The Efficacy and Safety of Clozapine Versus Chlorpromazine in Geriatric Schizophrenia

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Background: There has been an absence of controlled studies focusing specifically on neuroleptic treatment in the elderly schizophrenic population. Therefore, we conducted a 12-week double-blind comparison study to assess the efficacy and tolerability of clozapine and chlorpromazine in a group of elderly inpatients with chronic schizophrenia.

***Method*:** Forty-two elderly DSM-IV schizophrenic veterans were randomly assigned to clozapine or chlorpromazine and assessed for efficacy at baseline and at termination with the Positive and Negative Syndrome Scale (PANSS) and the Clinical Global Impressions scale (CGI). Side effects were also monitored. Medications were titrated, on the basis of clinical response and side effects, to a maximum dose of 300 mg/day of clozapine or 600 mg/day of chlorpromazine.

Results: The results suggest that both the chlorpromazine and clozapine groups improved their PANSS scores at termination compared with baseline, but the difference between the 2 groups was not statistically significant. The mean CGI scores reflecting severity of illness also demonstrated improvement in both groups over time. Both groups had similar incidences of side effects. One patient in each group had a life-threatening side effect. More patients taking clozapine had tachycardia and weight gain, while more chlorpromazine patients noted sedation.

Conclusion: We concluded that both clozapine and chlorpromazine are effective treatments for psychosis and behavioral disturbances in geriatric schizophrenia. Both agents had similar incidences of side effects. With careful monitoring and titration of dosage, both clozapine and chlorpromazine were fairly well tolerated in this population.

(J Clin Psychiatry 1999;60:41–44)

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Presented in part at the 149th annual meeting of the American Psychiatric Association, May 4–9, 1996, New York, N.Y.

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Few studies have investigated the pharmacologic treatment of elderly schizophrenic patients, despite their suffering and the financial burden they pose on society. Furthermore, almost no studies focus specifically on neuroleptic treatment in elderly schizophrenic patients. Available data suggest that elderly schizophrenic patients differ from younger ones with respect to the frequency and severity of neuroleptic-induced side effects (i.e., parkinsonian symptoms and tardive dyskinesia).[1–5] Although low doses of neuroleptics seem to be safe in elderly patients, many studies report a high incidence of side effects.

Clozapine has evolved as an efficacious therapy in the treatment-resistant schizophrenic population.[6] In addition, clozapine has been shown to differ significantly from conventional neuroleptics in its side effect profile. Data on the efficacy and safety of this drug in elderly schizophrenic patients, however, are not yet available. Therefore, we were interested in comparing the efficacy and safety of clozapine versus those of chlorpromazine in the treatment of psychosis in elderly schizophrenic patients. Chlorpromazine was chosen because previous studies in younger schizophrenic patients compared clozapine with chlorpromazine.[7] In addition, chlorpromazine has a side effect profile similar to that of clozapine, which would ensure the blindedness of the study.

METHOD

Patients were recruited via physician referral from the inpatient services of a suburban Veterans Affairs hospital. Patient inclusion criteria were (1) age of 55 years or greater, (2) diagnosis of chronic schizophrenia or schizoaffective disorder by DSM-IV criteria, (3) total score on the Positive and Negative Syndrome Scale (PANSS)[8] of at least 60, (4) inpatient status at the onset of the study and until medication dose was stabilized, (5) no depot neuroleptics within the past 4 weeks, and (6) general good health as determined by physical examination, laboratory tests, and electrocardiogram (ECG). Exclusion criteria were (1) significant neurologic disorder (e.g., dementia, history of cerebrovascular accident, episode of delirium within the past 3 months, intractable seizure disorder) and

(2) treatment with investigational drugs within the past 4 weeks.

Patients who met the inclusion-exclusion requirements were explained the study procedures, after which a written informed consent was obtained from each patient or his or her legal guardian. A psychiatrist (E.H.), who was blinded to the patients' treatment status, administered baseline PANSS and the Clinical Global Impressions scale (CGI).[9] The Abnormal Involuntary Movement Scale (AIMS),[9] at baseline and 4-week intervals, was used to measure treatment-emergent dyskinesia. Baseline laboratory testing (ECG, complete blood cell [CBC] count with differential, General Health Panel [Roche-Boeringer Mannheim, Indianapolis, Ind.]) was also performed. All psychotropic medication was gradually reduced and discontinued. As clinically permitted, the patients were maintained drug-free from 1 to 7 days. Patients taking stable doses of cardiac medication and other medications without psychotropic effects were maintained on treatment with those drugs throughout the study. The patients were randomly assigned, by the hospital pharmacist, under double-blind conditions, to clozapine or chlorpromazine packaged in identical capsules.

At the end of the washout period, patients were assigned to receive clozapine, starting with 12.5 mg, or chlorpromazine, 25 mg, daily for 3 days. Subsequent doses were clozapine, 25 mg/day, or chlorpromazine, 50 mg/day, for 3 more days. The medication was increased as tolerated to a daily dose of 300 mg for clozapine and 600 mg for chlorpromazine. These dosages were chosen because our colleagues' previous clinical experience from Pilgrim State Psychiatric Center had shown that these maximum doses are sufficient to obtain significant therapeutic responses in elderly patients and that they are clinically equivalent (M. Davidson, M.D.; P. D. Harvey, Ph.D.; M. Losonczy, M.D., Ph.D., oral communication, November 1994). The increments did not exceed 25 mg/day for clozapine or 50 mg/day for chlorpromazine. The titration period lasted 26 days, after which the subjects were maintained on a stable dose, which was administered in divided doses, for 8 weeks. If side effects occurred during the stable dose phase, a new stable dose was established. However, patients needed to receive a minimum of 50 mg/day of clozapine or 100 mg/day of chlorpromazine in order to remain in the study and to remain on a stable dose for 5 weeks for efficacy analysis.

For side effects, benztropine 0.5 mg p.o. was administered up to a total of 2 mg/day to treat medication-induced extrapyramidal symptoms. Patients were allowed to receive up to 1500 mg/day of chloral hydrate, when needed, to control agitation. For patients who developed any significant side effects, the medication was withheld and the schedule dropped back 1 titration. If side effects recurred, the highest tolerated dose was administered for the remainder of the study.

RESULTS

The mean age of the 18 patients enrolled in the chlorpromazine group was 68.5 years. Seventeen men and 1 woman received chlorpromazine. Ten patients were characterized as schizophrenic, paranoid type, 7 as undifferentiated, and 1 as catatonic. Thirteen patients were white, 2 were African American, and 3 were Hispanic. The mean duration of illness was 40 years, and the mean length of inpatient treatment was 17.5 years. By contrast, the mean age of the 24 patients in the clozapine group was 65 years; the group comprised 2 women and 22 men. Eleven patients were characterized as schizophrenic, paranoid type, 12 as undifferentiated, and 1 as catatonic. The clozapine group included 20 white and 4 African American patients. The mean duration of illness was 38 years, and the mean length of inpatient treatment was 19.4 years. All patients were chronically ill and had failed conventional treatment regimens: they had minimal response to clinical trials of 8 weeks' duration with 3 traditional neuroleptics of different classes in the 2 years prior to study entrance.

Of the 42 patients enrolled in the study, 34 (81%) completed a minimum of 5 weeks of stable dose medication. Five weeks was chosen because it was thought to be an adequate period of time to assess side effects and efficacy, especially given the lengthy titration phase. Side effects were reported in all 42 patients who entered the study, but data analysis for efficacy was performed only on the 34 patients who completed the minimum 5 weeks of treatment. Four subjects were removed from the study prior to the second week of stable dose medication. Two of these subjects were receiving clozapine, 2 chlorpromazine. Reasons for early termination in the clozapine group included agitation and agranulocytosis, whereas sedation and paralytic ileus were the reasons for discontinuation in the chlorpromazine group. The mean daily dose of clozapine for the 21 patients in the study was the maximum protocol dosage of 300 mg. The mean daily dose of chlorpromazine for 11 patients was 600 mg.

Patients taking clozapine and chlorpromazine were compared at baseline and at completion of the study. The pretest and posttest mean scores and standard deviations for the PANSS and the CGI are summarized in Table 1. The results of analyses of variance suggest that clozapine and chlorpromazine are equally effective. Both drugs demonstrated a significant improvement in psychopathology over time as measured by the PANSS total, positive, negative, and global scores and the CGI item 1, severity of disorder (F for time = 30.81, $p < .001$; $F = 13.2$, $p < .001$; $F = 22.40$, $p < .001$; $F = 24.23$, $p < .001$; and $F = 27.31$, $p < .001$, respectively). There were no overall effects of drug type ($F = .01$; $F = .03$; $F = .01$; $F = .20$, NS) or of drug × time interaction ($F = .61$; $F = .07$; $F = 1.03$; $F = .46$; $F = 1.84$, NS).

Table 1. Baseline and Termination Scores for the PANSS and the CGI[a]

	PANSS									
	Total Score		Positive Score		Negative Score		Global Score		CGI	
Treatment Group	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Baseline										
Clozapine	94.42	13.37	21.42	5.45	27.50	6.43	45.50	7.14	5.33	0.92
Chlorpromazine	91.71	14.50	20.44	4.69	27.00	7.40	43.72	8.70	4.84	0.86
Termination										
Clozapine	74.48	17.20	16.24	6.82	22.33	6.33	35.90	8.56	2.62	0.74
Chlorpromazine	77.23	18.16	16.85	5.64	23.08	6.50	37.31	9.60	3.15	1.34

[a]Abbreviations: CGI = Clinical Global Impressions scale, PANSS = Positive and Negative Syndrome Scale.

Table 2. Most Frequent Adverse Reactions

Adverse Reaction	Clozapine	Chlorpromazine	Total N of Patients
Hematologic abnormalities			
↑ White blood cell count	5	4	9
↓ White blood cell count	3	4	7
Sialorrhea	6	8	14
Sedation	3	6	9
Weight gain	5	3	8
Extrapyramidal side effects	4	4	8
Tachycardia	6	2	8
Hypotension	3	4	7
Other			
Weight loss	2	2	4
Slurred speech	1	0	1
Photosensitivity	1	0	1
Ileus	0	1	1

Regarding the comparisons of safety findings between the 2 groups, we found that both drugs had equal percentages of adverse reactions. Moreover, each group had one potentially fatal side effect (Table 2). In addition, 16 of 42 subjects developed hematologic abnormalities: 7 subjects (3 taking clozapine, 4 taking chlorpromazine) had a decreased white blood cell (WBC) count and 9 (5 taking clozapine, 4 taking chlorpromazine) had elevated WBC values. The 3 clozapine subjects (12% of total) had a decrease at 6 weeks after the initiation of the study; the decrease was abrupt rather than gradual. One subject had agranulocytosis, but his condition improved and his WBC counts returned to the baseline value upon discontinuation of the medication. In the chlorpromazine group, 4 (22.2% of total) had a decrease in WBC count at an average of 3 weeks; the drop was gradual and sustained. Two of the 3 subjects taking clozapine, but none taking chlorpromazine, had the medication discontinued owing to this decrease. The mean daily dose of clozapine at the time of the WBC decrease was 300 mg, while the mean daily dose of chlorpromazine was 412 mg. The differential in the chlorpromazine subjects was remarkable in that all 4 subjects had atypical lymphocytes and decreased total lymphocytes. There was no significant change in the red blood cell or platelet values in either group. No fever or seizures occurred in either group.

DISCUSSION

To date, there have been no studies in geriatric schizophrenia comparing the efficacy and side effects of clozapine with those of another neuroleptic. In the younger population, however, studies have shown clozapine to be efficacious in the treatment-resistant schizophrenic population. Traditional neuroleptics, including haloperidol and chlorpromazine, have also been found to be beneficial. We were interested in evaluating which of these 2 medications was more effective in treating the elderly patient with chronic schizophrenia. In addition, the side effect profile was a major concern because the elderly frequently have a lower threshold for tolerance to the side effects of medications normally well tolerated in the younger population.

An important finding in our study was the equality of efficaciousness of the 2 medications. While it is true that the baseline PANSS scores for the clozapine group were higher than those for the chlorpromazine group, the difference was not statistically significant. Both groups improved overall, and the improvement was not limited to either the positive or negative symptom scores.

Another important finding was the approximately equal number of side effects for the 2 groups. Each group had 1 patient with a very serious and potentially fatal side effect: agranulocytosis for the clozapine group and paralytic ileus for the chlorpromazine group. Both patients recovered, and there were no further negative consequences of the medications. In addition, both medications adversely affected the WBC count in a significant percentage of our sample of geriatric patients. Several possible mechanisms for this effect with chlorpromazine have been described in the literature,[10–12] the most prevalent theory being inhibition of DNA synthesis and cell division in the bone marrow in individuals who have a limited capacity for developing a compensating increase in leukopoiesis. On the other hand, clozapine may cause agranulocytosis by either toxic or immunologic mechanisms; the exact pathophysiologic mechanism remains unknown.[13–17]

Both groups also had similar incidences of 2 other side effects: hypotension and sialorrhea. Other side effects noted in patients in both groups were changes in weight, skin, speech, alertness, and heart rate.

One limitation of the study was the small sample size (for efficacy N = 34, for side effects N = 42). Thus, power was also small. For efficacy, even if there were a very large difference between the groups, with means 1

standard deviation apart, the power would only be .78 for a 2-sided test at the .05 significance level. Thus, for efficacy, this study cannot rule out the possibility of a moderate difference between the 2 drugs used.

In conclusion, both clozapine and chlorpromazine were found to be effective treatments for psychosis and behavioral disturbances in our patient population. Both drugs had approximately similar incidences of side effects, and both were found to adversely affect the WBC count in a significant percentage of our sample. On the basis of our findings, we conclude that clinicians should be alerted to the potential for hematologic abnormalities associated with the use of conventional neuroleptics such as chlorpromazine as well as newer agents such as clozapine. However, with careful monitoring and titration of dosage, both clozapine and chlorpromazine were fairly well tolerated in our population of geriatric patients with chronic schizophrenia.

Drug names: benztropine (Cogentin and others), chloral hydrate (Noctec), chlorpromazine (Thorazine and others), clozapine (Clozaril), haloperidol (Haldol and others).

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