Long-Term Maintenance Therapy With Quetiapine Versus Haloperidol Decanoate in Patients With Schizophrenia or Schizoaffective Disorder

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Objective: To compare the long-term efficacy and tolerability of oral quetiapine with those of intramuscular haloperidol.

Method: Patients with DSM-IV–diagnosed schizophrenia or schizoaffective disorder requiring long-term antipsychotic treatment were randomly assigned to open-label oral quetiapine or intramuscular haloperidol decanoate for 48 weeks. Clinicians were instructed to target dosing at 500 mg/day of quetiapine or 200 mg of haloperidol decanoate every 4 weeks. The Positive and Negative Syndrome Scale was used to assess efficacy; the Simpson-Angus Scale and the Barnes Akathisia Scale were used to assess safety and tolerability. For statistical analyses, a general linear mixed-model repeated-measures analysis of covariance was used, with change scores for dependent variables computed with the baseline score as covariate. Data were collected from 1998 to 2001.

Results: Thirty-five patients were enrolled, but 6 did not participate after being informed of their treatment assignment; 4 of the 6 withdrawals were assigned to haloperidol decanoate. Mean doses at week 48 were 493 mg/day of quetiapine (N = 16) and 170 mg/28 days of haloperidol decanoate (N = 9). Survival analysis showed no between-group differences in estimates of the number of patients remaining exacerbation-free over time. Both drugs were efficacious, but quetiapine was significantly better than haloperidol decanoate in controlling negative symptoms ($p < .05$). The incidence of extrapyramidal symptoms was low in both groups; patients receiving quetiapine showed significantly greater improvement in rigidity and akathisia ($p < .05$).

Conclusion: Oral quetiapine was as efficacious as intramuscular haloperidol in preventing symptom exacerbation over 48 weeks in patients with schizophrenia or schizoaffective disorder, with fewer extrapyramidal symptoms, especially rigidity and akathisia. Quetiapine was more efficacious than haloperidol decanoate in treating negative symptoms.

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Because schizophrenia and schizoaffective disorder are chronic illnesses, long-term treatment typically is required to keep symptoms under control and to prevent relapse. Antipsychotic drugs are effective in preventing relapse in patients with schizophrenia.[1] Yet when patients with any chronic illness are required to take medication over the long-term, adherence can be a problem, and this is particularly so for patients with schizophrenia.[2]

When adherence is an issue in patients with psychoses, one option for maintenance treatment is a long-acting depot formulation of a conventional antipsychotic, such as haloperidol decanoate, fluphenazine decanoate, or zuclopenthixol decanoate. Depot antipsychotics, which are administered as intramuscular injections every 2 to 4 weeks, may be useful in preventing relapse in patients who are nonadherent with oral antipsychotics.[2,3] Depot conventional antipsychotics, however, can cause the same adverse events, including extrapyramidal symptoms (EPS) and tardive dyskinesia, as their oral counterparts.[4]

Atypical antipsychotics, or second-generation antipsychotics, are also an option for maintenance therapy. Most atypical antipsychotics are available only as oral formulations or as short-acting intramuscular injections; at present, risperidone is the only second-generation antipsychotic available in a long-acting injectable formulation.

An advantage of the atypical agents over conventional antipsychotics is their generally lower risk of causing EPS and tardive dyskinesia.[5] Some patients may prefer an atypical antipsychotic for maintenance treatment because of this lower risk of movement disorders.

Whether patients are given a conventional or an atypical antipsychotic, the ultimate goal of maintenance treatment is relapse prevention. In general, in studies of schizophrenia or schizoaffective disorder of 1 year or longer, relapse was less common, and time to discontinuation was longer with oral atypical drugs compared with oral conventional agents.[6–11]

Oral quetiapine, an atypical antipsychotic, was selected as the comparator drug in this trial because it has proved effective over the long-term for treating schizophrenia. In an open-label extension phase of 3 double-blind randomized trials, quetiapine effectively controlled psychotic symptoms for up to 3 years.[12] In addition, quetiapine has a low risk of EPS and appears to be the only atypical antipsychotic without a dose-related increase in EPS.[13] The goal of this study was to compare the safety and efficacy, including exacerbation-free duration, of oral quetiapine with that of intramuscular haloperidol during long-term treatment.

METHOD

Patients with DSM-IV–diagnosed schizophrenia or schizoaffective disorder treated at clinics at the Stanford University School of Medicine in California, Stanford, the David Geffen School of Medicine, University of California, Los Angeles, or the Veterans Affairs Greater Los Angeles Healthcare System, Los Angeles, Calif., were eligible for this 48-week study. There were no specific inclusion or exclusion criteria. Patients requiring long-term therapy were randomly assigned to open-label treatment with oral quetiapine or intramuscular haloperidol decanoate. Clinicians were instructed to target dosing at 500 mg/day of quetiapine or 200 mg of haloperidol decanoate every 4 weeks. A 500-mg dose of quetiapine was considered reasonable for maintenance, but there was no upper dose limit; clinicians could increase the dose of quetiapine at the first sign of symptom exacerbation. Anticholinergic medications and benzodiazepines were allowed, but antipsychotics other than quetiapine were not permitted. Data were collected from 1998 to 2001.

The Positive and Negative Syndrome Scale (PANSS)[14] was used to assess efficacy. The severity of EPS was determined using the Simpson-Angus Scale[15] and the Barnes Akathisia Scale.[16] Data were also collected on the incidence of sedation. No other data on adverse events were collected. Assessments were made at baseline and at weeks 4, 8, 12, 24, 36, and 48. All ratings were performed by clinicians who were not aware of the patient's treatment assignment. Rater reliability was established using videotapes, and only raters who met preestablished reliability criteria were included.

All patients provided informed consent before participating in the study. Institutional Review Board approval was obtained from Stanford University, the University of California, Los Angeles, and the Veterans Affairs Greater Los Angeles Healthcare System.

Statistical Analysis

Data were analyzed through week 48 using a general linear mixed-model repeated-measures analysis of covariance design. Dependent variables were change scores computed from baseline, with the baseline score used as a covariate. The fixed effects were drug (quetiapine, haloperidol decanoate) × time (weeks 4, 8, 12, 24, 36, 48) in a crossed 2 × 5 factorial design. A main effect for site (Stanford, Calif., or Los Angeles, Calif.) was included to control for any overall differences in outcomes across treatments, but interactions by site were not included in the models because of the small sample sizes and the lack of basis for either expecting or interpreting such effects.

Maximum likelihood estimation was used, specifying compound symmetry for the covariance matrix of the repeated measures and using the asymptotically consistent estimator ("sandwich" estimator) to compute the estimated variance-covariance matrix of the fixed-effects parameters.

RESULTS

Thirty-five patients were enrolled in the study. Of these, 6 patients declined to participate after learning of their treatment assignment; 4 of the 6 refusals were for assignment to haloperidol decanoate. Of the remaining 29 patients, 19 were randomly assigned to the quetiapine group, and 10 were randomly assigned to the haloperidol decanoate group. Three patients taking quetiapine and 1 patient taking haloperidol decanoate dropped out during the cross-titration to study drug. The demographic data are shown in Table 1. Quetiapine dosages (SD) were 463 (158) mg/day and 493 (192) mg/day at weeks 12 and 48, respectively, while those for haloperidol decanoate were 157 (45) mg/28 days and 170 (45) mg/28 days.

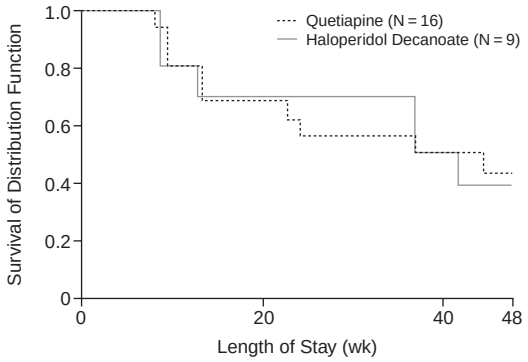
During this 48-week study, the number of participants in each treatment group decreased. Some patients withdrew consent, and others discontinued because of symptom exacerbation (the causes of symptom exacerbation were not documented). During the first 4 weeks of the study, 3 patients dropped out. Thus, at the first postbaseline assessment (week 4), data were collected from 22 exacerbation-free patients (15 in the quetiapine group, 7 in the haloperidol decanoate group). By the final assessment (week 48), only 12 patients (7 in the quetiapine group, 5 in the haloperidol decanoate group) remained in the study.

Table 1. Demographic Data at Study Entry for Schizophrenia and Schizoaffective Disorder Patients Randomly Assigned to Quetiapine or Haloperidol Decanoate[a]

Variable	Quetiapine (N = 16)	Haloperidol Decanoate (N = 9)
Age, mean (SD), y	41.3 (13.0)	44.0 (12.8)
Age at onset, mean (SD), y	26.5 (9.0)	24.5 (10.7)
Mean years of education (SD)	13.0 (1.6)	12.8 (1.8)
Male, N (%)	13 (81)	7 (78)
Non-Hispanic white, N (%)	5 (31)	4 (44)
Single, N (%)	10 (63)	8 (89)

[a]Twenty-five patients, N = 19 for quetiapine and N = 10 for haloperidol decanoate, were randomly assigned. Three patients taking quetiapine and 1 patient taking haloperidol decanoate were dropped during the cross-titration when they could not be successfully managed on the study drug.

Figure 1. Survival Curves for Schizophrenia and Schizoaffective Disorder Patients Treated With Quetiapine or Haloperidol Decanoate[a]



[a]Log-rank test: $\chi^2 = 0.08$, df = 1, p = .77.

In a survival analysis, no between-group differences were found in estimates of the number of patients remaining exacerbation-free over time (Figure 1).

Both treatment groups showed improvement in PANSS total scores and positive, negative, and general psychopathology subscale scores (Table 2); throughout the study, improvement in negative symptoms was significantly greater with quetiapine treatment compared with haloperidol decanoate treatment ($p < .05$) (Figure 2). Although PANSS negative symptom subscale scores improved to a greater extent in the quetiapine group, PANSS general psychopathology scores improved to a greater extent in the haloperidol decanoate group at week 36. There was essentially no difference in total PANSS scores between the 2 groups at any timepoint.

Although the occurrence of EPS was low in both treatment groups, changes from baseline to week 48 in rigidity and akathisia showed a significant difference in favor of quetiapine ($p < .05$). No new cases of tardive dyskinesia were reported during the study. Antiparkinsonian agents were rarely needed, and there was no difference between groups in use of these agents. There also was no difference in the incidence of sedation between groups.

Table 2. Mean (SD) Change From Baseline as Measured by the PANSS Total Score and Positive, Negative, and General Psychopathology Subscale Scores[a]

Week No.	Quetiapine (N = 15)	Haloperidol Decanoate (N = 7)
PANSS Total		
4	–9.5 (2.9)	–8.9 (3.2)
8	–6.3 (2.8)	–6.6 (6.2)
12	–2.0 (3.7)	–5.1 (3.2)
24	–2.7 (3.3)	–4.2 (4.5)
36	–4.4 (2.6)	–7.2 (3.2)
48	–2.0 (3.6)	0.6 (4.3)
PANSS Positive		
4	–2.0 (1.1)	–3.3 (1.6)
8	–1.2 (1.5)	–2.1 (2.9)
12	0.8 (1.4)	–3.0 (1.5)
24	0.3 (1.1)	–0.5 (2.7)
36	0.2 (1.1)	–0.3 (1.7)
48	1.0 (1.2)	1.5 (2.1)
PANSS Negative*		
4	–3.9 (0.6)	–0.2 (2.2)
8	–2.6 (0.9)	–1.6 (1.7)
12	–1.9 (1.3)	1.3 (1.2)
24	–3.6 (1.3)	–1.5 (1.5)
36	–2.9 (1.1)	–0.9 (1.2)
48	–3.2 (1.6)	–0.5 (0.7)
PANSS General		
4	–3.6 (1.6)	–5.4 (1.4)
8	–2.7 (1.1)	–3.2 (2.4)
12	–0.9 (1.7)	–3.4 (1.6)
24	0.5 (2.2)	–2.2 (1.6)
36	–1.7 (2.2)	–6.0 (1.2)
48	0.1 (1.9)	–0.4 (2.6)

[a]Post-randomization data were available for 22 of the 25 patients.
*$p < .05$, quetiapine vs. haloperidol decanoate.
Abbreviation: PANSS = Positive and Negative Syndrome Scale.

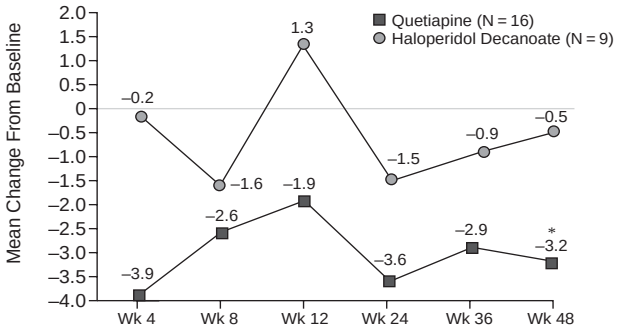
Although EPS and negative symptoms both improved to a greater extent in patients treated with quetiapine compared with those given haloperidol decanoate, we did not find a significant relationship between change in EPS and negative symptoms in either treatment group or in the entire patient population.

DISCUSSION

In this 48-week study, no significant differences were seen between oral quetiapine and intramuscular haloperidol in the rate of patients remaining exacerbation-free over time. Both quetiapine and haloperidol decanoate were efficacious in controlling psychotic symptoms, with quetiapine significantly more efficacious than haloperidol decanoate in alleviating negative symptoms. The incidence of EPS was low in both groups, but patients treated with quetiapine had significantly less rigidity and akathisia than did those given haloperidol decanoate. It is unclear whether the improvement in negative symptoms seen in the quetiapine group resulted from a direct effect of the medication or an indirect effect from the improvement in akathisia.

A search of recent literature revealed no other studies comparing the safety and efficacy of oral atypical antipsychotics with depot conventional antipsychotics for long-

Figure 2. Mean Change From Baseline on PANSS Negative Symptom Subscale Scores



*p < .05.
Abbreviation: PANSS = Positive and Negative Syndrome Scale.

term treatment. Although they did not compare safety and efficacy, in 2 chart review studies, Conley et al.[17,18] compared rehospitalization rates of patients discharged on oral atypical antipsychotics with those of patients given depot conventional antipsychotics. In the first publication, Conley et al.[17] reported rehospitalization rates at 1 year of 13% for patients given clozapine and 17% for those given risperidone; rates at 2 years were 13% and 34%, respectively. The authors compared these rehospitalization rates with those reported in the literature for fluphenazine decanoate (19%–31% of patients rehospitalized within 2 years) and concluded that the rate of rehospitalization is similar for oral atypical and depot conventional antipsychotics. In a more recent publication, Conley et al.[18] confirmed that rehospitalization rates for oral atypical antipsychotics were comparable to or lower than those of depot conventional agents.

The results presented indicate that use of an oral atypical antipsychotic may provide a well-tolerated and effective alternative to depot injections for maintenance therapy in patients with schizophrenia or schizoaffective disorder. Limitations of these findings are the small number of patients studied and the high rate of study dropouts. However, the dropout rate is common in studies of this type and only slightly higher than would have been predicted.

Oral antipsychotic administration may be preferred to intramuscular injection by some patients; in our study, a greater number of patients refused to participate after being assigned to treatment with haloperidol decanoate. Reasons for refusal included being randomly assigned to haloperidol and a dislike of receiving medication by injection. In addition, patients may be concerned about EPS and tardive dyskinesia. Quetiapine has a low risk of EPS across the dose range,[19] but haloperidol decanoate is as likely as oral haloperidol to cause movement disorders, including tardive dyskinesia.[4]

With chronic disorders requiring long-term treatment, adherence is key to improving outcomes. With depot drugs, adherence is guaranteed, provided patients return to the clinic for injections. It is unclear whether oral atypical antipsychotics improve patient adherence compared with oral conventional drugs.

Based on the findings in this 48-week, open-label, randomized trial, quetiapine is a reasonable option for maintenance therapy in patients with schizophrenia or schizoaffective disorder, especially for those who prefer oral administration to depot injection.

Drug names: fluphenazine (Prolixin and others), haloperidol (Haldol and others), quetiapine (Seroquel), risperidone (Risperdal).

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