactions (the number of patients reporting a new or worsened effect one or more times during double-blind treatment) are presented in Table 7 for the more frequent adverse reactions. This table is ordered by descending frequency of occurrence for patients receiving clozapine compared with chlorpromazine and benztropine.

Extrapyramidal side effects during the chlorpromazine and haloperidol treatment periods were largely masked by the prophylactic administration of benztropine. Rating-scale evidence of relative extrapyramidal side effects of the three active drug conditions (clozapine, chlorpromazine and benztropine, and haloperidol and benztropine) was provided by weekly assessments using the Simpson-Angus Scale for Extrapyramidal Side Effects. Figure 7 provides mean ratings for these patients throughout the entire course of study, showing a rise in such symptoms (excluding

Table 6.—No. of Patients Whose Condition Improved*

Drug	No. (%) of Patients Whose Condition Improved	All Others, No. (%)	Total, No. (%)
Clozapine	38 (30)	88 (70)	**126 (100)**
Chlorpromazine	5 (4)	136 (96)	**141 (100)**
Total	**43 (16)**	**224 (84)**	**267 (100)**

*The categorization is based on the last evaluation completed for each patient. $P<.001$ by two-tailed Fisher's exact test.

salivation) during the haloperidol and benztropine phase followed by a decrease during washout, with little subsequent benefit for patients treated with chlorpromazine and benztropine. However, clozapine-treated patients continued to improve further until the end of the six-week study period. This improvement was statistically significant at weeks 4, 5, and 6.

Although the impact of these treatments on tardive dyskinesia was not a focus of this study, changes in scores on the AIMS were also examined. The clozapine-treated patients had a significantly higher mean baseline score on the AIMS (8.8 vs 6.5). Analyses of covariance showed a trend for clozapine-treated patients to improve more on this measure ($P=.09$ by two-tailed test).

Dry mouth was more prominent in patients receiving chlorpromazine and benztropine (20%), while salivation was more characteristic of patients receiving clozapine (13%). In the cardiovascular area, hypotensive reactions occurred in 38% of patients treated with chlorpromazine and benztropine compared with 13% of clozapine-treated patients. However, tachycardia was more prevalent in clozapine-treated patients (17%).

In terms of miscellaneous adverse effects, benign temperature elevations not associated with laboratory test abnormalities were more frequent in clozapine-treated patients (13%). Three cases of hepatic enzyme elevations were judged to be clinically significant in the clozapine group compared with one in the chlorpromazine group. There were no reports of agranulocytosis in this cohort. (The cases that occurred in the United States were among individuals being treated according to an open-label "humanitarian" protocol.)

The two treatments did not differ in the proportion of patients who experienced a drop in total white blood cell count below 3.9×10^9/L (4.9% for clozapine and 3.3% for chlorpromazine). Thirteen percent of the clozapine-treated patients experienced a drop in neutrophils to below 0.50 of the total white blood cells compared with 20% of the patients receiving chlorpromazine.

COMMENT

The results of this 16-center investigation of 319 patients have implications for the understanding of chronic schizophrenia both methodologically and clinically. From the viewpoint of methodology, this study suggests some validity for a set of historical and prospective criteria defining refractoriness to treatment in schizophrenia—the conditions of fewer than 2% of patients selected improved after six weeks of treatment with haloperidol at daily dosages averaging over 60 mg/d at peak, and the conditions of fewer than 5% of patients treated with chlorpromazine improved with a peak dosage averaging 1200 mg/d. At several of the 16 collaborating sites, many patients who were initially judged to be refractory to treatment had not in fact received adequate trials of three different neuroleptic drugs in recent years, and some patients did respond to a change in pharmacologic treatment; those patients became ineligible for the trial. Obviously, the clinician treating the nonresponsive patient must strive for a balanced approach, avoiding both therapeutic nihilism and overzealous utilization of every imaginable pharmacologic or somatic treatment. Even patients who are apparently hopelessly ill deserve periodic reevaluation of ongoing pharmacotherapy and consideration of shifts to alternative treatments.

Table 7.—Most Frequent Adverse Reactions

Adverse Reaction	Clozapine ($n=126$), No. (%) of Patients	Chlorpromazine ($n=142$), No. (%) of Patients	P*
Drowsiness	26 (21)	18 (13)	.098
Tachycardia	21 (17)	16 (11)	.218
Constipation	20 (16)	17 (12)	.380
Dizziness	18 (14)	23 (16)	.735
Hypotension	16 (13)	54 (38)	<.001
Fever (hyperthermia)	16 (13)	6 (4)	.014
Salivation	17 (13)	2 (1)	<.001
Hypertension	15 (12)	7 (5)	.045
Headache	13 (10)	14 (10)	.999
Nausea/vomiting	12 (10)	17 (12)	.560
Dry mouth	6 (5)	28 (20)	<.001

*Based on two-tailed Fisher's exact test.

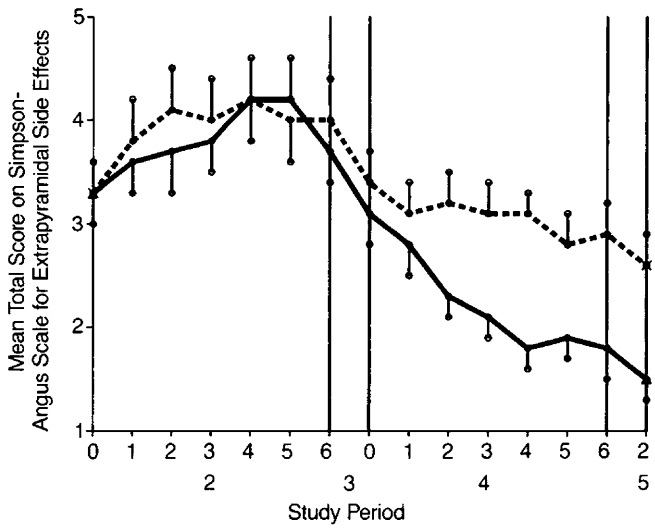

Fig 7.—Mean total scores (lower scores are better) on Simpson-Angus Scale for Extrapyramidal Side Effects, excluding salivation, for patients treated with clozapine (solid line, n = 116) or chlorpromazine and benztropine mesylate (broken line, n = 125) during period 2 (haloperidol and benztropine mesylate), period 3 (placebo washout phase), period 4 (double-blind phase), and period 5 (placebo washout phase).

The response to clozapine demonstrates that this subgroup of severely ill schizophrenic patients, previously considered by many to be beyond the reach of conventional therapy, does remain capable of experiencing substantial medication response. This further argues for the importance and feasibility of conducting carefully controlled, large-scale treatment trials in this patient population.

We believe that this is the first time any specific antipsychotic drug has been shown to be superior to another in a well-defined group of treatment-resistant patients who are unresponsive to haloperidol and other traditional neuroleptics. In addition, given the use of prophylactic benztropine in the chlorpromazine group, the evident superiority of clozapine cannot be attributed simply to a reduction in or lack of extrapyramidal side effects.

Much consideration went into the choice of haloperidol and chlorpromazine in this study design. Both drugs are

among the most widely used antipsychotic agents, and they represent the high- and low-potency ends of the spectrum. Chlorpromazine was believed to be the best comparison drug for the double-blind phase, because, in combination with prophylactic antiparkinsonian medication, its adverse-effect profile would be more similar to that of clozapine than the adverse-effect profile of haloperidol. Undoubtedly, one or both of these medications might have failed in the past in some patients included in this study, but this in no way diminishes the importance of clozapine's superiority in this design, since the intent was to identify patients who were unresponsive to available compounds.

Much deliberation also went into the decision to include prophylactic benztropine along with chlorpromazine and haloperidol. We believed that the potential advantages in enhancing the double-blind character of the study (by reducing the possibility of extrapyramidal side effects) argued for the use of benztropine, given that clozapine is relatively free from extrapyramidal side effects.

The superiority of clozapine in this clinical trial is impressive both because of the rigorous manner in which patients were defined and selected and because the superiority was consistent across such a full range of items and factors on the BPRS as well as the CGI Scale. These findings were confirmed and extended by the nurses' ratings. This superiority was not confined to a particular aspect or dimension of psychopathologic characteristics (eg, hallucinations, delusions, or suspiciousness) but involved all the major psychotic signs and symptoms associated with this patient group, including such negative items as blunted affect, emotional withdrawal, apathy, and disorientation. It might be suggested that the antimuscarinic potency of combined chlorpromazine and benztropine produced a cognitive dysfunction leading to disorientation or a worsening of some psychotic signs; however, the superiority of clozapine on the disorientation item resulted from improvement among patients receiving clozapine, not from a worsening among patients treated with chlorpromazine and benztropine.

Given these findings, there is an obvious need for further research to explore the mechanisms by which clozapine accomplishes its clinical effects and to identify possible predictors that might help to select, if possible, the subgroup of patients most likely to benefit. Since drug refractoriness probably occurs for various reasons, however, even this carefully chosen sample of schizophrenic patients remains heterogeneous.

There were no reports of agranulocytosis during this relatively brief study. At present, however, we believe that the apparently increased comparative risk of agranulocytosis requires that the use of clozapine be limited to selected treatment-resistant patients for whom the potential benefits are judged to outweigh the risks.

At the same time, research is under way that attempts to identify risk factors that might predispose certain individuals to the development of hematopoeitic suppression. Careful, regular monitoring of blood cell counts is necessary in patients receiving clozapine, and only those individuals who demonstrate significant benefits within the first four to six weeks should enter the period during which there is increased risk for the development of agranulocytosis (between the sixth and 18th weeks of treatment). With prompt drug discontinuation and proper medical treatment, this problem appears to be reversible within about two weeks, with no physical sequelae. For individuals suffering from treatment-resistant schizophrenia, the availability of clozapine, a potentially helpful treatment, is, in our view, a useful therapeutic advance. If even a small proportion of these patients can go on to adjust to life in the community, with the associated reduced need for long-term institutionalization, this has significance for public health and health financing.

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