The Effectiveness of Quetiapine Versus Conventional Antipsychotics in Improving Cognitive and Functional Outcomes in Standard Treatment Settings

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Objective: To examine the effectiveness of quetiapine versus conventional antipsychotics in improving cognitive and functional outcomes.

Method: Forty stable outpatients with DSM-IV schizophrenia treated in public outpatient clinics were randomly assigned to continue taking conventional antipsychotic medications or switch to quetiapine for 6 months, beginning September 1998 and ending July 2000. Neurocognitive and functional measures were obtained at study entry, 3 months, and 6 months by raters blinded to treatment. Group differences were examined using repeated-measures analyses of covariance for mixed models.

Results: The mean (SD) dose of conventional antipsychotics in chlorpromazine equivalents was 348.00 (348.28) mg/day; the mean (SD) dose of quetiapine was 319.25 (142.55) mg/day. A cognitive function summary score improved in the quetiapine group relative to the group treated with conventional antipsychotics over the 6-month period ($F = 5.80$, $df = 1,28.9$; $p < .023$). Patients taking quetiapine did better with respect to both verbal fluency (initiation) and verbal memory. There were also statistically significant group differences with respect to quality of life favoring the quetiapine group ($F = 4.87$, $df = 1,29$; $p < .04$). Differences were not found with respect to adaptive functioning.

Conclusion: Quetiapine improved cognition relative to conventional agents. After 6 months, groups differed by more than 1 standard deviation when baseline cognitive functioning was taken into account. No group differences were found with respect to improvements in community functioning. Improvements in adaptive functioning may lag behind improvements in cognition. Psychosocial programming may be necessary to translate gains in cognition into improvements in adaptive functioning.

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Three recent reviews of the literature have concluded that preliminary evidence supports the notion that patients taking atypical antipsychotics perform better on tests of cognitive function than do patients treated with conventional neuroleptics.[1–3] In well-designed, randomized, double-blind efficacy trials, risperidone, olanzapine, and quetiapine have all been found to improve performance on tests of cognitive function relative to haloperidol.[4–6] In treatment efficacy studies such as these, which are often conducted in specialized research settings, inclusion criteria are typically highly restrictive and specified medication dosing strategies are followed. It is often unclear whether the treatment group differences between conventional and atypical antipsychotics found in efficacy trials will be observed in trials conducted in traditional treatment settings where patient characteristics and prescribing practices vary more widely.

The effectiveness of atypical antipsychotics in real-world settings has most often been examined in "switch studies" in which a single group of patients treated with conventional agents are tested, switched to an atypical antipsychotic, and then tested again.[3] In a single-group switch study, patients may improve due to the practice effects that often occur with repeated administrations of

cognitive tests. Parallel-group designs, in which 1 group receives an atypical antipsychotic and another receives a conventional medication, are needed to determine whether improvements observed in cognitive functioning reflect more than practice effects.[3] Furthermore, an important limitation of the efficacy trials cited above is that changes in functional outcomes were not reported. Although cognitive deficits have been found to predict community functioning,[7–9] it is unclear whether improvements in cognition with atypical antipsychotics lead to improved adaptive and role functioning.

Quetiapine has been available in the United States for a shorter period of time than either risperidone or olanzapine, and there are fewer published data with respect to its impact on cognition relative to conventional antipsychotics.[3] The purpose of this study was to examine the effectiveness of quetiapine compared with conventional neuroleptics in improving cognitive and functional outcomes in a group of stable outpatients treated in standard community settings. The study addressed a relevant clinical issue, namely, would patients who were clinically stable on a conventional antipsychotic benefit from switching to quetiapine? We used a parallel-group design, in which patients treated with conventional antipsychotics were randomly assigned to either switch to quetiapine or to continue taking their current medications. Specific research questions were:

1. Is there a difference in cognitive performance for patients switched to quetiapine compared with patients who remain on conventional neuroleptic treatments?
2. What proportion of patients improves to a significant degree in each treatment group?
3. Is there a difference in functional outcomes and quality of life between treatment groups?
4. Do changes in cognition correlate with changes in functional outcome and quality of life?

METHOD

Subjects

Stable outpatients with schizophrenia were recruited from 1 of 3 community outpatient clinics in the San Antonio, Texas, area that are part of a single treatment agency. Diagnoses were based on the Structured Clinical Interview for DSM-IV (SCID).[10] Patients taking standard antipsychotic medications at a stable dose for at least 3 months were eligible for study participation if they were between the ages of 18 and 55 years; spoke English as their primary language; had no documented history of epilepsy, head injury, or mental retardation; and had no psychiatric hospitalizations for a minimum of 1 year before the study. In addition, patients had at least 1 of the following clinical indications that a change in medication may be beneficial: (1) moderate positive symptoms despite antipsychotic treatment (rated as 4 or higher on 1 of the 4 items measuring psychosis from the Brief Psychiatric Rating Scale expanded version [BPRS][11]), (2) moderate negative symptoms (4 or higher on the global score from the Negative Symptom Assessment [NSA][12]), (3) moderate neurologic side effects (3 or higher on any item of the Simpson-Angus Scale[13] or 4 or higher on any item of the Abnormal Involuntary Movement Scale [AIMS][14]), or (4) personal preference to change medications.

We did not limit the sample to only those patients taking haloperidol. Differences between haloperidol and atypical antipsychotics have been investigated in a number of randomized, double-blind efficacy trials.[4–6] Individuals who did not want or were unable to take haloperidol were excluded from these trials. Because we were studying effectiveness, we wanted to include a broader range of subjects.

Design

After a complete explanation of study procedures and medication side effects, patients signed a consent form approved by an institutional review board. Forty patients received baseline assessments and were then randomly assigned to continue taking their traditional antipsychotic medication or to be switched to quetiapine for a period of 6 months. Random assignment was made by an independent research coordinator who informed the treating physician of the group assignment. This was an open-label, rater-blinded study. All medication was prescribed and monitored by the patients' treating physicians in the community clinic. Dosing and crossover from traditional medications to quetiapine were based on the clinical judgment of the treating physician, except that patients switched to quetiapine were required to stop taking all standard antipsychotic medications 1 month after beginning quetiapine treatment. Patients were assessed at 3 months and again at 6 months after baseline by raters who were unaware of the medication status of the patient.

Neurocognitive Assessments

Tests for the cognitive battery were selected to cover domains known to be impaired in patients with schizophrenia. Measures were obtained at study entry and at 3 and 6 months. All examiners were master's-level psychologists who were trained by a neuropsychologist before administering and scoring neurocognitive tests. The tests, putative domains, and scores generated are presented in Table 1. Equivalent alternate forms were administered where indicated. As in the Purdon et al.[5] study, we used published means and SDs for large control samples to convert scores from the battery described in Table 1 into Z-score form, corrected for age, education, and gender where appropriate.[15,16] The Z-scores reflect, in SD units, how each patient's score compares to scores for

Table 1. Neurocognitive Test Battery

Cognitive Domain	Test	Scores Generated
Verbal fluency (initiation)	Verbal Fluency Letters	Total letters
	Verbal Fluency Categories[a]	Total categories
Cognitive flexibility	Wisconsin Card Sorting Test (Nelson Modification)	Number of categories Number of perseverations
Verbal memory (immediate recall, working memory, and list learning)	California Verbal Learning Test	Total score for trials 1–5
	Digit Span[a]	Total digits forward and backward
Selective attention	Stroop Color-Word Test	Total correct in the color-word condition
Global functioning	Based on all tests listed above	Mean of Z-scores for each domain were added together. Coefficient alpha for cognition scores = .78, indicating that individual domain scores can be meaningfully combined into a composite score.

[a]Alternate forms used for repeated testing.

control subjects with similar demographics. Test scores within each domain were added together to form domain scores. Domain scores were then added together to produce a cognitive function summary score.[5] The coefficient alpha for individual cognitive domain scores ranged from .73 to .80. The coefficient alpha for the summary score was .78, indicating that individual domain scores can be combined meaningfully into this composite. A recent meta-analysis by Green et al. indicates that cognition summary scores are better predictors of community functioning than individual test scores.[17]

Diagnostic, Symptom, and Functional Assessments

Raters and reliability. All raters completed comprehensive reliability training as part of a university-based schizophrenia research program. Diagnoses were made by master's-level psychologists who had attained a reliability of 0.95 (Kappa statistic) for a diagnosis of schizophrenia versus all other diagnoses on 10 criterion interviews. Prior to rating symptoms and functional outcome, master's-level research assistants were required to reach a reliability of 0.80 intraclass correlation coefficient overall for each scale on a series of 10 criterion videotapes. In addition, raters needed to achieve this same criterion for each item making up the positive and negative symptom factors of the BPRS.[11] As recommended by Ventura et al., regular reliability meetings were held to minimize rater drift.[11] Assessments were conducted by the same group of raters irrespective of the specific outpatient clinic attended by the subject.

Symptomatology. Positive symptoms were assessed at baseline, 3 months, and 6 months using the expanded version of the BPRS.[11] Scores vary from 1 to 7, with higher scores indicating greater levels of symptomatology. The positive symptom factor is composed of items assessing unusual thought content, suspiciousness, hallucinations, and conceptual disorganization.

Negative symptoms were assessed at baseline, 3 months, and 6 months using the NSA.[12] Scores vary from 0 to 6, with higher scores reflecting more severe negative symptoms. A total score computed by adding the subscale scores reflects the overall level of negative symptoms.

Neurologic symptoms. The AIMS[14] was completed at baseline only as part of patient screening to determine eligibility for the study. The AIMS assesses abnormal movements on a 1 to 5 scale, with higher scores reflecting more severe involuntary movements.

The Simpson-Angus Scale,[13] which assesses side effects of traditional neuroleptics, was administered at baseline and 3 and 6 months. Scores vary from 0 to 4, with higher scores indicating more side effects. A mean of all items represented severity of side effects.

Adaptive functioning and quality of life. Adaptive, or community, functioning was assessed at baseline and 3 and 6 months using the Multnomah Community Ability Scale (MCAS).[18] The MCAS assesses activities of daily living, social competence, and behavior problems. Higher scores reflect better functioning. A total score was used as a global measure of community functioning.

Quality of life was assessed at baseline and 3 and 6 months using the Heinrichs-Carpenter Quality of Life Scale (QLS).[19] The QLS assesses the quality of relationships, occupational role, sense of purpose, and the possession of common objects. Higher scores indicate better quality of life. A mean of all items was used to represent overall quality of life.

Data Analysis

All analyses were performed by statisticians who were unaware of the designation of patients in treatment groups. Group differences at baseline with respect to demographic variables were assessed using t tests for continuous variables and chi-square tests for categorical variables.

Our primary outcome variable was the cognitive function summary score. Differences by treatment group over time were examined using a repeated-measures analysis of covariance (ANCOVA) for mixed models.[20] The covariate was the baseline cognitive function summary score. This analysis models the change in variables of interest

Table 2. Patient Demographics

Variable	Conventional Antipsychotic (N = 20)	Quetiapine (N = 20)
Men, N	15	12
Women, N	5	8
Age, mean (SD), y	42.09 (7.34)	44.22 (6.65)
Race, N		
White	4	7
Mexican American	13	9
African American/Asian/mixed	3	4
Education, mean (SD), y	11.05 (3.89)	11.78 (3.07)
Reasons for entry into study, N		
Positive and negative symptoms plus side effects	9	11
Positive and negative symptoms only	4	2
Positive symptoms only	3	1
Negative symptoms only	2	1
Side effects only	0	4
Desire to change medications	2	1
No. taking benztropine at baseline	13	12

Table 3. Baseline Antipsychotic Medication

Medication	N	Dose, mg Mean (SD)
Haloperidol	20	9.1 (9.5)
Fluphenazine	6	10.0 (7.1)
Thiothixene	6	10.5 (13.1)
Thioridazine	4	200.0 (117.3)
Loxapine	2	35.0 (21.2)
Perphenazine	1	16 (N/A)
Mesoridazine besylate	1	100 (N/A)

Abbreviation: N/A = not applicable.

over the follow-up period taking into account individual differences in baseline score. Similar analyses were used for the BPRS Psychosis Factor, NSA total score, MCAS total score, and QLS mean score. All analyses were 2-tailed, and included all randomized patients with a baseline and at least 1 follow-up assessment.

Assumptions for the repeated-measures ANCOVA (i.e., homogeneity of variance, normality) were satisfied for all analyses. We verified that compound symmetry fit the data better than a general variance/covariance matrix for the repeated measures. Degrees of freedom were determined by the Satterthwaite method, which adjusts the F value for observations that may be missing at any timepoint.[21] Specific domains of cognition or adaptive function were to be examined only in the context of a significant finding for the summary or total score. Significance levels for tests of individual domain scores are presented both uncorrected and corrected for multiple comparisons (i.e., number of individual cognitive domains examined) using the Bonferroni technique. This technique is considered overly conservative in a situation in which variables are highly correlated[3] (as in the present study).

To examine whether changes in cognitive function were associated with changes in adaptive function and quality of life, we calculated Pearson correlation coefficients between the change scores for the cognition summary score (baseline to endpoint) and change scores for the MCAS total and QLS mean scores.

RESULTS

Demographics

Forty patients were enrolled in the study. Demographics and reasons for entry into the study are presented in Table 2 for each treatment group. Mean doses for all antipsychotic medications at baseline and numbers of patients treated with each are presented in Table 3. There were no statistically significant differences between groups with respect to demographic variables including age, education, gender, ethnicity, reason for entrance into the study, and proportion taking benztropine ($t < 1.0$, $\chi^2 < 2.3$, $p > .30$). There were no significant differences between groups at baseline with respect to cognitive function, symptoms, or neurologic measures (Table 4).

Withdrawals

Patients were withdrawn from the study when clinically indicated, based on the judgment of the treating physician. Withdrawals included 3 patients taking conventional antipsychotics (1 relocated, 1 for lack of efficacy, and 1 was jailed) and 3 patients taking quetiapine (2 for lack of efficacy and 1 for side effects) who dropped out before the second assessment at 3 months, leaving a total of 34 evaluable patients. One additional patient in the quetiapine group was excluded from the analysis because he was unable to perform cognitive testing (scores > 10 SDs below the mean of control patients). Results of data analyses presented in Table 4 remain unchanged if this patient is included. Six additional patients dropped out before the 6-month assessment: 4 taking conventional antipsychotics (2 for lack of efficacy, 1 refused ratings, and 1 for side effects) and 2 taking quetiapine (1 for lack of efficacy and 1 refused ratings).

Dosing

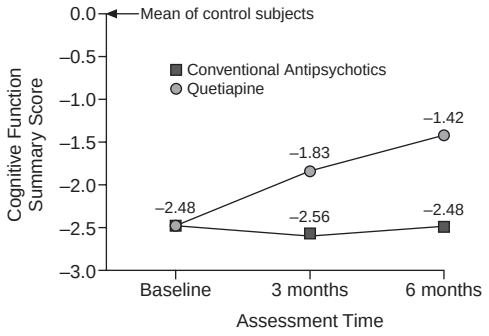
The mean (SD) dosage of quetiapine at the 3- and 6-month assessment was 303.95 (129.71) mg/day and 319.25 (142.55) mg/day, respectively. The mean (SD) dosage of conventional antipsychotic medication in chlorpromazine equivalents was 352.50 (350.37) mg/day at the beginning of treatment and 348.00 (348.28) mg/day at the end of the study. There were no significant changes in mean dose over time in either treatment group ($t < 1.01$, $p > .30$). These small mean differences in doses between timepoints reflect that some subjects dropped out of the study rather than that doses were changed from the 3 to the 6 month assessment. None of the patients treated with quetiapine were taking benztropine at endpoint versus almost 60% of patients (N = 10) treated with conventional antipsychotics.

Table 4. Dependent Variables at Baseline by Treatment Group[a]

Variable	Conventional Treatment (N = 20)	Quetiapine (N = 20)	t Test for Group Differences
Verbal fluency score[b]	–1.95 (1.70)	–2.99 (2.66)	t = 1.31, df = 1,23.3; p > .20
Wisconsin Card Sort score[b]	–1.86 (2.80)	–3.68 (4.61)	t = 1.32, df = 1,22.5; p > .20
Verbal memory score[b]	–1.62 (1.67)	–2.03 (1.61)	t = 0.71, df = 1,29.8; p > .50
Stroop Color Word Test score[b]	–2.85 (1.74)	–3.83 (2.73)	t = 1.18, df = 1,23.6; p > .25
Summary cognition score	–1.98 (1.23)	–2.90 (2.22)	t = 1.41, df = 1,21.2; p > .17
BPRS positive symptom factor score	2.45 (1.44)	2.38 (1.18)	t = 0.16, df = 1,29.9; p > .87
NSA total score	13.23 (3.24)	13.73 (4.62)	t = –0.35, df = 1,24.7; p > .73
Simpson-Angus Scale score	0.31 (0.29)	0.51 (0.35)	t = –1.75, df = 1,27.1; p > .10
MCAS total score	65.53 (8.34)	64.47 (9.15)	t = 0.34, df = 1,28.6; p > .73
QLS score	3.09 (1.00)	3.01 (1.11)	t = 0.23, df = 1,28.4; p > .82

[a]Values for each treatment group are mean (SD) scores.
[b]All cognitive function scores presented in Z-score form represent standard deviations from the mean of normative samples. Data for normative samples from Mitrushina et al.[15]
Abbreviations: BPRS = Brief Psychiatric Rating Scale, MCAS = Multnomah Community Ability Scale, NSA = Negative Symptom Assessment, QLS = Quality-of-Life Scale.

Figure 1. Mean Cognitive Function Summary Score Over Time by Treatment Group



Symptom and Neurologic Side Effect Results

There were no significant differences between the groups during follow-up with respect to symptomatology or neurologic side effects ($F < 1.0$, $p > .30$ for group, time, and group-by-time).

Cognition Results

Primary outcome variable: cognitive function summary score. Patients in the quetiapine group performed better than those taking conventional antipsychotics with respect to the cognitive function summary score. Results indicated a significant main effect of group ($F = 5.80$, $df = 1,28.9$; $p < .023$) and nonsignificant time and group-by-time effects ($F = 2.26$, $df = 1,25.3$; $p < .15$ and $F = 1.07$, $df = 1,25.3$; $p < .32$, respectively). Hence, the analysis showed a between-group treatment effect but no differences in slope from months 3 to 6, suggesting that differences between the treatments remained stable throughout the follow-up period. At the end of 6 months, the groups differed by more than 1 SD when baseline cognitive functioning was taken into account. The average level of the baseline score and follow-up means adjusted for scores at baseline are shown in Figure 1. (Actual baseline scores are shown in Table 4.) The group effect remained significant when changes in positive symptoms, negative symptoms, and side effects were used as additional covariates. Benztropine use could not be used as a covariate due to its redundancy with treatment group (none of the quetiapine patients were taking benztropine); however, we reanalyzed the data by excluding all patients taking benztropine and found that significant group differences remained. We ran an additional ANCOVA with baseline medication (haloperidol versus not haloperidol) included as a grouping variable. There was no significant medication-by-group or medication-by-group-by-time interaction ($p > .20$) indicating that the effects of quetiapine on cognitive function did not depend on which type of conventional antipsychotic subjects were taking at baseline.

Additional cognitive function variables. Because we found a significant difference between the 2 groups during follow-up with respect to summary cognitive function score, we wanted to determine which domain scores contributed to this finding. Patients in the quetiapine group performed better with respect to verbal fluency (initiation) than did those taking conventional antipsychotics ($F = 7.12$, $df = 1,29$; $p < .013$). Effects for time and group-by-time were nonsignificant ($F = 3.81$, $df = 1,27.4$; $p < .061$ and $F = 0.01$, $df = 1,27.4$; $p < .94$, respectively). The group difference for verbal fluency (initiation) remained statistically significant when controlling for multiple comparisons. Furthermore, patients in the quetiapine group performed better than those taking conventional antipsychotics with respect to verbal memory. There was a nonsignificant group effect ($F = 3.47$, $df = 1,29$; $p < .073$), a nonsignificant effect for time ($F = 0.37$, $df = 1,24.8$; $p < .55$), and a significant group-by-time interaction ($F = 4.13$, $df = 1,24.8$; $p < .05$). Comparisons at specific times indicated that the groups differed significantly with respect to verbal memory only at 6 months ($p < .02$).

Figure 2. Verbal Fluency (initiation) Over Time by Treatment Group

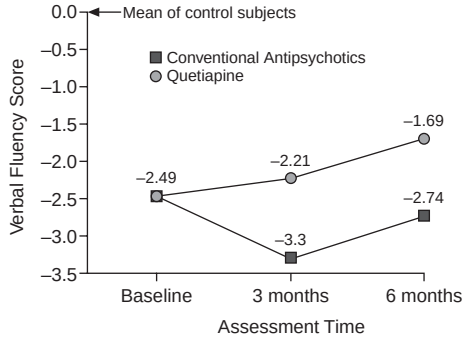
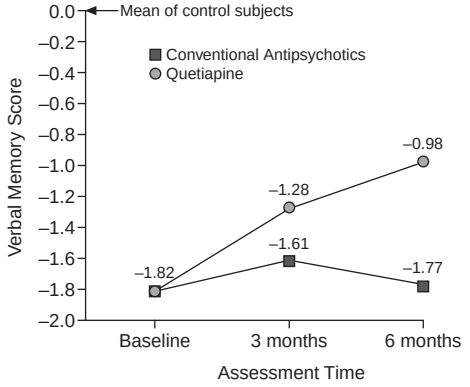


Figure 3. Verbal Memory Over Time by Treatment Group[a]



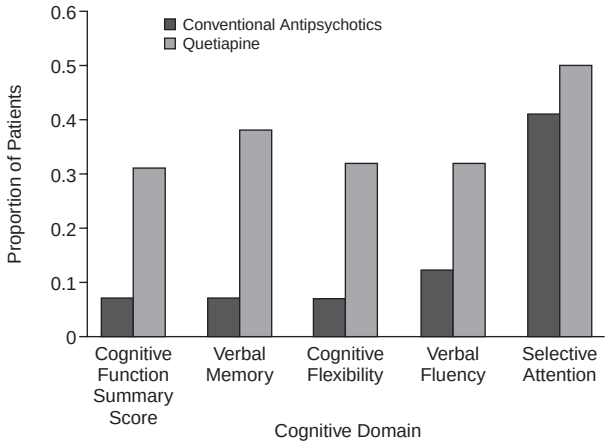
[a]Assessed via California Verbal Learning Test and Digit Span.

This difference does not reach statistical significance when controlling for multiple comparisons. Results of ANCOVAs for verbal fluency and verbal memory were unchanged when controlling for changes in symptomatology and side effects. Least squares means for verbal fluency (Verbal Fluency Letters and Verbal Fluency Categories[22]) and verbal memory (California Verbal Learning Test[23] and Digit Span[22]) and the average level of the baseline scores for each analysis are shown in Figures 2 and 3. (Actual baseline scores can be found in Table 4.)

There were no statistically significant group or group-by-time differences on the Stroop Color-Word Test[24] ($p > .20$) or the Wisconsin Card Sorting Test ($p > .12$).[16] Similar results for cognitive function variables were obtained using other analyses, including endpoint analyses with last-observation-carried-forward and multivariate ANCOVA examining the individual cognitive test scores together in 1 analysis.

Effect sizes. Effect sizes, calculated using changes in least squares means from baseline to last-observation-carried-forward, for verbal fluency and verbal memory were 0.71 and 0.48, respectively. These effect sizes are larger than those reported in a recent review of the literature by Harvey and Keefe.[3]

Figure 4. Proportion of Patients Improving 1 Standard Deviation From Baseline Performance by Group



Proportion of patients significantly improved in cognitive function. According to Bellack and colleagues,[25] large improvements in cognitive function of at least 1 SD would be necessary to significantly improve adaptive functioning. In an effort to understand the magnitude of cognitive change, groups were compared with respect to the proportion of patients in each group that improved 1 SD over the course of treatment on the summary cognitive function score and each domain score. Results graphed in Figure 4 indicate that a greater proportion of patients improved in the quetiapine group compared with the conventional antipsychotics group. Group differences in proportions of patients improving significantly reached statistical significance for verbal memory ($\chi^2 = 4.93$, df = 1, $p < .03$) and showed a positive trend for the cognition summary score ($\chi^2 = 3.57$, df = 1, $p < .06$).

Adaptive Functioning and Quality of Life

There were no differences between groups in adaptive functioning (MCAS total scores $F = 1.03$, df = 1,29.3; $p < .32$; $F = 0.50$, df = 1,25.8; $p < .49$; and $F = 0.03$, df = 1,25.9; $p < .86$ for group, time, and group-by-time, respectively). However, patients in the quetiapine group had better quality of life scores during the follow-up period than those in the conventional group ($F = 4.87$, df = 1,29; $p < .04$). The effect size for this difference was 0.58. Effects for time and for group-by-time were not statistically significant ($F = 0.01$, df = 1,25.2; $p < .95$ and $F = 0.75$, df = 1,25.7; $p < .40$, respectively). No significant relationship was found between change scores for cognition and those for adaptive functioning or quality of life ($t < 0.30$, $p > .19$).

DISCUSSION

Patients treated with quetiapine showed improved overall cognitive performance compared with patients treated with standard antipsychotics. The greatest effects were in the domains of verbal fluency and verbal memory. After 6 months of treatment, stable outpatients treated with quetiapine performed better than 1 SD above those who remained on conventional antipsychotic treatments, given their scores at baseline. This difference of 1 SD represents a large effect size by standard indices and is clinically meaningful.[3,25,26] Differences of this magnitude are likely to be necessary to improve community functioning.[25] These robust cognitive improvements were found in patients being treated in standard outpatient clinics.

The cognitive function summary score, verbal memory, verbal fluency, and card sorting scores improved 1 SD in approximately 33% of patients treated with quetiapine compared with only 6% of patients (or 12% with respect to verbal fluency) who remained on conventional treatment. The memory domain score was composed, in part, of scores from the California Verbal Learning Test.[23] Practice effects or learning are expected to occur on this test.[3] A learning effect was not observed in patients who remained on standard neuroleptic treatments, while patients taking quetiapine performed more similarly to control subjects who show improvements over time with repeated administrations of this task.[27]

Treatment effects were not due solely to improvements in symptomatology or side effects or to benztropine use. It is possible that side-effect changes would be related to improvements in cognition if side effects were rated more comprehensively. In addition, the full extent of the effects of benztropine could not be investigated in this study due to the almost complete redundancy between benztropine use and treatment group. The data presented here suggest that there may be a direct effect of quetiapine relative to conventional antipsychotics on cognition for patients with schizophrenia. However, since in clinical practice, benztropine is routinely prescribed with conventional antipsychotics to address specific side effects, it is less important whether the improvements in cognitive function result from treatment with quetiapine or from the decrease in side effects and use of benztropine.

Results of the current study correspond closely to those in a recent treatment efficacy study of quetiapine versus haloperidol, which reported that scores assessing verbal memory (story recall) and fluency were improved in the quetiapine group relative to the haloperidol group.[6]

It is possible that changes in adaptive functioning may lag behind cognitive improvements, so that a longer follow-up may be necessary to see improvements in functional outcome. Data reported here do not support the conclusion that adaptive functioning was improved with quetiapine treatment compared with standard antipsychotic treatment. Furthermore, we did not find a relationship between improvements in cognition and improvements in adaptive functioning. It is possible that the relationship between cognitive improvement and improvements in community functioning are weak or nonexistent in some contexts. However, it is more likely that cognitive improvements may merely set the stage for improvements in role functioning. Psychosocial programming and more opportunities for independence may be necessary before gains in cognition are reflected in improved adaptive functioning.

A significant group difference in quality of life favoring the quetiapine-treated group was found. To our knowledge, this is the first randomized, rater-blinded study to find quality-of-life improvements with quetiapine relative to conventional antipsychotics. Although the difference between groups in this study appears small in clinical magnitude, this finding suggests that quality of life should be more thoroughly investigated in efficacy studies of quetiapine with longer follow-up periods.

The present study had several methodological limitations. The most obvious limitation was the single-blind design of the trial. Because the goal of this study was to examine the effectiveness of this medication in standard community treatment settings, a double-blind design was not possible. However, with only 1 double-blind efficacy trial of quetiapine and cognition published to date, the results of this study are important in demonstrating the potential effectiveness of this medication in public outpatient clinics.

In addition to design issues, the sample size for this study was small. Attempts to replicate these results in a larger sample would be important to pursue. Moreover, patients who were available for recruitment for this study (i.e., those still receiving conventional antipsychotics) were likely to be patients who had the fewest side effects and complained the least about traditional treatments.

Furthermore, conventional medications at baseline assessment differed across patients. Although it is possible that different conventional antipsychotic medications could have differential effects on cognition, this notion is not supported by previous research nor the current results.[28] It is also somewhat likely that our clinically stable subjects entered this study taking conventional antipsychotics that had worked for them to some degree, in terms of either efficacy or side effect profile. Therefore, the design allowed us to examine the effectiveness of quetiapine compared to a conventional medication that was likely to be a "workable standard" for each particular subject.

Another relevant issue is that medication dosing was not standardized. Doses of quetiapine used by physicians at our community clinics were generally at the lower end of the effective dose range (150–700 mg/day). Results may have been different if higher doses of quetiapine were used. In a recent efficacy study, we found that only a

higher dose of quetiapine (600 vs. 300 mg/day) significantly improved cognition relative to haloperidol.[6] The lower doses used in the present study may have been effective due to the stability of this outpatient sample. Issues of dosing and sample effects need to be studied more extensively.

Finally, while patient groups were not significantly different on cognition scores at baseline, the group switched to quetiapine scored more poorly on average at baseline than patients who were assigned to remain on conventional antipsychotic treatments. This supports our use of ANCOVA to analyze the data but may also raise the concern that improvements in the quetiapine group represent, in part, improvements due to regression toward the mean. However, regression toward the mean (which is 0 in the general population) would presumably affect both groups. As seen in Figure 1, there is very little regression toward the mean in the group remaining on conventional antipsychotic treatments. These methodological issues suggest that attempts to replicate these findings should be encouraged.

Despite the methodological issues, our results are consistent with published efficacy data, suggesting that patients whose illness is stable with conventional antipsychotics may receive significant cognitive benefit from being switched to quetiapine. Clinical state was unchanged by the switch in medication despite robust positive effects on cognition. Furthermore, treatment with quetiapine may improve quality of life, and the benefits of quetiapine in this area relative to other atypical antipsychotics should be investigated in future research.

Drug names: benztropine (Cogentin and others), fluphenazine (Prolixin, Permitil, and others), haloperidol (Haldol and others), loxapine (Loxitane and others), mesoridazine besylate (Serentil), olanzapine (Zyprexa), perphenazine (Trilafon and others), quetiapine (Seroquel), risperidone (Risperdal), thiothixene (Navane and others).

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