Clozapine and Haloperidol in Moderately Refractory Schizophrenia

A 6-Month Randomized and Double-blind Comparison

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Background: Despite the demonstrated efficacy of clozapine in severely refractory schizophrenia, questions remain regarding its efficacy for primary negative symptoms, comparison with a moderate dose of a first-generation antipsychotic, and adverse effects during a longer-term trial. This study examined its efficacy in partially responsive, community-based patients, compared clozapine with moderate-dose haloperidol, and extended treatment to 6 months.

Methods: Randomized, double-blind, 29-week trial comparing clozapine (n=37) with haloperidol (n=34). Subjects with schizophrenia who were being treated in community settings at 3 collaborating clinical facilities were enrolled.

Results: Subjects treated with haloperidol were significantly more likely to discontinue treatment for lack of efficacy (51%) than were those treated with clozapine (12%). A higher proportion of clozapine-treated subjects met an a priori criterion of improvement (57%) compared with haloperidol-treated subjects (25%). Significantly greater improvement was seen in symptoms of psychosis, hostile-suspiciousness, anxiety-depression, thought disturbance, and total score measured on the Brief Psychiatric Rating Scale. No differences were detected in negative symptoms using the Brief Psychiatric Rating Scale or the Schedule for Assessment of Negative Symptoms. Subjects treated with clozapine experienced more excess salivation, dizziness, and sweating and less dry mouth and decreased appetite than those treated with haloperidol.

Conclusions: Compared with a first-generation antipsychotic given in a moderate dose, clozapine offers substantial clinical benefits to treatment-refractory subjects who can be treated in the community. Advantages are seen in a broad range of symptoms but do not extend to negative symptoms.

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DESPITE ADVANCES in treatment of schizophrenia, more than 10% of totally disabled individuals in the United States have this disease, although it affects only 1% of the population.[1,2] The introduction of chlorpromazine hydrochloride and other conventional antipsychotic agents revolutionized the care of schizophrenia. These medications provide dramatic improvement in psychotic symptoms and reduce risk for relapse, but recent estimates of patients with partial or poor response exceed 40%.[3,4]

Clozapine was the first medication to produce significantly greater improvement than conventional antipsychotics in carefully selected, treatment-refractory patients.[5] Subsequent studies confirmed clozapine's effectiveness.[6-10] Controlled trials that showed greatest symptom improvement with clozapine were relatively brief (ie, 6-10 weeks).[6-8] Longer randomized trials found significant reduction in rehospitalization rather than symptoms.[9,10]

Questions remain about the efficacy of clozapine for primary negative symptoms.[11-13] Kane et al[5] studied subjects withdrawn from high-dose haloperidol therapy (mean dosage, 60 mg/d) and compared clozapine with high-dose chlorpromazine plus benztropine mesylate (mean maximum dosage, 1200 mg/d).[5] They reported significantly greater improvement in the Brief Psychiatric Rating Scale (BPRS) anergia factor, which could be attributed to reduction in extrapyramidal adverse effects.[14] The time course of clozapine response also remains in question.

Open and uncontrolled reports suggest that clozapine improves social and cognitive functioning[15] and overall quality of life.[16] Rosenheck et al[17] report that clozapine facilitates psychosocial treatment participation, enhancing effects on quality of life and long-term symptom outcome.

SUBJECTS AND METHODS

We conducted a 6-month, double-blind, prospective, random-assignment trial comparing clozapine (target dosage, 500 mg/d) with haloperidol (target dosage, 10 mg/d). Identical protocol and procedures were followed at 3 centers, including the West Los Angeles Veterans Affairs and University of California–Los Angeles (UCLA) Medical Centers; Hillside Hospital, North Shore–Long Island Jewish Health System, Glen Oaks, NY; and the Western Psychiatric Institute and Clinic and Mayview State Hospital, Pittsburgh, Pa. The study was approved by the institutional review boards at Long Island Jewish Medical Center, the University of Pittsburgh, UCLA, Mayview State Hospital, and the West Los Angeles Veterans Affairs Medical Center. Seventy-one subjects provided informed consent and were randomized to treatment. Computer-generated randomization schedules (blocked by site) were provided to each site; sealed envelopes with treatment assignment were available to clinical personnel if needed to break the blind.

SUBJECTS

Inclusion criteria consisted of *DSM-III-R*[18] diagnosis of schizophrenia or schizoaffective disorder by one of the authors using a diagnostic checklist, 20 to 55 years of age, and living in the community or judged clinically treatable in the community despite psychotic symptoms. Partial or poor response was defined by documented treatment failure in 2 trials of conventional antipsychotics at dosages equivalent to or greater than chlorpromazine hydrochloride, 600 mg/d, for at least 6 weeks (high-dose qualification) and 1 trial of a conventional agent at dosages equivalent to chlorpromazine hydrochloride, 250 to 500 mg/d, for the same length of time (low-dose qualification). Patients for whom a low-dose trial could not be documented received prospective dose reduction for 4 weeks or less if clinical worsening was seen. Only patients who met symptom criteria for inclusion after such treatment (a rating of at least moderate on 1 of the following 4 BPRS items[19,20]: conceptual disorganization, suspiciousness, hallucinatory behavior, and unusual thought content) entered the trial.

Exclusion criteria consisted of receipt of psychotropic medication therapy other than antipsychotics (eg, antidepressants or mood stabilizers) that could not be discontinued, documented history of intolerance to haloperidol at dosages of 4 mg/d or more because of disabling extrapyramidal adverse effects, diagnosis of neuroleptic malignant syndrome with recurrence on rechallenge,

evidence that refractoriness was related to medication noncompliance, organic brain disease (eg, epilepsy or brain tumor), mental retardation that precluded understanding study participation or assessment procedures, chronic medical illness that made study participation inappropriate, *DSM-III-R* diagnosis of substance abuse or dependence[18] within 6 months, current treatment with medication(s) for other medical conditions that may have psychotropic effects or agranulocytosis risk or may interfere with drug absorption or metabolism, total white blood cell count below $3.5 \times 10^3/\mu L$ (3500/mm^3), and pregnancy.

Subject recruitment strategies varied. At Hillside Hospital, inpatient admissions were reviewed daily, and patient rosters at Queens Day Treatment Center, Jamaica, NY, a facility that serves patients with chronic illness, were reviewed quarterly. At the University of Pittsburgh, patient rosters in the Schizophrenia Treatment and Research Center (outpatient clinic and day hospital) were reviewed with primary clinicians quarterly. At Mayview State Hospital, a satellite facility of the University of Pittsburgh, admission service rosters were reviewed weekly and continuing care service rosters were reviewed quarterly. Recruitment at UCLA took place in the Mental Health Clinic and Inpatient Service of the West Los Angeles Veterans Affairs Medical Center and the Aftercare Clinic of the UCLA Neuropsychiatric Hospital. Clinicians in each setting were asked by recruiters to refer refractory individuals. If patients met study criteria and provided informed consent, their treatment was transferred to the research clinic.

All subjects were competent to give informed consent. Competency was assessed by asking the patients to describe in their own words the essential elements of the informed consent document. Potential subjects who were unable to appreciate risks, benefits, or discomforts of the study were considered ineligible.

Subjects receiving fluphenazine decanoate or haloperidol decanoate received oral haloperidol or fluphenazine for 2 injection intervals before beginning double-blind dosage titration.

TREATMENT IMPLEMENTATION

Dosage Titration

Medication was administered under double-blind conditions. Clozapine therapy was begun at a test dosage of 12.5 mg/d on day 1. Haloperidol therapy was begun at a dosage of 5 mg/d. Identical capsules contained haloperidol or clozapine in a 1:50 ratio with a range of 200 to 800 mg of clozapine or 4 to 16 mg of haloperidol. Dosage was gradually increased to a target dosage of 500 mg/d for clozapine or

The present trial was designed to address several questions regarding clozapine's effects. First, community-dwelling and hospitalized patients were included. Second, we compared clozapine with haloperidol decanoate given in moderate doses and used a gradual titration schedule to assess whether clozapine's efficacy for negative symptoms was a function of reduction of extrapyramidal adverse effects. Third, this study extended double-blind observation to 29 weeks to assess long-term response. Three to 6 months is considered adequate to assess clozapine's usefulness in routine clinical care.[9,10] A trial duration of 6 months may also allow discrimination of negative symptoms from akinesia. Since clozapine is the only medication specifically labeled for treatment of refractory schizophrenia and is associated with high cost and increased risk for agranulocytosis, such information is sorely needed to inform clinical practice.

RESULTS

SAMPLE CHARACTERISTICS

Table 1 displays demographic and psychiatric characteristics by treatment. Subjects were comparable to those in

10 mg/d for haloperidol within 5 weeks. Simultaneously, current antipsychotic and all other psychotropic medication therapies were gradually decreased. Haloperidol-treated subjects received benztropine mesylate, 2 mg twice daily. Clozapine-treated subjects received matching placebo. To maintain the blind, all subjects had a weekly blood draw. Titration could be slowed or stopped below the target dose if subjects could not tolerate the standard titration schedule because of adverse effects. At the Hillside Hospital and UCLA sites, outpatients were hospitalized for initial dosage titration. At the University of Pittsburgh, subjects recruited as outpatients had initial dosage titration in the community and were seen by research personnel at least 3 times a week for the first 4 weeks of dosage titration.

Double-blind treatment continued for up to 29 weeks. Dosage could be increased beyond the target dosage to 800 mg/d for clozapine or 16 mg/d for haloperidol if symptoms did not improve or if initially controlled symptoms re-emerged. Dosage could be reduced to 200 mg/d for clozapine or 4 mg/d for haloperidol in response to adverse effects. The only other psychotropic medication allowed was lorazepam after the first week. Medication was dispensed labeled with day of the week and morning (AM) or afternoon (PM). Patients returned remaining medication supplies at weekly visits, and pills were counted. Most outpatients in the study lived in supervised settings where medication taking was observed by staff. Family members were questioned about compliance by telephone, if patients lived with them.

Ancillary Clinical Services

Clinical programs at the centers differed, but all shared a common treatment philosophy, ie, provision of services tailored to patient needs determined by a treatment team. Subjects were seen at least weekly by a research treatment team including a psychiatrist, nurse, and ancillary clinical personnel. Progress and problems were discussed in weekly research team meetings that reviewed recommendations for clinical services and developed strategies for enhancing patient engagement and compliance. Decisions regarding subjects' continued study participation were also made at these meetings. If subjects had clinical treatment teams, they continued to receive services through those teams, and such services were coordinated with the research team.

OUTCOME MEASURES

Psychopathology was assessed using the BPRS,[19,20] the Schedule for Assessment of Negative Symptoms (SANS),[21] and Clinical Global Impressions Scale (CGI).[22] Adverse effects were monitored using the Simpson Angus Scale for Extrapyramidal Side Effects–Hillside Version,[23] Barnes Akathisia Scale,[24] a checklist of adverse effects, and the Abnormal Involuntary Movements Scale.[25] Full assessments were completed at baseline and weeks 5, 11, 17, and 29. The BPRS and CGI were also completed at weeks 1, 2, 3, and 4 and then biweekly throughout the trial. Research psychiatrists who completed psychopathology assessments received initial joint training for administration of the BPRS and SANS at the Hillside Clinical Research Center. Subsequently, cross-site reliability was monitored through ongoing conference calls. Assessment cores of National Institute of Mental Health research centers monitored within-site reliability.

DATA ANALYSIS

We used analysis of variance (ANOVA) for continuous variables and logistic or multinomial regression for categorical variables, including terms for treatment, site, and site × treatment interaction, to evaluate demographic and psychiatric history characteristics.

Time to treatment discontinuation for lack of efficacy was based on a clinical judgment made by the research treatment team. This criterion and time to 20% improvement in the 4 psychotic symptoms used to qualify subjects for study inclusion were the primary outcome measures. Survival analysis was used to evaluate the following outcomes: time to discontinuation of study medication for any reason; time to discontinuation for lack of clinical efficacy; time to 2 consecutive ratings of 20% improvement in BPRS psychotic symptoms; and time to remission, defined by 20% improvement and no psychotic symptom rated worse than mild. In the survival analyses of time to discontinuation for any reason and for lack of efficacy, other reasons (eg, adverse effects, subject decision to withdraw) were treated as "withdrawn alive" at time of discontinuation. Computation of rate differences and confidence intervals followed the method outlined by Borenstein.[26]

Psychopathology (BPRS factors thought disturbance, hostility-suspiciousness, activation, anergia, and anxiety-depression and SANS affective flattening, alogia, avolition-apathy, and anhedonia-asociality global ratings) were evaluated for all subjects (n = 71) at the last available time point. Ratings of adverse effects at 5 weeks or the last available time point before that were drawn from the Simpson Angus Scale, the Barnes Akathisia Scale, and the checklist of adverse effects. Each measure of psychopathology and adverse effects was included as the dependent variable in an ANOVA that tested the effects of treatment, site, and site × treatment. The α level in all analyses was .05 (2-tailed).

other studies of refractory schizophrenia. The mean ages were 40 and 41 years for the haloperidol and clozapine treatment groups, respectively. Most subjects were male and had never been married. Mean age at first hospitalization was 23 years in the haloperidol group and 24 years in the clozapine group. Slight differences were found between groups for mean number of hospitalizations (9 vs 11) and mean number of months in the hospital in the 17 years since illness onset (17 vs 27). Both groups had received neuroleptic medication for approximately 16 years.

Subjects had a history of relatively good premorbid functioning; more than half had at least some college education and were characterized by appropriate functioning to 19 years of age in the the haloperidol group and 21 years in the clozapine group. During the premorbid period, more than two thirds of all subjects were characterized as having functioned at least moderately well. Their longest period of sustained employment was less than 3 years.

DOSAGE

Dosages of clozapine and haloperidol were calculated for subjects still in treatment at given times. Dosage was pro-

Table 1. Demographic and Psychiatric History Characteristics of Trial Participants*

	Treatment Group†	
	Haloperidol (n = 34)	Clozapine (n = 37)
Site, No. of patients		
Hillside Hospital, Glen Oaks, NY	11	11
ULCA	16	17
WPIC	7	9
Sex, No. (%) male	24 (71)	26 (70)
Race, No. (%) white‡	24 (71)	25 (68)
Age, mean (SD), y	40 (8)	41 (10)
Marital status, No. (%) never married§	20 (59)	29 (78)
Living arrangement, No. (%)‖		
Parental	10 (30)	10 (27)
Conjugal, alone or collateral	11 (33)	16 (43)
Structured environment	12 (36)	11 (30)
Education, No. (%)		
Beyond high school	19 (56)	21 (57)
Completed high school	9 (26)	10 (27)
Less than high school	6 (18)	6 (16)
Level of premorbid functioning, No. (%)		
Very well	9 (27)	12 (33)
Moderately well	18 (55)	13 (36)
Poorly	6 (18)	11 (31)
Highest occupation, No. (%)¶		
Clerical, skilled manual, administrative, and above	17 (53)	24 (65)
Semiskilled or less, or never worked	15 (47)	13 (35)
Longest employment, mean (SD), mo	34 (43)	32 (35)
Age to which functioned well, mean (SD), y	19 (6)	21 (5)
Age at first psychiatric illness, mean (SD), y	20 (6)	22 (5)
Age at first hospitalization, mean (SD), y	23 (5)	24 (7)
Years since first hospitalization, mean (SD), y	17 (8)	17 (11)
No. of previous hospitalizations, mean (SD)#	9 (8)	11 (10)
Months of hospitalization, mean (SD)	17 (21)	27 (38)
Months of neuroleptic exposure, mean (SD)	203 (96)	195 (119)
Extrapyramidal adverse effects in conjunction with neuroleptic treatment, No. (%)		
Never, rarely, or sometimes	12 (40)	21 (58)
Frequently	18 (60)	15 (42)
Use of antiparkinsonian medication in conjunction with neuroleptic treatment, No. (%)		
Never, rarely, or sometimes	4 (13)	6 (17)
Frequently	26 (87)	30 (83)

*Site, treatment, and site × treatment effects were tested for all variables. Analyses of continuous variables used analysis of variance, whereas categorical variables were analyzed using logistic or multinomial regression. UCLA indicates University of California–Los Angeles; WPIC, Western Psychiatric Institute and Clinic, Pittsburgh, Pa.

†No significant main effects for treatment or site × treatment interactions were found for any variables.

‡Site effect for race, χ^2_2 = 9.26; $P<.01$ (for white subjects, UCLA had 7 [52%] vs WPIC with 14 [88%]).

§Site effect for marital status, χ^2_3 = 15.82; $P<.01$ (for never-married subjects, Hillside had 20 [91%] vs UCLA with 18 [55%]).

‖Site effect for living arrangements χ^2_4 = 15.99; $P<.01$ (for structured environment, Hillside had 4 [18%] vs WPIC with 8 [50%]).

¶Site effect for highest occupation of patient χ^2_2 = 12.63; $P<.01$ (for semiskilled or less or never worked, Hillside had 7 [32%] vs WPIC with 12 [80%]; UCLA had 9 [28%] vs WPIC with 12 [80%]).

#Site effect for number of previous hospitalizations, F_2 = 3.47; $P<.05$ (mean [SD] for Hillside, 7 [5]; for UCLA, 3 [11]).
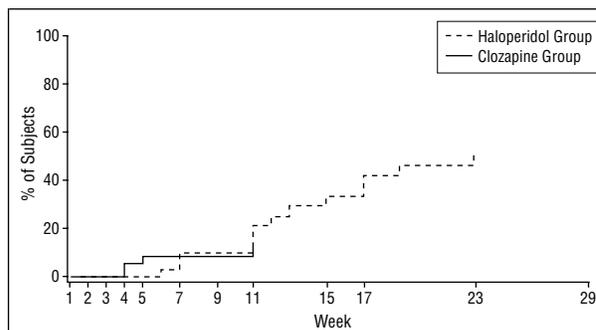
Figure 1. Time to discontinuation of study medication specifically for lack of clinical response. The clozapine group included 37 subjects; the haloperidol group, 34 (Wilcoxon χ^2_1, 5.58; $P=.02$).

mg/d) at week 5 (n=29). Subsequently, clinical response influenced dosage. For haloperidol, dosage increased to 14.3 mg/d (SD, 6.4 mg/d) at week 11 (n=22), 15.7 mg/d (SD, 6.5 mg/d) at week 17 (n=14), and 18.9 mg/d (SD, 7.0 mg/d) at week 29 (n=9). For clozapine, dosage remained relatively constant, ie, 491 mg/d (SD, 127 mg/d) at week 11 (n=28), 506 mg/d (SD, 174 mg/d) at week 17 (n=25), and 523 mg/d (SD, 171 mg/d) at week 29 (n=25).

DURATION OF STUDY PARTICIPATION

Subjects randomized to clozapine were significantly more likely to complete 29 weeks of receiving study medication than were subjects assigned to haloperidol. By week 29, 22 (66.7%) of the haloperidol-treated patients were discontinued from the study compared with 13 (35.1%) of the clozapine-treated patients, a 32% difference (Wilcoxon χ^2_1, 4.59; $P=.03$). Three haloperidol- and 2 clozapine-treated patients were discontinued from the study due to adverse effects.

Figure 1 shows the cumulative proportions of subjects discontinued from the study specifically for lack of efficacy; by 29 weeks, 50.5% of haloperidol-treated subjects discontinued for lack of efficacy compared with 11.6% of clozapine-treated subjects, a 39% difference (Wilcoxon χ^2_1, 5.58; $P=.02$).

PSYCHOTIC SYMPTOMS

A second major criterion for response was 20% improvement on the 4-item BPRS psychosis cluster, as shown in **Figure 2**. A subject was classified as *improved* if this score decreased 20% from baseline for at least 2 consecutive assessments and was classified as not improved otherwise. (The 20% improvement is based on BPRS ratings scaled from 1 to 7.) Subjects who discontinued treatment for lack of efficacy—improved or not—were excluded from the at-risk sample at discontinuation.

Separation between groups was seen by week 4, when 39% of clozapine-treated subjects and 19% of haloperidol-treated subjects met this criterion. By 29 weeks, the proportions classified as improved were 56.6% for the clozapine group compared with 24.8% for the haloperidol group, a 32% difference (Wilcoxon χ^2_1, 5.88; $P=.02$).

These criteria for improvement are based on change from baseline and do not require that the subject meet

tocol driven during the first 5 weeks. The mean dosage of haloperidol was 5 mg/d at week 1 and 10 mg/d (SD, 1.3 mg/d) at week 5 (n=29); the mean dosage of clozapine was 141 mg/d (SD, 28 mg/d) at week 1 and 433 mg/d (SD, 122

an absolute threshold of symptom absence. For this reason, the outcome represents improvement rather than remission. In fact, in this population of patients with chronic illness, 1 (3%) of the haloperidol-treated patients and 7 (19%) of the clozapine-treated patients would have been rated as in remission at study conclusion if *remission* is defined by the 20% improvement criterion and no symptom in the BPRS psychosis cluster rated greater than mild (Fisher exact test, $P=.06$; 1 *df*).

Table 2 presents means and SDs over time by treatment group for symptom factors of the BPRS, global ratings of the SANS, and psychiatrists' ratings of severity and improvement for observed cases.

Changes in psychopathology from baseline to last rating indicate improvement at end point for each subject. **Figure 3** shows change from baseline to final rating for the BPRS total score and all BPRS subscales. For comparison, scores were converted to the 7-point severity scale by dividing by the number of items. For the psychosis subscale, the haloperidol-treated group showed a decrease of 0.2 point, whereas the clozapine-treated group showed an improvement of 0.8 point, an overall difference of 1 scale point. The mean rating at final evaluation was 3.2 for the clozapine group, closer to mild than moderate, compared with 4.2 for the haloperidol group. Mean improvement between groups at end point (including the baseline measure, site, and site × treatment in the analysis) had a 95% confidence interval (CI) of 0.5 to 1.5 (treatment effect, $F_1=18.37$; $P<.001$).

OTHER PSYCHOPATHOLOGY SYMPTOMS

Figure 3 shows that the advantage of clozapine to haloperidol is 0.8 scale point for thought disturbance. A difference of 0.6 scale point in anxiety-depression reflects improvement in the clozapine group and deterioration in the haloperidol group. A smaller effect (closer to 0.5 scale point) is evident for the BPRS total score and the hostile-suspiciousness factor. A significant effect was not evident for the anergia or activation factors.

The CGI ratings show a similar pattern of treatment effects. Severity of illness is rated on a 7-point scale; 4 indicates moderately ill and 5, markedly ill. The mean rating at final evaluation was 4.0 for clozapine compared with 5.0 for haloperidol, a difference of 1.0 scale point in favor of clozapine. Mean improvement between the groups at end point (including the baseline measure, site, and site × treatment in the analysis) had a 95% CI of 0.4 to 1.4 (treatment effect, $F_1=14.77$; $P<.001$). The CGI improvement scale is a 7-point scale; 3 indicates minimally improved and 4, no change. The mean final rating for clozapine-treated subjects was 3.0 compared with 4.2 for the haloperidol-treated subjects, a difference of 1.2 points. Mean improvement between the groups at end point (including site and site × treatment in the analysis) had a 95% CI of 0.7 to 1.9 (treatment effect, $F_1=19.30$; $P<.001$).

NEGATIVE SYMPTOMS

There were no treatment differences on the SANS global composite (sum of the 4 global ratings). Means for the haloperidol group changed from 9.8 to 10.4 at final rat-
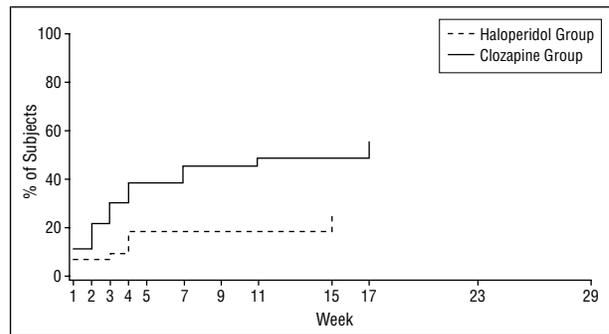

Figure 2. Time to first of 2 consecutive ratings of 20% improvement on the Brief Psychiatric Rating Scale psychosis subscale. The clozapine group included 37 subjects; the haloperidol group, 34 (Wilcoxon χ^2_1, 5.88; $P=.02$).

ing, whereas means for the clozapine group changed from 10.3 to 9.7 at final rating. Mean improvement between the groups on the 20-point scale (including the baseline measure, site, and site × treatment in the analysis) had a 95% CI of –0.7 to 2.3 (treatment effect, $F_1=1.12$; $P=.29$).

We considered the possibility that our failure to identify a treatment effect in negative symptoms might be the result of the relatively low baseline level of negative symptoms, and we repeated the analysis with subjects whose baseline negative symptoms fell in the top 50%. Even in this subgroup, the initial level of negative symptoms was modest and no treatment effect was identified.

ADVERSE EFFECTS

The ANOVAs used to evaluate adverse effects used ratings completed at 5 weeks or last available observation if that occurred before 5 weeks. Clozapine-treated subjects experienced more salivation, sweating, and dizziness; haloperidol-treated subjects experienced more dry mouth and decreased appetite (**Table 3**). No other adverse effects were significantly different between treatment groups. Since adverse effects may break the blind, the correlation of adverse effects and responder/nonresponder status was examined. None of these correlations was significant, although the correlation for dry mouth approached significance ($r=0.22$; $P=.07$).

COMMENT

These findings extend our understanding of clozapine's efficacy in comparison with first-generation antipsychotics. Benefits are seen for subjects who can be treated in the community despite poor or partial response to conventional antipsychotics. These advantages occur in subjects who had not responded previously to either high or low dosages of conventional medication. This study is the first to consider the possibility of an improved response to low doses of antipsychotics in patients who have failed to respond to high doses. Some patients who no longer met symptom criteria after dose reduction were excluded from the trial. We used a moderate dose of haloperidol coupled with benztropine to address the possibility that the advantage for clozapine resulted primarily from reduction of adverse effects in contrast to the comparator group. In fact, our findings regarding dos-

Table 2. Symptom Ratings of Psychopathology by Time and Treatment*

	Patient Groups									
	Baseline		Week 5		Week 11		Week 17		Week 29	
Measure	Clozapine (n = 37)	Haloperidol (n = 34)	Clozapine (n = 31)	Haloperidol (n = 32)	Clozapine (n = 29)	Haloperidol (n = 19)	Clozapine (n = 27)	Haloperidol (n = 14)	Clozapine (n = 23)	Haloperidol (n = 11)
BPRS										
Anxiety-depression	9.9 (3.9)	9.9 (3.8)	8.2 (3.2)	10.8 (4.2)	7.8 (2.8)	10.2 (4.4)	7.9 (3.5)	10.4 (3.9)	7.9 (3.5)	9.0 (4.0)
Anergia	8.5 (3.1)	7.8 (3.2)	7.4 (2.3)	6.9 (3.3)	7.8 (3.2)	8.9 (2.6)	7.8 (2.7)	6.4 (3.2)	7.8 (3.6)	7.1 (4.3)
Thought disturbance	14.7 (4.4)	13.8 (4.4)	11.3 (3.7)	12.7 (4.8)	11.2 (4.1)	12.8 (4.2)	11.1 (4.5)	12.8 (4.5)	11.6 (4.2)	11.9 (4.3)
Activation	6.1 (2.3)	5.3 (2.1)	4.8 (1.7)	5.7 (2.1)	4.4 (1.5)	4.8 (1.4)	4.6 (1.6)	5.6 (2.4)	4.2 (1.5)	4.8 (2.1)
Hostile-suspiciousness	8.0 (3.2)	7.9 (2.7)	6.6 (3.3)	7.9 (3.2)	6.7 (2.9)	7.5 (2.3)	6.5 (2.6)	8.6 (2.8)	6.0 (2.0)	7.4 (2.7)
Psychosis cluster	16.3 (3.9)	16.1 (4.2)	12.5 (4.0)	15.2 (5.2)	12.5 (4.4)	15.1 (4.1)	12.3 (4.7)	15.4 (4.8)	12.1 (3.5)	14.8 (5.7)
Total	47.4 (10.3)	44.7 (9.3)	38.4 (9.6)	44.0 (10.9)	38.0 (8.9)	42.1 (8.3)	37.9 (9.6)	43.7 (11.9)	37.5 (90)	40.2 (12.2)
CGI										
Severity of illness	5.0 (0.8)	4.8 (0.9)	4.2 (1.1)	4.6 (1.0)	4.3 (1.0)	4.4 (0.7)	4.2 (1.2)	4.6 (0.8)	4.0 (1.0)	4.6 (1.0)
Improvement	NA	NA	2.9 (0.8)	3.8 (1.2)	2.7 (0.6)	3.6 (1.1)	2.8 (0.7)	3.6 (0.7)	2.8 (0.8)	3.6 (1.4)
SANS global ratings										
Affective flattening	2.6 (1.0)	2.3 (1.1)	2.3 (0.9)	1.9 (1.1)	2.2 (0.7)	2.1 (1.0)	2.3 (0.9)	1.8 (1.1)	2.3 (1.1)	2.0 (1.2)
Alogia	2.0 (0.9)	2.1 (1.1)	1.9 (0.9)	2.0 (1.0)	1.9 (0.8)	2.3 (1.1)	1.9 (1.1)	2.0 (0.8)	2.0 (1.0)	2.1 (1.3)
Avolition-apathy	2.7 (1.1)	2.6 (1.4)	3.0 (1.0)	2.6 (1.4)	2.8 (1.2)	2.9 (1.3)	2.5 (1.2)	2.3 (1.2)	2.7 (1.1)	2.9 (1.3)
Asociality-anhedonia	2.8 (1.0)	2.8 (1.1)	2.9 (1.0)	2.6 (0.9)	2.9 (1.0)	2.7 (0.9)	2.9 (1.0)	2.3 (1.1)	2.8 (1.1)	2.5 (1.4)

*Data are given as mean (SD). BPRS indicates Brief Psychiatric Rating Scale[19,20]; CGI, Clinical Global Impressions Scale[22]; SANS, Scale for the Assessment of Negative Symptoms[21]; and NA, not available.
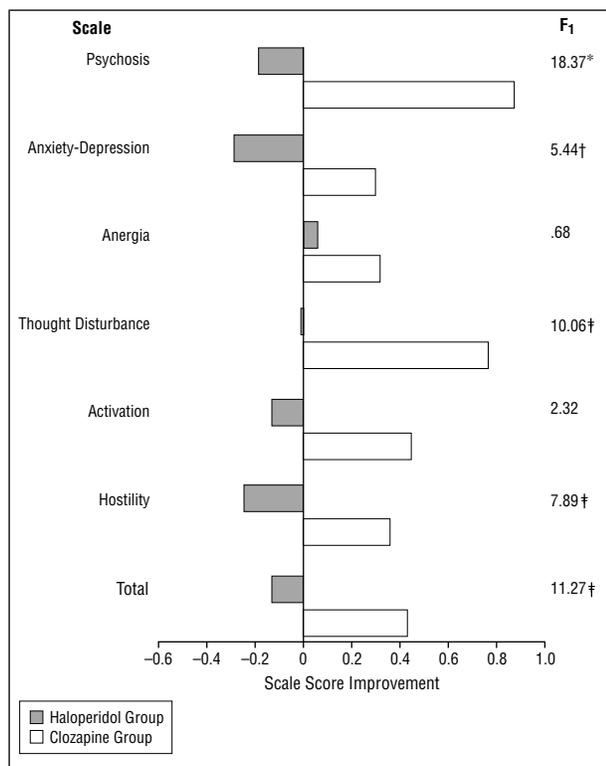

Figure 3. Scale score improvement from baseline to final rating for Brief Psychiatric Rating Scale subscales and total score for all randomized subjects. The clozapine group included 37 subjects (n=36 for thought disturbance); the haloperidol group, 34. All subscales are displayed using change based on a 7-point scale to allow meaningful comparisons. Asterisk indicates $P<.001$; dagger, $P<.05$; and double dagger, $P<.01$.

age suggest that clinicians were not satisfied with the response of some haloperidol-treated subjects who remained in the study. Haloperidol dosage was increased in more responsive patients, since less responsive patients had discontinued the therapy.

Benefit increased rapidly during the 29-week trial, suggesting that treatment exposure to clozapine produced rapid response. Had the trial been 4 weeks long, about 39% of subjects would have met the relatively modest 20% improvement criterion that was attained by 57% in the trial. At 11 weeks, 54% had met this criterion.

How do these findings fit with results of other randomized trials comparing clozapine with conventional antipsychotics? Kane et al[5] compared clozapine with high-dose chlorpromazine in a 6-week trial. Response was defined as a reduction in BPRS total score of greater than 20% from baseline plus a posttreatment CGI score of mild or less or a posttreatment BPRS total score of 35 or lower. Response rates were 30% for clozapine compared with 3.5% for chlorpromazine, a difference of 27% (95% CI, 18%-31%).

The Maryland study[6,8] compared clozapine with haloperidol given in a moderate dosage in a 10-week trial. Response was defined as a 20% or greater decrease in BPRS positive symptom scores and a BPRS positive symptom score of less than 8. Response rates were 44% for clozapine compared with 5.5% for haloperidol, a difference of 39% (95% CI, 5%-49%).

Rosenheck et al[9] compared clozapine and haloperidol in a 1-year trial. Excluding crossovers, the proportions of patients improving 20% or more on the total Positive and Negative Syndrome Scale in the clozapine group were 30% at 6 weeks, 30% at 6 months, and 42% at 1 year. Improvement rates for the haloperidol group were 14%, 14%, and 31%, respectively. Differences in results of comparisons at 6 weeks and 6 months were significant, but the difference of 11% at 1 year was not.

In a randomized but nonblind effectiveness study using the same response criteria as the study by Kane et al[5] (excluding crossovers), Essock et al[10] reported that 62% of the clozapine-treated patients had responded at 24 months compared with 49% of the usual-care subjects (a nonsignificant difference).

In the present trial, we found a 57% improvement with clozapine after 29 weeks. In the 3 double-blind efficacy studies, improvement rates increased (30% at 6 weeks, 44% after 10 weeks, and 57% after 29 weeks) as trial length increased, suggesting an advantage to longer treatment with clozapine, qualified by differences in definition of improvement.

Our findings, as well as those of other recent studies, suggest that the clozapine advantage is not just a function of comparison with a high dose of a conventional antipsychotic. However, these studies underscore that improvement is not always remission. We used a liberal definition of remission in our trial (20% improvement in psychotic symptoms and no psychosis item rated above mild). Only 3% of haloperidol- and 19% of clozapine-treated subjects met this criterion. Perhaps less severely ill patients or those with a shorter duration of illness (our subjects had been ill for a mean of 17 years) would be more likely to experience remission.

Findings are most consistent for positive signs and symptoms. We saw effects for a range of symptoms, including psychosis, anxiety/depression, thought disturbance, and hostility, with the notable exception of negative signs. Our inability to detect differences between clozapine and haloperidol on negative symptoms may result in part from the low levels of negative symptoms in our subjects. However, even when we restricted analysis to the smaller group of subjects who manifested some negative symptoms, we did not see an effect. Given the small differences we found, it is unlikely that a larger study would have been more informative. In contrast to effects on positive symptoms that are seen even in comparisons with low-dose conventional agents, effects on negative symptoms might be, to some extent, a function of the high dose of a comparator agent. Another possibility is that the exclusion of patients who responded to low doses of conventional antipsychotics eliminated subjects who showed negative symptom response in other trials.

The next generation of studies regarding clozapine needs to compare it with the next generation of antipsychotics. The sparse existing literature comparing clozapine and risperidone is inconclusive because of the small number of subjects involved (<100 in total) and because of methodological questions.[27,28] Recently published guidelines for the treatment of schizophrenia uniformly recommend at least 1 trial with a second-generation antipsychotic before proceeding to clozapine.[29,30] However, these recommendations are based on expert opinion rather than experimental studies.

On balance, clozapine provides substantial clinical advantages for patients who experience persistent psychotic symptoms. It is a difficult medication to use, with potentially severe adverse effects and the need for continued monitoring of the white blood cell count, which is mandatory in the United States. That mandate has been reduced by the Food and Drug Administration from weekly to biweekly after 6 months, but any ongoing monitoring requirement is infrequent among psychotropic medications. The positive findings of this study, added to others in the literature, should encourage psychiatrists to try clozapine for patients who continue to have residual symptoms and to use it long enough to see maximal benefit.

Table 3. Treatment-Emergent Adverse Effects by Treatment at Week 5 Observation*

Adverse Effects	Treatment Group	
	Haloperidol (n = 34)	Clozapine (n = 37)
Barnes Akathisia Scale[24] global clinical assessment	0.97 (1.13)	0.46 (0.74)
Simpson Angus Scale[23]		
Rigidity of major joints (overall)	0.48 (0.71)	0.23 (0.55)
Tremor (overall)†	0.33 (0.69)	0.23 (0.43)
Salivation‡	0.21 (0.48)	0.63 (1.03)
Akinesia	0.33 (0.60)	0.29 (0.57)
Treatment Emergent Symptom Scale		
Insomnia	1.35 (0.54)	1.27 (0.56)
Drowsiness	1.82 (0.63)	2.14 (0.82)
Dry mouth§	**1.50 (0.51)**	**1.19 (0.46)**
Nasal congestion	1.26 (0.45)	1.43 (0.50)
Blurred vision	1.50 (0.66)	1.38 (0.59)
Constipation	1.53 (0.79)	1.57 (0.65)
Excess salivation‖	**1.21 (0.41)**	**2.14 (0.86)**
Sweating¶	**1.12 (0.33)**	**1.41 (0.72)**
Nausea/vomiting/indigestion/ abdominal pain	1.41 (0.56)	1.35 (0.54)
Diarrhea	1.18 (0.46)	1.05 (0.23)
Hypotension	1.06 (0.24)	1.27 (0.61)
Syncope/dizziness/lightheadedness on standing#	**1.44 (0.50)**	**1.81 (0.74)**
Tachycardia	1.29 (0.46)	1.54 (0.73)
Fever	1.03 (0.17)	1.00 (0.00)
Dermatologic/rash	1.06 (0.24)	1.08 (0.28)
Anorexia/decreased appetite**	**1.41 (0.61)**	**1.05 (0.23)**
Headache	1.26 (0.51)	1.38 (0.72)

*Site, treatment, and site × treatment effects were tested for all variables using analysis of variance. Data are given as mean (SD). Significant drug effects are given in boldface. If data were not available at week 5, data from the most recent observation were used. The number in the first 5 analyses was 68 because of missing values. Higher scores on all scales indicate greater severity. Abbreviations for sites are given in the first footnote to Table 1.
†Site effect, F_2=7.16; P<.01 (mean [SD], UCLA, .03 [.17] vs Hillside, .50 [.60]; UCLA .03 [.17] vs Pittsburgh .54 [.88]).
‡Site effect, F_2 = 3.24; P<.05 (mean [SD], Hillside, 0.14 [0.35] vs UCLA, 0.67 [1.08]). Drug × site interaction effect, F_2 = 3.74; P<.05 (mean [SD], UCLA/clozapine 1.12 [1.27] vs Hillside/clozapine, 0.90 [0.30]; UCLA/clozapine, 1.12 [1.27] vs Pittsburgh/clozapine, 0.29 [0.49]; UCLA/clozapine, 1.12 [1.27] vs Hillside/haloperidol 0.18 [0.40]; UCLA/clozapine, 11.2 [1.27] vs Pittsburgh/haloperidol, 0.33 [0.52]; and UCLA/clozapine, 1.12 [1.27] vs UCLA/haloperidol, 0.19 [0.54]).
§Drug effect, F_1 = 7.70; P<.01.
‖Drug effect, F_1 = 28.37; P<.001.
¶Drug effect, F_1 = 5.17; P<.05.
#Drug effect, F_1 = 10.18; P<.01. Site effect, F_2 = 3.75; P<.05 (mean [SD], Pittsburgh, 1.94 [0.85] vs UCLA, 1.42 [0.61]). Drug × site interaction effect, F_2 = 5.09; P<.01 (mean [SD], Pittsburgh/clozapine, 2.44 [0.73] vs Hillside/clozapine, 1.73 [0.47]; Pittsburgh/clozapine, 2.44 [0.73] vs UCLA/clozapine, 1.53 [0.72]; Pittsburgh/clozapine, 2.44 [0.73] vs Hillside/haloperidol, 1.73 [0.47]; Pittsburgh/clozapine, 2.44 [0.73] vs Pittsburgh/haloperidol, 1.29 [0.49]; and Pittsburgh/clozapine, 2.44 [0.73] vs UCLA/haloperidol, 1.31 [0.48]).
**Drug effect, F_1 = 10.21; P<.01.

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