Medication Continuation and Compliance: A Comparison of Patients Treated With Clozapine and Haloperidol

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Background: This study compares medication continuation and regimen compliance with the atypical antipsychotic medication clozapine versus the conventional antipsychotic haloperidol.

Method: Data from a 15-site double-blind, randomized clinical trial (N = 423) were used to compare patients with DSM-III-R schizophrenia assigned to clozapine or haloperidol in terms of duration of participation while taking the randomly assigned study drug (continuation) and the proportion of prescribed pills that were taken (compliance). Multiple regression analysis was used to determine the relationship of baseline characteristics and measures of clinical change to continuation for the entire sample and for patients assigned to each medication.

Results: Patients assigned to clozapine continued taking the study drug for a mean of 35.5 weeks as compared with only 27.2 among patients assigned to haloperidol ($F = 4.45$, $df = 1,422$; $p = .0001$). No differences were found between the groups in the proportion of prescribed pills that were returned at any timepoint. Among patients assigned to haloperidol, poorer continuation was associated with being older and greater continuation with receiving public support. Among patients on clozapine treatment, continuation was poorer among African American patients and greater among patients who showed reduced clinical symptoms and akathisia. Continuation with clozapine was greater even after adjusting for these factors.

Conclusion: Continuation with medication is greater with clozapine than haloperidol and is partly explained by greater symptom improvement and reduced side effects. No differences were found in regimen compliance.

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Over the past 10 years, atypical antipsychotic medications such as clozapine, risperidone, and olanzapine have been shown in randomized prospective clinical trials to be significantly more efficacious than conventional antipsychotic medication in the treatment of schizophrenia and to have markedly fewer extrapyramidal side effects (EPS).[1–5] It has been widely speculated that one reason for the greater effectiveness of these medications in ordinary clinical practice is that, owing to their superior side effect profiles, patients are more willing to take them and therefore to adhere to prescribed treatment regimens over sustained periods of time. Medication noncompliance has been shown to be a major reason for relapse in schizophrenia and, as a result, a source of substantial health care cost.[6] Because of its evident importance to clinical outcomes, investigators have been working to understand and improve compliance through various behavioral interventions.[7–10]

No published reports, however, have examined the impact of atypical antipsychotic medications on medication continuation (i.e., the duration of participation or time to drug discontinuation) or regimen compliance (i.e., the proportion of prescribed pills actually taken), nor have any studies sought to determine whether greater continuation or compliance with these medications is attributable to the reduction in symptoms or side effects or other factors.

This study uses data from a previously published 12-month randomized clinical trial[5] of clozapine and halo-

peridol that demonstrated significant advantages of clozapine compared with haloperidol in reducing symptoms and side effects and improving quality of life. Because patients and clinicians were blind to drug assignment, this is an opportune data set in which to (1) compare continuation and regimen compliance among patients assigned to the 2 medications, (2) identify baseline factors and specific dimensions of clinical improvement that are associated with increased medication compliance, and (3) determine whether factors affecting compliance with clozapine differ from those affecting compliance with haloperidol.

METHOD

Data for this study are from a double-blind trial in which patients at 15 Veterans Affairs (VA) medical centers were randomly assigned to clozapine or haloperidol and treated for 12 months.

Entry Criteria

Hospital use criteria. Trial eligibility was limited to treatment-refractory schizophrenics with a history of high inpatient use defined as 30 to 364 days of hospitalization for schizophrenia during the previous year.

Clinical criteria. Patients were also required to meet the following clinical eligibility criteria: (1) DSM-III-R diagnostic criteria for schizophrenia on the Semi-structured Clinical Interview for Diagnosis[11]; (2) refractoriness criteria that included persisting psychotic symptoms despite adequate treatment trials involving 2 different neuroleptic drugs at dosages equivalent to or greater than 1000 mg/day of chlorpromazine for at least 6 weeks, or lower dosage if the patient was unable to tolerate 1000 mg/day of chlorpromazine equivalents; (3) symptom severity criteria that included a total score on the Brief Psychiatric Rating Scale (BPRS)[12] of at least 45, a minimum score on the Clinical Global Impressions-Severity scale[13] of at least 4 (moderately ill), BPRS scores of at least 4 (moderate) on 2 of the following 4 items: conceptual disorganization, suspiciousness, hallucinatory behavior, and unusual thought content; and (4) criteria of serious social dysfunction for the previous 2 years.

After providing written informed consent to participate in the study and completing baseline assessments, patients were randomly assigned to a treatment condition, and treatment was initiated.

Treatment

The protocol required weekly clinic visits after random assignment to double-blind treatment with either clozapine (100–900 mg/day) or haloperidol (5–30 mg/day). Haloperidol-treated patients also received benztropine mesylate (2–10 mg/day) for prophylactic control of EPS, whereas clozapine patients received a matching benztropine placebo. Haloperidol-treated patients participated in the weekly blood counts that are required for clozapine treatment. The required clozapine blood monitoring protocol was followed. Thus, all patients received their weekly prescription of medication only after their blood had been drawn for a white blood cell count. Patients were instructed to return all unused medication each week, and the number of returned pills was documented for use in estimating the proportion of prescribed pills that had not been taken each week.

A broad range of adjunctive psychotherapeutic and rehabilitative treatments were offered to study subjects and were standardized across participating sites with a case management system that used a structured treatment planning module based on a comprehensive menu of locally available services.[14]

Assessment of Medication Compliance

Medication continuation was defined as the number of weeks of participation in double-blind treatment with the randomly assigned study drug. Regimen compliance was measured by 1 minus the proportion of prescribed pills that were returned each week, i.e., 1 minus the number of returned pills divided by the total number that had been prescribed. Medication continuation and compliance were analyzed for 2 groups of patients—the full sample and those patients who continued taking blind medication for at least 6 weeks.

Assessment of Clinical Status

Symptom outcomes were assessed with the structured clinical interview for the Positive and Negative Syndrome Scale (PANSS) for schizophrenia.[15] Social functioning and quality of life were evaluated with the Heinrichs-Carpenter Quality of Life Scale (QLS), a clinician-rated scale.[16] Medication side effects were assessed with the Barnes Akathisia Scale,[17] the Abnormal Involuntary Movement Scale (AIMS) for tardive dyskinesia,[18] and the Simpson-Angus Scale for extrapyramidal syndromes.[19] Assessments were conducted at 6 weeks and at 3, 6, 9, and 12 months after randomization. A weekly checklist documented other adverse reactions.

Analysis

Data analysis proceeded in several steps. First, the groups were compared on baseline measures to determine the success of the randomization procedure. Second, analysis of variance was used to compare patients assigned to clozapine and haloperidol on the 2 measures of compliance. Third, a series of bivariate analyses were used to identify baseline characteristics such as age, race, and duration of illness that were associated with each measure of compliance over the course of the trial.

Fourth, multiple regression analysis was used to determine the relationship of baseline characteristics and measures of clinical change to the measures of medication

continuation. By subtracting baseline from follow-up scores, a series of measures were created that reflect change from baseline in 4 areas: (1) symptoms (PANSS), (2) quality of life (QLS), (3) EPS (Simpson-Angus), and (4) akathisia (Barnes measure). A dichotomous variable representing treatment assignment (clozapine vs. haloperidol) was included in these models to determine whether the relationship of clozapine and compliance persisted even after controlling for other potentially explanatory factors (e.g., changes in symptoms of side effects). Separate models were analyzed to predict early compliance in the entire sample using 6-week change measures as predictors. Then, to evaluate predictors of compliance after the initial exposure to medication, the analysis was repeated for the sample of patients who were still taking the study drug at 6 weeks using 3-month clinical change measures as predictors of subsequent compliance. In each of these analyses, we used change from baseline to the end of the next rating interval as a predictor of continuation during the remainder of the trial. Because the outcome variable is a time-to-event variable, these analyses were repeated using Cox regression analysis.

Finally, we conducted a set of parallel (i.e., separate) regression models on patients assigned to clozapine and haloperidol to identify specific factors affecting medication continuation for patients taking each drug.

RESULTS

Comparison of the randomized groups in the intent-to-treat sample revealed no significant differences on any baseline characteristic.[5] The sample (N = 423) was a mean ± SD of 43.6 ± 8.0 years old, 97.9% male (as expected in a veteran sample), 66.4% white, 29.6% African American, 3.8% Hispanic, and 0.2% other ethnicity. Only 7.1% were married with 57.8% never married, 32.7% separated or divorced, and 2.4% widowed. Mean level of education was 12.4 ± 1.6 years. Only 13.5% had been employed regularly in the past 3 years, and 86.8% received public support payments from either the VA or the Social Security Administration. Almost two thirds (65.6%) had a lifetime history of alcohol abuse, and 25.8% had a lifetime history of cocaine abuse. Mean baseline scores were 91.6 ± 14.7 (range, 30–210) on the PANSS, 39.9 ± 17.0 (range, 0–180) on the QLS, 5.2 ± 4.6 (range, 0–40) on the Simpson-Angus EPS scale, and 3.3 ± 3.4 (range, 0–14) on the Barnes Akathisia Scale. The sample had a mean of 110.0 ± 88.8 days in the hospital during the year before study entry.

Patients participated in the double-blind trial for a mean of 31.2 ± 20.0 weeks out of a maximum of 52, and while taking the double-blind study drug, they returned a mean of 19.5% of their prescribed pills during the first 6 weeks of the trial, 15.1% during the period from 6 weeks to 3 months, and 12.3% from 3 months to 6 months.

Table 1. Multiple Regression Analysis of Predictors of Medication Continuation: Duration of Study Participation

Variable	Full Sample		6-Week Participants	
Mean duration, d	34.2		39.8	
N	375		297	
r^2 Model	0.18		0.15	
Independent Variable	Coefficient	p Value	Coefficient	p Value
Age, y	–0.26	.02	–0.32	.002
African American (1 = African American)	–5.05	.02	–4.75	.02
Hispanic (1 = Hispanic)	11.53	.51	5.46	.72
Public support (1 = receipt of funds)	13.65	.0006	0.90	.86
Lifetime alcoholism (1 = present)	–3.50	.08	–4.42	.04
Lifetime cocaine use (1 = present)	–2.66	.26	–4.70	.01
Education, y	–0.54	.32	–0.67	.23
Change in symptoms[a]	–0.18	.003	–0.05	.41
Change in EPS[a]	0.39	.16	–0.04	.85
Change in akathisia[a]	–0.29	.31	–0.34	.23
Change in quality of life[a]	0.10	.20	0.14	.05
Clozapine	8.32	.0001	3.01	.07

[a]Change from 0 to 6 weeks in first model, change from 0 to 13 weeks in second model. For change in symptoms, extrapyramidal side effects (EPS), and akathisia, a positive coefficient signifies an increase or worsening. For change in quality of life, a positive coefficient signifies an improvement.

Continuation and Compliance

Statistically significant differences were observed between treatment groups in the duration of participation in the trial. Patients assigned to clozapine participated for a mean ± SD of 35.5 ± 19.9 weeks compared with 27.2 ± 20.2 among patients assigned to haloperidol, a significant difference of 8.3 weeks (F = 4.45, df = 1,422; p = .0001). No differences were found between the groups in the proportion of prescribed pills that were returned during any of the 3 time periods.

Predictors of Continuation

Multiple regression analysis of the sample from the beginning of the trial shows that older age and being African American were associated with briefer duration of participation in double-blind treatment, and public support with longer participation (Table 1). The only clinical measure associated with prolonged participation was a greater reduction in symptoms (the negative sign on the coefficient indicates that as symptoms decline, duration of participation increases). There was no association between improvement in side effects from baseline and duration of participation in the trial. Even after adjusting for these factors, clozapine was highly significantly associated with longer participation in the trial (F = 4.43, df = 12,362; p < .0001).

Among those still taking the originally assigned study medication at 6 weeks, older veterans, African American veterans, and those with a history of alcoholism or cocaine use had significantly shorter participation in the

Table 2. Multiple Regression Analysis of Predictors of Medication Continuation

	Haloperidol				Clozapine			
Variable	Full Sample		6-Week Participants		Full Sample		6-Week Participants	
Mean duration, d	29.8		39.8		38.9		42.5	
N	193		131		182		165	
r^2 Model	0.16		0.12		0.20		0.14	
Independent Variable	Coefficient	p Value	Coefficient	p Value	Coefficient	p Value	Coefficient	p Value
Age, y	–0.51	.002	–0.53	.003	–0.04	.81	–0.17	.250
African American (1 = African American)	–2.63	.36	–3.45	.34	–6.55	.03	–5.76	.02
Hispanic (1 = Hispanic)	N/A	N/A	N/A	N/A	11.05	.51	0.97	.94
Public support (1 = receipt of funds)	16.23	.003	9.89	.25	11.02	.06	–4.33	.49
Lifetime alcoholism (1 = present)	–3.95	.13	–3.74	.22	–0.98	.74	–4.19	.11
Lifetime cocaine use (1 = present)	–3.73	.23	–4.18	.23	–4.40	.22	–3.70	.22
Education, y	–1.23	.12	–1.18	.24	0.30	.70	–0.23	.71
Change in symptoms[a]	–0.11	.21	0.07	.45	–0.20	.013	–0.16	.03
Change in EPS[a]	0.33	.43	0.25	.50	0.58	.12	–0.48	.16
Change in akathisia[a]	0.69	.10	–0.48	.29	–1.22	.002	–0.14	.68
Change in quality of life[a]	0.09	.39	0.08	.50	0.15	.17	0.17	.06

[a]Change from 0 to 6 weeks in first model, change from 0 to 13 weeks in second model. For change in symptoms, extrapyramidal side effects (EPS), and akathisia, a positive coefficient signifies an increase or worsening. For change in quality of life, a positive coefficient signifies an improvement.

remainder of the trial. Also, those patients with improved QLS scores had longer participation. No significant relationship was observed with any clinical factors or with assignment to clozapine (see Table 1). Similar results were found using Cox regression analysis.

Stratified analysis of continuation among patients assigned to haloperidol showed that only younger age and receipt of public support payments were associated with extended participation from the beginning of the trial, and only younger age from the 6-week point (Table 2).

Among patients assigned to clozapine, in contrast, neither age nor public support was associated with prolonged participation (see Table 2). In the entire sample of patients assigned to clozapine, being African American was associated with briefer participation, and reduced symptoms of schizophrenia and reduced akathisia were associated with more prolonged participation (the negative signs on the coefficients indicate that as symptoms and signs of akathisia decline, duration of participation increases). Among patients assigned to clozapine who were still participating in the trial at 6 weeks, being African American and the degree of symptom increase remained significantly associated with briefer participation.

The fact that African American patients who were treated with clozapine were less compliant than others may be explained by the fact that they were more likely to experience more weight gain than whites. At 6 weeks, 25% of African Americans versus 15% of whites reported significant weight gain ($\chi^2 = 2.32$, df = 1, p = .13), and at 3 months, 38% of African Americans reported weight gain versus 18% of whites ($\chi^2 = 6.32$, df = 1, p = .01). When weight gain is entered as a covariate into the multiple regression models, African Americans are no longer significantly more likely to stop treatment. It should be noted that in bivariate analyses, weight gain was associated with assignment to clozapine treatment (r = 0.13, p < .02 at 6 weeks; r = 0.12, p < .04 at 3 months) as well as with symptom reduction (r = –0.26, p < .0001 at 6 weeks; r = –0.22, p < .0001 at 3 months) and longer continuation of treatment (r = 0.17, p < .001 at 6 weeks; but r = 0.06, p = .28 at 3 months). Thus, weight gain explains the briefer duration of medication continuation among African Americans, over and above these other effects.

DISCUSSION

This study confirmed clinical impressions that patients treated with clozapine are more tolerant of prescribed medication than those treated with haloperidol since they remained on treatment with double-blind randomly assigned medication for a longer period of time. However, on a measure of regimen compliance (the proportion of prescribed pills that were returned), no differences were found between groups, possibly because study physicians saw these patients frequently and could therefore minimize side effects by titrating the dosages of prescribed medications to tolerable limits, at least in the short run. A major strength of this study is that, because of its double-blind design, neither patients nor their clinicians knew which medication patients were taking, although well-known differences in the side effect profiles of the 2 medications make the blind less than perfect.

The strongest predictors of continuation in the entire sample, other than taking clozapine, were younger age, race, receipt of public support payments, and symptomatic improvement. Unexpectedly, reduction in side effects was not associated with greater continuation over and above the impact of clozapine. This finding was not due to low baseline side effect levels, since scores on the Simpson-Angus Scale for EPS were higher than those re-

ported in other studies[1] and were high enough to allow highly significant differences between the clozapine and haloperidol groups by 6 weeks.[5]

Among patients who stayed in the trial for at least 6 weeks, lifetime alcoholism and cocaine use were also important predictors of reduced participation.

Among patients treated with clozapine, however, those with greater reductions in symptoms of both schizophrenia and akathisia stayed on treatment with their medication longer, suggesting that both the greater efficacy and lower side effects associated with clozapine at least partially explain its greater tolerability. Akathisia has been reported by others as the side effect most consistently associated with noncompliance in patients with schizophrenia.[20] The fact that African American patients who were treated with clozapine were less tolerant than others may be explained by the fact that they were more likely to experience weight gain.

Younger age and receipt of public support payments were associated with increased medication continuation among patients treated with haloperidol, presumably because older patients are less tolerant of EPS associated with conventional antipsychotic medications and perhaps because patients receiving public support are generally more accepting of authority and therefore more willing to tolerate the discomfort associated with prescribed medication.

Several limitations of this study deserve comment. First, the proportion of returned pills is not an ideal measure of compliance since it depends on conscientious return of unused pills. However, this was probably less of a problem in this study than in others because patients were seen weekly and medication usage was carefully monitored because of the risk of agranulocytosis with clozapine. Further studies comparing adherence with atypical and conventional antipsychotic medications, and its clinical consequences, should be undertaken using the superior measurement methods available through microelectronic monitoring with computerized bottle caps that record the date and time of each bottle opening.[8,10]

Second, duration of adherence to double-blind study medication as presented here may also be an imperfect measure of medication continuation, since some patients may have stopped medication on the recommendation of their clinicians. Unfortunately, data on clinician pharmacotherapy recommendations are not available. As a result, we cannot differentiate whether the discontinuation was specifically suggested by the clinician, initiated unilaterally by the patient, or was a decision made by both the clinician and the patient. Although this study cannot address the specific issue of patient-initiated versus clinician-initiated drug discontinuation, our findings do identify behavioral predictors of continuation regardless of who made the decision.

CONCLUSION

Continuation with medication is greater with clozapine than haloperidol and is partly explained by greater symptom improvement and reduced side effects. No differences were found in regimen compliance (i.e., the percentage of pills taken) between the clozapine and haloperidol groups.

Drug names: benztropine (Cogentin and others), chlorpromazine (Thorazine and others), clozapine (Clozaril and others), haloperidol (Haldol and others), olanzapine (Zyprexa), risperidone (Risperdal).

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