A Single-Blind, Randomized Trial Comparing Quetiapine and Haloperidol in the Treatment of Tardive Dyskinesia

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Background: While the atypical antipsychotics should ultimately reduce the prevalence of tardive dyskinesia, it is likely to remain a significant clinical problem for a long time to come. No strategy has clearly emerged as the treatment of choice for tardive dyskinesia. Atypical antipsychotics have reduced propensities for producing acute extrapyramidal symptoms (EPS) and possibly tardive dyskinesia and may be effective in treating patients with established tardive dyskinesia.

Method: This 12-month, randomized, investigator-blinded study compared the efficacy of quetiapine (N = 22) and haloperidol (N = 23) in treating patients with DSM-IV schizophrenia or schizoaffective disorder and established tardive dyskinesia. Dyskinesia was assessed using the Extrapyramidal Symptom Rating Scale (ESRS) dyskinesia subscale scores and the Clinical Global Impression (CGI) dyskinesia scores. Other EPS, weight, serum prolactin level, and glycosylated hemoglobin level were also assessed. Subjects were enrolled in the study between April 2000 and March 2002.

Results: Mean endpoint doses were 400 mg/day of quetiapine and 8.5 mg/day of haloperidol. Compared with the haloperidol group, the quetiapine group showed significantly greater improvements in ESRS dyskinesia (6 and 9 months [$p \leq .01$]) and CGI dyskinesia (from 6 months onward [$p < .05$] and with repeated-measures analysis [$p = .002$]). Response rate (≥ 50% symptom reduction) was greater with quetiapine than haloperidol (64% [9/14] and 37% [6/16] at 6 months; 55% [6/11] and 28% [4/14] at 12 months). Other EPS decreased significantly with quetiapine at 3 ($p = .01$), 6 ($p = .01$), and 9 ($p = .002$) months. Serum prolactin levels decreased with quetiapine but increased with haloperidol, differing significantly between the groups at endpoint ($p = .005$). No significant changes in weight or glucose metabolism were recorded in either group.

Conclusion: Quetiapine effectively reduces the severity of tardive dyskinesia and is well tolerated in patients with established tardive dyskinesia.

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While the new generation of atypical antipsychotics may ultimately reduce its prevalence, tardive dyskinesia is likely to remain a significant clinical problem for a long time to come. Tardive dyskinesia is a common complication of conventional antipsychotic treatment, and worldwide clinicians continue to use these agents extensively for the treatment of psychosis. Five percent of patients on treatment with conventional antipsychotics develop tardive dyskinesia per year for the first 8 years, with an average reported prevalence rate of approximately 20% depending on the patient populations studied.[1] Even the use of very low doses of conventional antipsychotics does not protect against the development of tardive dyskinesia.[2] The condition is underrecognized in clinical settings.[3] Although in many cases the disorder is mild and nondistressing, tardive dyskinesia symptoms contribute to social and vocational impairment, as well as to the further stigmatization of psychotic illness. Some patients develop more severe symptoms, which are extremely distressing and disabling and may even be life-threatening.[4]

Treatment of tardive dyskinesia is problematic, and no strategy has emerged that is clearly the treatment of choice.[5] Although antipsychotic drug withdrawal is a course of action that needs to be considered, this may result in an exacerbation of the tardive dyskinesia symptoms in the short term,[6,7] as well as an increased risk of psychotic relapse.[5] There are no controlled trials assessing the effect of dose reduction or intermittent dosing strategies, such as drug holidays.[8] Paradoxically, ongoing treat-

ment with a conventional antipsychotic may suppress and even improve symptoms,[9] particularly in the short term.[10] With the exception of clozapine,[4,11,12] and possibly branched-chain amino acids,[13] little evidence exists to indicate efficacy for any treatment modality for tardive dyskinesia. There is no good evidence to support the use of benzodiazepines,[14] cholinergic agents,[15] vitamin E,[16] melatonin,[17] γ-aminobutyric acid,[16] calcium channel blockers,[18] or various miscellaneous treatments such as endorphins, essential fatty acids, ganglioside, insulin, lithium, naloxone, estrogen, cyproheptadine, phenylalanine, piracetam, stepholidine, tryptophan, and electroconvulsive therapy.[19]

While earlier clozapine studies suggested modest efficacy after extended periods of treatment,[4,11] a more recent study[12] indicated efficacy after a relatively brief period of treatment (5 to 6 weeks) and at a relatively low dose. However, the moderate improvements in tardive dyskinesia need to be weighed against the higher reported morbidity and poorer tolerability of clozapine.[11] There are indications that the newer atypical antipsychotic agents, with a reduced propensity to produce acute extrapyramidal symptoms (EPS), are also less likely to cause tardive dyskinesia. This raises the possibility that they may also have an antidyskinetic effect in patients with established tardive dyskinesia. However, while a reduction in dyskinesia scores has been reported in patients with chronic schizophrenia treated with risperidone compared with placebo,[20] efficacy has yet to be demonstrated in samples of patients with tardive dyskinesia.[5] Quetiapine is a novel antipsychotic that, like clozapine, has a reported incidence of acute EPS across the dose range that is no different from that of placebo.[21] Quetiapine appears to be associated with a low risk of tardive dyskinesia in adult[22] and elderly[23] patients. Its low striatal D_2 receptor binding profile,[24] rapid release from D_2 receptors,[25] possible neuroprotective action,[26] and lack of antimuscarinic activity (reported to exacerbate tardive dyskinesia)[27] theoretically make it a particularly good candidate for the treatment of tardive dyskinesia.

The aim of this study was to evaluate the efficacy of quetiapine compared with haloperidol in treating schizophrenic patients with established tardive dyskinesia in a controlled design over a 12-month period. Previous tardive dyskinesia treatment trials have often been limited by very small samples, brief durations, and lack of a blinding procedure. The present study was designed with these potential pitfalls in mind.

METHOD

Patients

Inpatients and outpatients from Stikland and Tygerberg Academic Hospitals, as well as surrounding community clinics in greater Cape Town, South Africa, were screened for the presence of tardive dyskinesia. Men and women aged 18 to 65 years were considered for inclusion if they met DSM-IV criteria and Schooler and Kane criteria[28] for the diagnosis of tardive dyskinesia. The latter criteria comprise (1) a history of at least 3 months' cumulative antipsychotic exposure; (2) the presence of at least moderate abnormal, involuntary movements in 1 or more body areas or at least mild abnormal, involuntary movements in 2 or more body areas; and (3) an absence of other conditions that might produce abnormal, involuntary movements. Additionally, patients were required to have a DSM-IV diagnosis of schizophrenia or schizoaffective disorder. Exclusion criteria were neurologic disease, any general medical condition that may cause movement disorders, psychiatric disorder not stabilized, and current clozapine treatment. The study protocol and patient information and consent procedures were approved by the University of Stellenbosch Ethics Committee, and all subjects provided written informed consent to participate. The study complied with International Conference on Harmonization Guidelines for Good Clinical Practice.[29]

Study Design

This study was an investigator-blinded, parallel-group comparison of flexible doses of quetiapine and haloperidol in patients with tardive dyskinesia. After an initial screening visit, subjects were tapered from all psychotropic medication over a 2-week period (although a shorter period was allowed if there was concern regarding the clinical status of the patient during this period). Subjects were then randomly assigned to receive either quetiapine or haloperidol for a 50-week treatment period. The dose of medication was titrated over 7 days to the starting dose (haloperidol: 5 mg/day for 4 days, 10 mg/day for 3 days; quetiapine: 100 mg/day for 2 days, 200 mg/day for 2 days, 300 mg/day for 2 days, 400 mg/day for 1 day). At the end of the titration period, all patients were receiving either quetiapine 400 mg/day or haloperidol 10 mg/day. Thereafter, flexible dose adjustment was allowed at the discretion of the investigator, according to the status of psychiatric and motor symptoms, up to maximum doses of haloperidol 20 mg/day and quetiapine 800 mg/day. Haloperidol dose was adjusted in 2.5-mg increments, and quetiapine dose was adjusted in 100-mg increments. Medication compliance was assessed by pill counts at each visit.

Concomitant medications allowed were benzodiazepines for agitation or insomnia and anticholinergic agents in the event of treatment-emergent or worsening EPS. Medications not allowed were other antipsychotics or other medication known to improve or exacerbate movement disorders.

Assessments were conducted at 2-week intervals for the first 6 weeks and 4-week intervals thereafter until the completion of the trial (50 weeks of treatment). Patients were assessed by means of the following scales: Extra-

pyramidal Symptom Rating Scale (ESRS),[30] Clinical Global Impression (CGI) for dyskinesia (from item 58 of the ESRS), and Positive and Negative Syndrome Scale (PANSS).[31] The investigators were experienced psychiatrists who participated in training sessions. The interrater reliability testing concordance coefficients were above 0.8 for the ESRS and PANSS. Blood samples for serum prolactin and glycosylated hemoglobin (HbA_{1c}) were collected at screening and every 3 months. Subjects were weighed at screening and every 3 months.

Primary Analysis

The primary outcome of interest was the change in dyskinesia scores over time. Severity of dyskinesia was assessed by the ESRS dyskinesia subscale scores (items 49–55) and the CGI dyskinesia scores. Treatment groups were compared at 3, 6, 9, and 12 months. The percentage change in scores from baseline to endpoints at 6 and 12 months was calculated. The percentage of responders was also calculated at 6 and 12 months (response was defined as ≥ 50% reduction in ESRS dyskinesia subscale and CGI dyskinesia scores).

Secondary Analysis

The effect of the treatments on psychotic symptoms was assessed by means of the PANSS. Other EPS (parkinsonism, including an item for akathisia, and dystonia) were assessed by means of the ESRS total score minus the ESRS dyskinesia subscale score. Mean group values for weight, body mass index (BMI), serum prolactin and glycosylated hemoglobin were compared at 3-month intervals.

Statistical Analyses

The sample size was not based on formal statistical criteria. We initially conducted an observed cases (OC) analysis for between-group comparisons. To assess the treatment effects over time and address the problem of missing values due to subject withdrawals, we performed 2 analyses on the intent-to-treat population. We employed a repeated-measures mixed-effects modeling approach for the primary efficacy measures (change in dyskinesia scores) and a last-observation-carried-forward approach for the secondary measures.[32] For the repeated-measures mixed-effects model, plots of dyskinesia scores versus time indicated some dependence between the 2 variables, and that this could adequately be represented by a straight line. The model we fitted assigned a slope and an intercept to every subject; they are, therefore, the random effects. The variation between times within subjects was modeled via an "unstructured" option. The Student t test was used to compare the treatment groups with respect to continuous variables. Significance tests were performed at a 2-sided alpha level of .05. Results are expressed as mean ± SD.

Table 1. Baseline Demographic and Clinical Details of Patients Receiving Quetiapine or Haloperidol[a]

Variable	Quetiapine (N = 22)	Haloperidol (N = 23)
Male:female, N	14:8	15:8
Age, y	49.2 ± 14.5	50.1 ± 8.6
ESRS dyskinesia score	10.8 ± 5.0	13.8 ± 5.7
CGI dyskinesia score	4.0 ± 0.9	4.0 ± 0.9
ESRS total score	35.0 ± 12.8	37.2 ± 15.8
Duration of psychosis, y	15.9 ± 11.7	17.4 ± 10.6
Antipsychotic dose prior to randomization, chlorpromazine equivalents	393.6 ± 420.7	234.5 ± 142.3

[a]Values shown as mean ± SD unless otherwise noted.
Abbreviations: CGI = Clinical Global Impression, ESRS = Extrapyramidal Symptom Rating Scale.

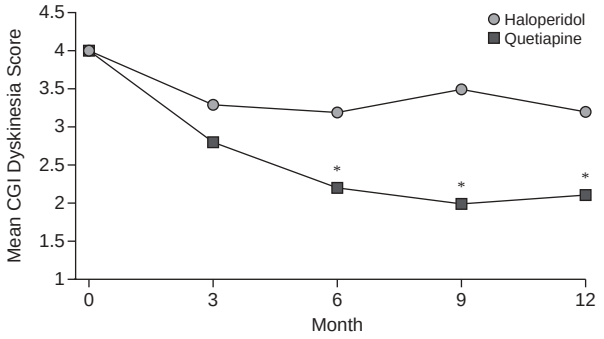
RESULTS

Forty-seven subjects entered the study between April 5, 2000, and March 13, 2002. Two were excluded (1 withdrew before reaching the target treatment dose, and 1 had unrelated medical illness). Therefore, the analysis was conducted on 22 subjects in the quetiapine group and 23 in the haloperidol group. Baseline demographic and clinical details were similar for the 2 treatment groups (Table 1). Ten quetiapine-treated subjects failed to complete the trial, for the following reasons: worsening of psychosis (N = 7), noncompliance (N = 1), withdrawal of consent (N = 1), and pregnancy (N = 1). In the haloperidol group, 8 subjects did not complete the trial, due to worsening of psychosis (N = 4); noncompliance (N = 1); withdrawal of consent (N = 1); severe, persistent dystonia (N = 1); and disallowed concomitant treatment (N = 1). For the OC analysis, the sample sizes for quetiapine and haloperidol were, respectively, 19 and 21 at 3 months, 15 and 16 at 6 months, 13 and 16 at 9 months, and 12 and 15 at 12 months. The mean ± SD endpoint doses were 400 ± 147.7 mg/day for quetiapine and 8.5 ± 5.6 mg/day for haloperidol.

Effect of Treatment on Tardive Dyskinesia

For both treatment groups, there was a significant reduction in ESRS dyskinesia subscale scores from baseline to endpoint ($p < .0001$). For the OC analysis, quetiapine-treated patients showed significantly greater improvement than haloperidol-treated subjects at 6 ($p = .01$) and 9 ($p = .004$) months, but not at 12 months ($p = .1$). For the CGI dyskinesia scores, the quetiapine patients had significantly better scores than those treated with haloperidol at 6 ($p = .03$), 9 ($p = .001$), and 12 months ($p = .03$) (Figure 1). In the repeated-measures, mixed-effects model analysis, both treatments produced significant dyskinesia reductions as reflected by the baseline-to-endpoint total change scores. There were statistically significant differences between treatments in the rates of change in the CGI dyskinesia scores (but not the ESRS dyskinesia sub-

Figure 1. CGI Dyskinesia Scores Over 12 Months for Patients Receiving Quetiapine or Haloperidol



*p < .05.
Abbreviation: CGI = Clinical Global Impression.

scale scores). The model demonstrated that CGI dyskinesia scores declined significantly more in subjects taking quetiapine than in those taking haloperidol ($F = 10.52$, $df = 1,43$; $p = .002$). The response rates (≥ 50% CGI dyskinesia score reduction) for quetiapine and haloperidol, respectively, were 64% (9/14) and 37% (6/16) at 6 months and 55% (6/11) and 28% (4/14) at 12 months.

Effect of Treatment on Psychosis

Baseline PANSS scores were low in each treatment group, as patients were required to be clinically stable to be eligible for the study. There were no differences at any stage between the 2 treatment groups for the PANSS total scores or for the PANSS positive, negative, or general psychopathology subscale scores (Table 2).

Tolerability

Extrapyramidal symptoms. The quetiapine-treated subjects showed a significantly greater reduction of EPS other than dyskinesia at 3, 6, and 9 months ($p = .01$, $p = .01$, and $p = .002$, respectively), but not at 12 months ($p = .3$). Fourteen subjects (61%) in the haloperidol group required ongoing or newly prescribed anticholinergic medication compared with 6 subjects (27%) in the quetiapine group.

Weight and glucose metabolism. The mean body weights did not change significantly throughout the study and did not differ significantly between groups (Table 3). Glycemic control as evaluated by HbA_{1c} level also did not change throughout the study for the quetiapine-treated (baseline = 6.4 ± 1.1%; endpoint = 6.1 ± 2.4%) or haloperidol-treated (baseline = 7.0 ± 2.4%; endpoint = 5.5 ± 1.2%) patients, and there were no between-group differences.

Serum prolactin level. For the haloperidol-treated patients, the mean ± SD serum prolactin levels increased from 15.2 ± 9.2 ng/mL at baseline to 25.5 ± 14.9 ng/mL at endpoint, while for the quetiapine group, they decreased from 25.4 ± 23.3 ng/mL at baseline to 9.1 ± 10.2 ng/mL at endpoint. Endpoint values differed significantly between the groups ($p = .005$).

DISCUSSION

The results of this study confirm previous case reports[33–35] suggesting that quetiapine is an effective treatment for tardive dyskinesia. While both treatments were associated with improvement in dyskinesia, the quetiapine-treated patients did significantly better. The beneficial effect of quetiapine was substantial and sustained, as exemplified by the finding that 55% of the subjects achieved ≥ 50% reduction in dyskinesia at the end of the trial, with their mean CGI dyskinesia scores declining from 4 (moderate) at baseline to 2 (borderline) at endpoint.

Our findings confirm that, paradoxically, antipsychotics (including conventional antipsychotics) are effective in reducing the severity of tardive dyskinesia.[9] While previous work indicated an antidyskinetic effect in short-term studies, the long-term outcome of continuous antipsychotic treatment in patients with tardive dyskinesia was unknown.[5] The present study indicates that this effect is enduring. Furthermore, we found no indication of worsening of tardive dyskinesia, even in the haloperidol-treated subjects, thus supporting the observation that tardive dyskinesia does not seem to progress with ongoing antipsychotic treatment.[5]

The underlying mechanism of the beneficial effect on dyskinesia is not clear. The fact that substantial improvement was apparent even after 12 weeks of treatment suggests an either early masking or suppressant effect on tardive dyskinesia. However, the sustained improvement in the quetiapine-treated subjects supports a direct antidyskinetic effect with this agent. Although not directly confirmed in our trial, the results of another study suggest that this may well be the case for atypical antipsychotics. Withdrawal of clozapine after 12 months of treatment was not associated with an exacerbation of tardive dyskinesia symptoms, whereas withdrawal of haloperidol was.[11]

Our results are also of interest in that they provide data on the long-term use of quetiapine under blinded conditions. Psychotic symptoms were comparable in both groups at baseline and throughout the treatment period. This finding was not unexpected despite a previously reported superior response rate for quetiapine over haloperidol,[36] as a requirement for selection was a stable psychiatric condition, and the baseline PANSS scores were low. Quetiapine-treated patients had fewer other EPS (parkinsonism, akathisia, and dystonia) and were prescribed less anticholinergic medication. Whereas serum prolactin levels increased in the haloperidol group, they

Table 2. Baseline and 12-Month Positive and Negative Syndrome Scale (PANSS) Scores in Patients Receiving Quetiapine or Haloperidol (mean ± SD)

	Quetiapine		Haloperidol	
PANSS Score	Baseline	Endpoint	Baseline	Endpoint
Total	55.5 ± 12.9	49.2 ± 11.5	57.0 ± 14.1	51.5 ± 15.4
Positive	10.8 ± 4.4	8.0 ± 2.1	10.7 ± 5.4	9.3 ± 3.9
Negative	19.4 ± 5.5	20.0 ± 6.1	20.6 ± 5.9	18.8 ± 5.1
General psychopathology	25.5 ± 5.9	21.1 ± 5.2	25.6 ± 6.1	23.3 ± 7.7

Table 3. Body Weight in Patients Receiving Quetiapine or Haloperidol (mean ± SD)

Timepoint	Quetiapine (kg)	Haloperidol (kg)
Baseline	71.9 ± 21.3	66.6 ± 11.7
3 mo	77.0 ± 22.5	66.5 ± 11.2
6 mo	71.0 ± 25.8	66.8 ± 11.0
9 mo	71.7 ± 22.3	66.0 ± 10.6
12 mo	71.2 ± 2.0	66.9 ± 11.1

decreased in the quetiapine group. Differences between the groups were highly significant, in keeping with findings in previous short-term studies.[21] Neither treatment group showed a tendency toward persistent weight gain, and glycemic control was also maintained in both groups.

It deserves to be noted that 10 (45%) of the quetiapine-treated subjects and 8 (34%) of the haloperidol-treated subjects were withdrawn from the trial. While the dropout rates did not differ significantly between the groups, and were in line with what could be expected from a controlled study over 12 months,[37] the relatively low doses of quetiapine used may also be partially responsible for these rates. The most common reason for withdrawal in the quetiapine group was worsening of psychosis (31%). The low doses prescribed probably reflect the fact that investigators were primarily concerned with motor symptoms and were reluctant to use higher doses of antipsychotics in subjects with tardive dyskinesia. Future studies should further address this issue.

The following factors limit the generalization of our findings. First, the sample size was relatively small, thereby increasing the chances of type II errors. (A substantially larger sample in a tardive dyskinesia study would be difficult to obtain from a single site, however, as recruiting these subjects proved to be difficult—it took us 2 years to complete enrollment for this study.) This problem was compounded by the high withdrawal rate associated with trials of long duration such as this. Second, the dose of quetiapine was lower than that generally recommended in clinical practice. While the use of higher doses may have reduced the number of dropouts due to worsening of psychosis, it is not clear what the effect would have been on dyskinesia symptoms. Finally, our study did not investigate whether the improvement in dyskinesia was maintained after discontinuation of quetiapine.

CONCLUSION

The best treatment for tardive dyskinesia is prevention. In this regard, the use of atypical antipsychotics as first-line medications is likely to reduce the incidence of tardive dyskinesia. Patients with established tardive dyskinesia who are taking conventional antipsychotics are candidates to be switched to an atypical antipsychotic.[38] While clozapine has been reported to be moderately effective, its use in the treatment of tardive dyskinesia is limited by the risk of agranulocytosis[38] and poor tolerability.[11] To date, no other controlled studies have evaluated the efficacy of other atypical antipsychotics in the treatment of tardive dyskinesia. Quetiapine appears to be effective and well tolerated in tardive dyskinesia and seems to be a good treatment option for these patients.

Drug names: clozapine (Clozaril and others), cyproheptadine (Periactin and others), estrogen (Premarin and others), haloperidol (Haldol and others), lithium (Eskalith, Lithobid, and others), naloxone (Suboxone, Narcan, and others), quetiapine (Seroquel), risperidone (Risperdal).

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