Randomized, Double-blind 6-Month Comparison of Olanzapine and Quetiapine in Patients With Schizophrenia or Schizoaffective Disorder With Prominent Negative Symptoms and Poor Functioning

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Abstract: This study compared the effects of olanzapine (OLZ) with those of quetiapine (QUE) for improving negative symptoms in patients diagnosed with schizophrenia or schizoaffective disorder who had prominent negative symptoms and marked deficits in social or occupational functioning. In this 6-month, multicenter, double-blind clinical trial, patients were randomized to treatment with OLZ (n = 171, 10–20 mg/d) or QUE (n = 175, 300–700 mg/d). Patients were treated at community mental health centers and assigned case managers who developed individualized psychosocial treatment plans. The primary efficacy measure was the reduction in negative symptoms using the Scale for the Assessment of Negative Symptoms. Secondary measures assessed changes in functioning, psychopathology, and treatment tolerability. Treatment with OLZ or QUE led to a significant reduction in negative symptoms, with no between-group difference (P = 0.09). Both treatment groups also showed significant improvement on most efficacy measures. Olanzapine-treated patients showed significantly greater improvement on positive symptoms and on several measures of functioning including Global Assessment of Functioning Scale, Quality of Life Instrumental Role domain, and level of effort in psychosocial or occupational rehabilitation programs. Significantly more OLZ-treated patients completed the study (52.6% OLZ, 37.7% QUE, P = 0.007). Treatment differences in safety were relatively small and not thought to be clinically relevant. Patients with schizophrenia who manifest prominent negative symptoms and marked functional deficits demonstrated significant improvement in negative symptoms after treatment with OLZ or QUE. Greater improvement in positive symptoms and a greater study completion rate may hold relevance to enhanced functional outcomes observed after OLZ therapy.

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Negative symptoms in schizophrenia are important in affecting the psychosocial and occupational functioning of patients. Numerous studies have shown an association between the presence of negative symptoms and poor psychosocial functioning, poor work performance, and impaired relationships.[1–7] Thus, although patients appear to be in remission when their positive symptoms remit, the presence of prominent negative symptoms may hinder their ability to achieve rehabilitative and social reintegration goals. By improving negative symptoms, an opportunity may exist to optimize the functional outcomes of patients.

Antipsychotic drugs play an important role in the treatment of negative symptoms, and the atypical antipsychotics (as a class) have been shown to be superior to conventional drugs in this regard.[8] Studies using path analytic approach suggest that negative symptoms are directly responsive to antipsychotic therapy, and the greater reduction in negative symptoms observed with the atypical antipsychotics over conventional agents include both direct and indirect improvements via changes in other symptom domains or extrapyramidal symptoms (EPS).[9–11]

There are some data, however, to suggest that the atypical antipsychotics may differ from each other in their ability to reduce negative symptoms. In 2003, Davis and colleagues[12] reported that clozapine, amisulpride, risperidone, and olanzapine (OLZ) were superior to conventional antipsychotics in reducing global schizophrenia symptoms including negative symptoms, whereas other second-generation antipsychotics were not. An earlier meta-analytic study found that risperidone and OLZ were more effective than haloperidol in treating global schizophrenia symptoms and negative symptoms, whereas quetiapine (QUE) was as effective as haloperidol for overall symptoms, but slightly less effective than haloperidol for negative symptoms.[13] A separate meta-analysis of data from 3 placebo- and 5 haloperidol-controlled clinical trials of QUE has shown no evidence for greater symptom improvement compared with haloperidol.[14]

In the current study, patients with schizophrenia or schizoaffective disorder who had prominent negative symptoms and were experiencing at least moderate difficulty in social or occupational functioning were randomized to treatment with OLZ or QUE for up to 6 months in the context of community-based treatment. Based on previous

findings,[12–14] it was hypothesized that OLZ would be more effective than QUE in reducing negative symptoms in this patient population and secondarily, that such improvement would be associated with greater reductions in psychopathology and enhanced psychosocial functioning.

MATERIALS AND METHODS

Subjects

Participants (N = 346) were outpatients who met diagnostic criteria for schizophrenia or schizoaffective disorder according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*. All participants met inclusion criteria for prominent negative symptoms, defined as a Positive and Negative Syndrome Scale (PANSS) score of greater than or equal to 4 (moderate) on at least 3, or greater than or equal to 5 (moderately severe) on at least 2 of the 7 negative scale items; and for social and functional impairment, defined as a Global Assessment of Functioning Scale (GAF) score of less than or equal to 60 (moderate difficulties). All patients gave written informed consent before entering the study. The study protocol was approved by appropriate institutional review boards for each site.

Procedure

This was a multicenter, randomized, double-blind study comparing the efficacy of OLZ with QUE for psychopathology, functional outcomes, and safety (Fig. 1). During study period 1, patients were screened for eligibility using medical history, psychiatric and physical examinations, vital signs, electrocardiograms, and clinical laboratory tests. During study period 2, all patients who met entry criteria were randomized to receive OLZ or QUE using a 1:1 ratio. Patients' current antipsychotic medications were tapered off as their study medication was initiated. During study period 3, patients were titrated up to their clinically optimal dose of study drug (OLZ, 10–20 mg/d in 5-mg increments; QUE, 300–700 mg/d in 100-mg increments). Dosage increases could occur at 7-day intervals after visit 4. Dosage decreases could occur at any time; however, the dose could not decrease below 10 mg/d for OLZ or 300 mg/d for QUE. Patients who required more than 2 dose decreases or dosages less than the minimum allowed were discontinued from the study. Dosing was flexible, and investigators were encouraged to use the highest doses necessary in both treatment groups. All study medication was administered twice daily. Each patient was treated at community mental health centers and assigned case managers, who developed a 6-month treatment plan for illness management and recovery in collaboration with the patient.

Patients were assigned to treatment groups based on a computer-generated randomization code. The randomization was balanced by using permuted blocks and was stratified by site. All study medication was identical in appearance and was dispensed to subjects by study site personnel. Olanzapine was administered in 5- and 10-mg capsules. Quetiapine was administered in 25- , 100- , and 200-mg dose capsules. Study medication was packaged in blister cards. Each card contained a week's (7 days plus 2 extra days) supply of medication.

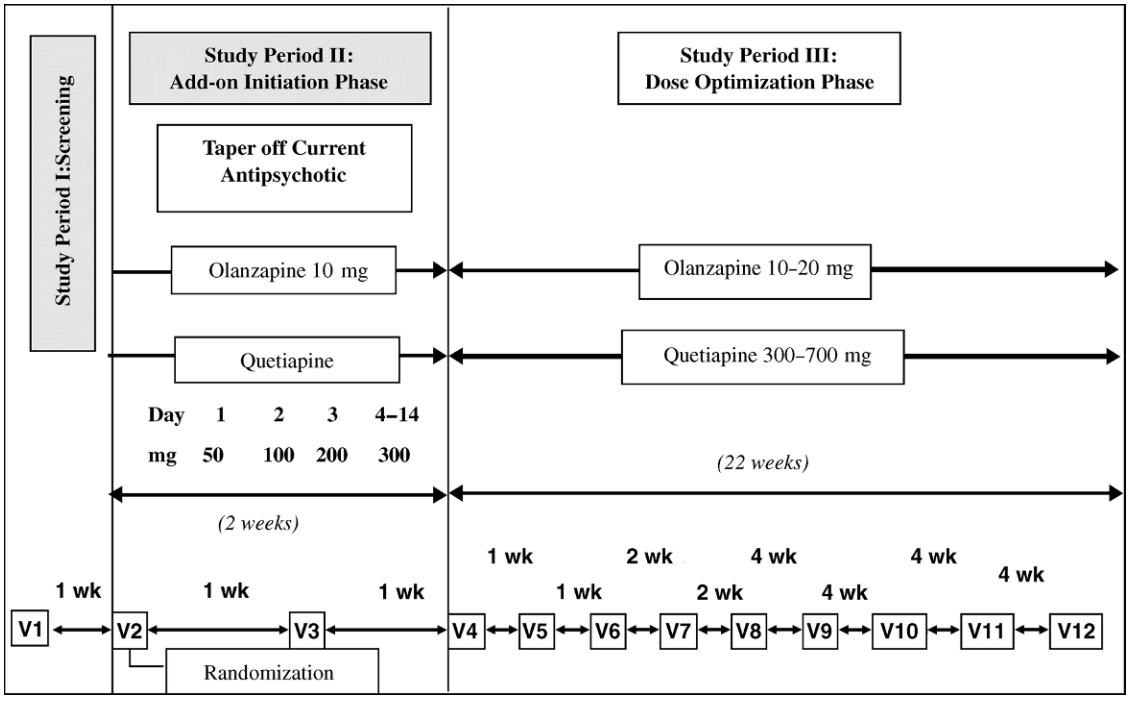

FIGURE 1. Study design.

Outcome Measures

The Scale for Assessment of Negative Symptoms (SANS)[15] was the primary outcome measure in this study. Secondary outcome measures included levels of psychopathology, levels of functioning, and medication safety and tolerability. Psychopathology was measured with the PANSS,[16] including total score and scores on the PANSS positive, negative, and general psychopathology subscales; the Clinical Global Impression Scale (CGI)[17]; the Calgary Depressive Scale[18]; and the Illness factors subscale of the Case Manager Rating Scale–Plus (CMRS+).[19–21] Levels of functioning were measured with the Global Assessment of Functioning, *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, the Quality of Life Scale (QLS)[22] and its 4 subscales, the psychosocial factors subscale of the CMRS+,[19–21] and the Patient Functioning Questionnaire (PFQ), a clinician-rated measure developed for this study.

The PFQ was designed to assess the following: (*a*) patient's level of participation in psychosocial or occupational rehabilitation programs (6-point scale; 1 = no participation, 6 = highest level of participation), (*b*) level of effort the patient exhibited in the program (5-point scale; 1 = no effort, 5 = highest effort level), and (*c*) change in level of participation (7-point scale; 1 = greatest improvement, 7 = greatest decline).

Treatment-emergent adverse events and changes in laboratory analytes were assessed throughout the study. Scales designed to measure EPS were also used, including the modified version of the Simpson-Angus Scale[23] for pseudoparkinsonian symptoms, the Barnes Akathisia Scale[24] for akathisia, and the Abnormal Involuntary Movement Scale[17] for tardive dyskinesia. In addition, the use of anticholinergic medication was assessed.

Statistical Methods

Treatment group differences on baseline characteristics were compared using analysis of variance for continuous variables and Fisher exact test for categorical variables. Change from baseline to end point (last observation carried forward [LOCF]) on continuous variables, such as SANS, GAF, QLS, CMRS, PANSS, Calgary Depressive Scale, and EPS, was analyzed for treatment effect using analysis of variance with terms for treatment, site, and treatment-by-site interaction. Wilcoxon signed rank test was used to test within-group significance from 0 based on the changes. All categorical outcome measures, such as study completion rates and rates of adverse events, were compared between treatments using Fisher exact test. Kaplan-Meier estimators of time to discontinuation were calculated for both treatment groups, and the treatment group difference was tested using the log-rank test.

Per protocol, all data analyses were performed on an intent-to-treat basis. For the analysis of change from baseline to end point, only patients with baseline and at least 1 postbaseline measure were included. All *P* values were based on 2-tailed tests; *P* values less than 0.05 were selected to represent a statistically significant difference. All analyses were conducted with Statistical Application Software, (SAS Worldwide Headquarters, SAS Institute Inc., Cary, NC).

RESULTS

Patient Characteristics

A total of 346 patients were randomized to either OLZ (n = 171) or QUE (n = 175) treatment. The 2 treatment groups did not differ significantly in patient demographics, illness characteristics, or baseline functioning (Table 1). Mean baseline GAF score was 43, indicating serious functional impairment at study entry. Mean baseline body weight of approximately 90 kg and mean baseline body mass index (BMI) of more than 30 indicated that patients were overweight or obese at study entry.

Dosing

The mean modal dose during the study was 15.6 ± 4.3 mg/d for OLZ-treated patients and 455.8 ± 156.3 mg/d for QUE-treated patients. The percent of patients on OLZ therapy who had a modal dose of 10, 15, and 20 mg/d over the course of the study were 32.3%, 24.0%, and 43.7%, respectively. For patients on QUE therapy, the percentage of patients with a modal dose of 300, 400, 500, 600, and 700 mg/d was 35.3%, 26.3%, 7.0%, 10.3%, and 21.2%, respectively.

Efficacy Measures

Negative Symptoms

Over the 6-month study period, both treatment groups showed a significant reduction in negative symptoms (Table 2). The OLZ treatment group demonstrated a mean

TABLE 1. Patient Baseline Characteristics*

	OLZ (n = 171)	QUE (n = 175)
Sex (male/female %)	66.7/33.3	65.1/34.9
Age (years, mean ± SD)	41.67 ± 9.53	40.45 ± 9.61
Race (%)		
White	53.2	50.3
African descent	37.4	37.1
Hispanic	7.6	9.7
Other	1.8	2.9
Diagnosis (%)		
Schizophrenia	66.1	66.9
Schizoaffective bipolar	25.1	22.9
Schizoaffective depression	8.8	10.3
Onset age of psychosis (years, mean ± SD)	24.16 ± 8.73	22.59 ± 7.62
Duration of Illness (years, mean ± SD)	17.57 ± 9.65	17.78 ± 9.39
Baseline GAF (mean ± SD)	43.24 ± 8.71	43.19 ± 9.73
Baseline body weight (kg, mean ± SD)	91.79 ± 20.72	89.49 ± 22.40
Baseline BMI (mean ± SD)	31.15 ± 7.00	30.25 ± 6.64

*There were no significant differences between treatment groups in baseline characteristics.

TABLE 2. Efficacy Measures Mean Change From Baseline to End Point

			Baseline		End Point		Change		*P*	
Measure	**Therapy**	**n**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Within Group**	**Vs QUE**
SANS total score	OLZ	166	61.4	17.4	49.4	20.6	−12.0	18.9	<0.001	0.090
	QUE	169	60.1	18.4	51.8	21.1	−8.3	20.1	<0.001	
Affective flattening/blunting	OLZ	166	2.8	0.9	2.2	1.0	−0.6	1.0	<0.001	0.859
	QUE	169	2.7	1.0	2.2	1.1	−0.5	1.0	<0.001	
Alogia	OLZ	166	2.4	1.1	1.8	1.2	−0.6	1.2	<0.001	0.586
	QUE	169	2.3	1.1	1.8	1.2	−0.5	1.2	<0.001	
Avolition-Apathy	OLZ	166	2.8	1.0	2.3	1.2	−0.5	1.2	<0.001	0.598
	QUE	169	2.9	1.1	2.5	1.2	−0.4	1.3	<0.001	
Anhedonia-Asociality	OLZ	166	3.3	0.9	2.9	1.1	−0.4	1.1	<0.001	0.201
	QUE	169	3.3	0.9	3.0	1.1	−0.3	1.2	0.005	
Attention	OLZ	166	2.6	1.2	2.1	1.2	−0.5	1.1	<0.001	0.163
	QUE	169	2.7	1.2	2.4	1.2	−0.3	1.2	0.003	
PANSS total score	OLZ	166	84.1	12.8	72.8	19.3	−11.3	18.3	<0.001	0.151
	QUE	169	85.2	14.8	78.0	22.8	−7.2	21.2	<0.001	
PANSS positive score	OLZ	167	18.3	4.7	16.0	5.7	−2.3	5.4	<0.001	0.022
	QUE	169	19.0	5.2	18.3	7.1	−0.7	6.6	0.176	
PANSS negative score	OLZ	167	25.5	3.7	21.5	6.1	−4.0	5.8	<0.001	0.919
	QUE	169	25.5	4.0	21.9	6.5	−3.6	6.0	<0.001	
PANSS general psychopatholgy score	OLZ	166	40.4	7.6	35.5	10.0	−4.8	9.7	<0.001	0.057
	QUE	169	40.7	8.3	37.9	11.2	−2.8	10.9	0.002	
CGI severity	OLZ	123	4.2	0.6	3.7	0.9	−0.5	1.0	<0.001	.020
	QUE	137	4.3	0.7	4.1	1.1	−0.2	1.1	0.020	
CGI improvement	OLZ	118	—	—	3.2	1.1	−0.8	1.2	<0.001	<0.001
	QUE	125	—	—	3.8	1.6	−0.2	1.6	0.149	
CDS total score	OLZ	165	6.0	4.8	4.3	4.6	−1.7	4.5	<0.001	0.428
	QUE	169	5.8	4.6	4.4	4.7	−1.4	4.8	<0.001	
CMRS+−illness factor	OLZ	148	32.9	7.3	29.0	7.4	−3.9	7.4	<0.001	0.021
	QUE	148	33.2	7.6	31.4	8.9	−1.8	8.0	0.002	

CDS indicates Calgary Depressive Scale.

reduction from baseline to end point (LOCF) on the SANS total score of 12.0 points, and the QUE treatment group demonstrated a mean reduction of 8.3 points. This between-group difference was not significant (P = 0.09). No differentiation was made between primary and secondary negative symptoms.

Other Efficacy Measures

A summary of changes in other measures of efficacy after treatment with OLZ or QUE is provided in Table 2. In general, both groups showed significant improvement in most measures of psychopathology. The OLZ group demonstrated significantly greater improvement than the QUE group in PANSS positive subscale (P = 0.022), CGI severity scale (P = 0.020), and CGI improvement scale (P < 0.001). In addition, case managers reported significantly greater improvement in CMRS+−illness factors in patients treated with OLZ compared with patients treated with QUE (P = 0.021).

Functional Outcomes

Olanzapine-treated patients demonstrated significantly greater improvement in the GAF score compared with patients treated with QUE (P = 0.01; Table 3). A significantly greater proportion of patients in the OLZ treatment group as compared with the QUE treatment group achieved a GAF increase of at least 5 points (half decile) (60.9% and 40.0%, respectively, P < 0.001) and 10 points (full decile) (42.8% and 29.3%, respectively, P = 0.024).

On the QLS, OLZ-treated patients achieved significantly greater improvement on the Instrumental Role domain than did the QUE treatment group. The QLS Instrumental Role domain measures the level of, satisfaction with, and occupational role functioning.

On the PFQ, significantly greater improvement in effort level was observed in the OLZ treatment group (0.52 ± 1.36, P < 0.001) compared with that observed in the QUE treatment group (0.06 ± 1.39, P = 0.80) (P = 0.014).

The treatment groups did not differ significantly on any of the other functional measures (ie, QLS total, and QLS

TABLE 3. Functional Outcome Measures Mean Change From Baseline to End Point

			Baseline		End Point		Change		*P*	
Measure	**Therapy**	**n**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Within group**	**Vs QUE**
GAF	OLZ	138	43.2	8.7	49.5	13.3	6.2	11.7	<0.001	0.007
	QUE	140	43.2	9.7	45.6	14.6	2.4	14.0	0.089	
QLS total score	OLZ	143	51.7	18.9	55.9	23.5	4.2	17.9	0.005	0.632
	QUE	143	53.4	20.6	55.8	23.2	2.4	18.5	0.230	
Common objects/activities	OLZ	144	6.2	2.4	6.4	2.5	0.2	2.1	0.394	0.926
	QUE	143	6.4	2.7	6.6	2.7	0.2	2.2	0.196	
Instrumental role	OLZ	144	7.2	6.3	9.0	7.3	1.8	5.6	<0.001	0.029
	QUE	144	7.8	6.3	8.2	7.3	0.4	5.2	0.624	
Interpersonal relations	OLZ	144	18.3	8.5	19.6	9.6	1.3	8.5	0.063	0.267
	QUE	144	18.5	9.3	19.7	9.2	1.2	8.6	0.081	
Intrapsychic foundation	OLZ	144	19.9	6.9	20.8	7.6	0.9	6.3	0.041	0.609
	QUE	143	20.8	7.1	21.2	8.1	0.4	7.1	0.312	
CMRS+–psychosocial function	OLZ	100	31.4	8.4	29.5	9.2	−1.9	5.7	<0.001	0.482
	QUE	95	29.8	8.3	29.1	8.4	−0.6	6.8	0.178	
PFQ–level of participation	OLZ	124	2.9	2.2	3.3	2.2	0.4	1.9	0.013	0.810
	QUE	126	3.0	2.2	3.4	2.2	0.4	1.9	0.025	
PFQ–level of effort	OLZ	124	2.4	1.4	3.0	1.5	0.5	1.4	<0.001	0.014
	QUE	125	2.6	1.5	2.7	1.5	0.1	1.4	0.804	
PFQ–change in functioning	OLZ	124	4.0	0.8	3.7	0.9	−0.3	1.1	0.002	0.144
	QUE	125	4.0	0.9	4.0	1.1	−0.1	1.4	0.764	

domain scores for common object/activities, interpersonal relations and intrapsychic foundation, CMRS+–psychosocial functioning scale, and the PFQ-level of participation and change in functioning).

Treatment Duration

Olanzapine-treated patients were more likely to continue the course of therapy during the 6-month study with a completion rate of 52.6% compared with 37.7% for the QUE group ($P = 0.007$). The difference in treatment duration was mainly driven by a significantly greater number of QUE-treated patients discontinuing the study because of poor response or worsening of symptoms (32.0% and 12.9%, respectively, $P < 0.0001$). All other reasons for treatment discontinuation were not significantly different between treatment groups (Table 4).

Kaplan-Meier curves estimating time to study discontinuation revealed a significant group difference in treatment discontinuation ($P = 0.010$), with fewer patients treated with OLZ discontinuing the study compared with patients treated with QUE (Fig. 2). The median time (95% confidence interval) to treatment discontinuation from any cause was approximately 4 months (3–6 months) for patients in the QUE treatment group. The median time to treatment discontinuation could not be estimated for the OLZ treatment

TABLE 4. Reasons for Early Study Discontinuation

	OLZ (n = 171)	QUE (n = 175)	*P*
Psychiatric adverse event*	12.9	32.0	<0.0001
Nonpsychiatric adverse event†	2.9	6.3	0.200
Criteria not met/compliance	10.5	5.7	0.117
Lost to follow-up	7.0	5.1	0.506
Patient decision	11.6	11.4	1.00
Physician decision	2.3	1.1	0.444
Sponsor decision	0	0.5	1.000

*Refers to adverse events reflecting poor response or symptom worsening for psychiatric symptoms, depression, or anxiety.
†Refers to adverse events reflecting intolerability of medication.

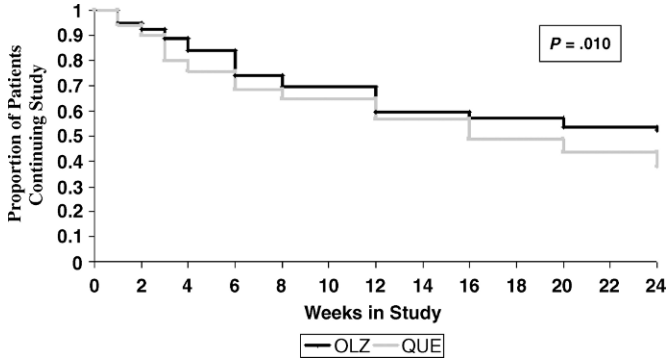

FIGURE 2. Time to all-cause study discontinuation (treatment difference, $P = 0.010$).

group because the rate of study discontinuation was less than 50%.

Safety and Tolerability

Treatment-emergent adverse events were defined as adverse events that occurred or worsened after treatment with the study drugs. The following treatment-emergent adverse events were associated with QUE treatment significantly more often than with OLZ treatment: psychosis (OLZ, 2.9%; QUE, 9.7%; $P = 0.014$), pain (OLZ, 2.3%; QUE, 7.4%; $P = 0.044$), and anorexia (OLZ, 0%; QUE, 4.6%; $P = 0.007$). There were no treatment-emergent adverse events that occurred significantly more often with OLZ than with QUE therapy. Events with a rate of 10% or greater in either treatment group included headache (OLZ, 8.8%; QUE, 14.3%; $P = 0.131$) and somnolence (OLZ, 24%; QUE, 22.9%; $P = 0.899$).

Patients on OLZ therapy had a mean weight increase of 1.03 ± 5.78 kg over the 6-month treatment period, whereas patients on QUE therapy had a mean increase of 0.39 ± 4.74 kg (between-treatment difference, $P = 0.223$). Regarding changes in BMI, an increase in BMI of 0.36 ± .9.5 was observed in the OLZ treatment group and an increase of 0.12 ± 1.57 in the QUE treatment group (between-treatment difference, $P = 0.174$). Two (1.2%) patients on OLZ therapy and 1 (0.6%) patient on QUE therapy reported treatment-emergent weight gain during the study (between-treatment difference, $P = 0.62$). No patient reported weight gain as the reason for study discontinuation.

Regarding changes in laboratory analytes, several statistically significant differences were noted between the OLZ and QUE treatment groups (Table 5). All of the observed differences were relatively small.

The treatment groups did not differ significantly on change in the Simpson-Angus Scale total score, the Barnes Akathisia Scale global measure, or the Abnormal Involuntary Movement Scale total score. There were no differences in the use of anticholinergic medication between the 2 treatments.

DISCUSSION

This study compared the effects of OLZ and QUE in reducing negative symptoms and in improving overall functioning of patients with prominent negative symptoms who were experiencing moderate difficulty in social or occupational functioning. Contrary to our hypothesis, no statistically significant difference was observed in the reduction of negative symptoms during the 6-month study period between patients treated with OLZ and those treated with QUE, as both treatment groups experienced significant reductions in negative symptoms. Analysis of secondary outcome measures revealed, however, significantly greater improvement in positive symptoms, in global measures of psychopathology, and in overall level of functioning in OLZ-treated patients compared with those treated with QUE. Significantly more patients in the OLZ treatment group completed the 6-month study compared with patients in the QUE treatment group, a finding which may have influenced the observed treatment group differences and led to greater clinical and functional improvements in the OLZ-treated group.

The current findings are inconsistent with the results of several meta-analyses demonstrating an advantage of treatment with OLZ and other atypical antipsychotics, including clozapine and risperidone (but not QUE), in reducing negative symptoms compared with typical antipsychotics.[12–14] More recently, a comparator study has reported significant improvement in negative symptoms following treatment with QUE compared with haloperidol decanoate.[25] These findings as a whole may suggest greater benefit of QUE in treating negative symptom than previously reported.

One possible caveat to the current analysis might have been the inclusion of patients with the deficit syndrome who

TABLE 5. Laboratory Analytes Showing Significant Between-group Differences Mean Change From Baseline to End Point

			Baseline		Change		*P*	
Measure	**Therapy**	**n**	**Mean**	**SD**	**Mean**	**SD**	**Within Group**	**Vs QUE**
Hematocrit 1 (unit given)*	OLZ	148	0.43	0.04	0.00	0.03	0.558	0.014
	QUE	152	0.43	0.04	0.00	0.03	0.189	
Mean cell hemoglobin concentration (mmol/L-Fe)	OLZ	148	20.97	1.00	0.13	0.93	0.241	0.002
	QUE	152	21.15	0.92	−0.13	1.00	0.110	
Leukocyte count (GI/L)	OLZ	148	7.78	2.43	0.36	2.27	0.196	0.003
	QUE	152	8.20	2.55	−0.48	2.05	0.002	
Neutrophils, segmented (GI/L)	OLZ	148	4.85	2.08	0.36	2.09	0.165	0.004
	QUE	152	5.27	2.17	−0.40	1.92	0.002	
Mean cell volume (CMV) (fL)	OLZ	148	87.80	6.38	−0.16	3.57	0.613	0.012
	QUE	152	87.58	5.57	0.58	3.83	0.095	
Uric acid (μmol/L)	OLZ	150	344.55	92.35	18.24	72.68	0.003	0.001
	QUE	153	346.66	82.56	−4.16	55.32	0.521	

*Although a significant group difference in hematocrit values was observed, the changes were relatively small (OLZ, 0.0004; QUE, 0.0024).

present with severe or prominent negative symptoms and who tend to be less responsive to treatment with antipsychotics and therefore potentially less sensitive to between-treatment differences.[26] To explore the possibility that treatment responses were differentially affected by inclusion of deficit patients, a proxy measure was used to identify deficit patients in each group.[27] We found that relatively few study participants met criteria for the deficit syndrome, and the numbers were similar in both treatment groups (n = 10, OLZ; n = 11 QUE; data not shown). This finding suggests that reduction in negative symptoms observed after treatment with OLZ or QUE was not differentially affected by a disproportionately large number of patients with deficit syndrome. The proxy measure is not, however, as valid and reliable as the Schedule for Deficit Syndrome[28] and may have underestimated the true prevalence of deficit syndrome in the study sample.

Although both OLZ and QUE therapy led to a significant reduction in negative symptoms, results from several secondary analyses found a significant advantage for OLZ over QUE therapy on several psychosocial outcome measures (ie, GAF, QLS Instrumental Role domain, and PFQ-effort level). Previous studies have demonstrated a benefit of OLZ in improving patients' psychosocial functioning using the GAF,[29,30] the CMRS+−psychosocial functioning scale,[31,32] the Quality of Life Scale,[33−35] the Seville Quality of Life Questionnaire,[36] and assessment of work-related activities.[35] Less data are currently available to support the efficacy of QUE in enhancing functional outcomes, as noted in recent reviews.[37,38] Although QUE, OLZ, and risperidone therapies were previously found to be associated with comparable improvements on psychosocial functioning in a longitudinal naturalistic observational study,[39] QUE was not found to offer significantly greater psychosocial benefits when compared with haloperidol in a randomized, rater-blinded, 6-month study of patients with schizophrenia.[40]

It was somewhat surprising to find that the greater improvement in functioning did not seem to parallel the improvement in negative symptoms observed in both treatment groups. Improvement in other symptom domains may also be relevant to functioning, and in the present study, significantly greater improvement in positive symptoms was observed in patients treated with OLZ. There is some evidence showing that positive symptoms can negatively affect psychosocial and occupational functioning,[6,41,42] although several studies have suggested otherwise.[1,4] In general, when a correlation between positive symptoms and functional outcomes is observed, the magnitude is usually smaller than that observed for other outcome measures such as negative symptoms.[6,7]

Alternatively, the inability to show improvement in functioning in the QUE treatment group in the face of significant improvement in negative symptoms may reflect decreased treatment exposure, as significantly more patients in the OLZ treatment group completed the 6-month study compared with patients in the QUE treatment group. This finding is consistent with the recently published results of the double-blind, active-control CATIE trial sponsored by the National Institute of Mental Health in which time to discontinuation of treatment for any cause was longer in the OLZ group compared with patients treated with QUE or risperidone.[43] Other studies[44,45] reporting discontinuation rates after treatment with OLZ, QUE, risperidone, or haloperidol have also reported a lower rate of study discontinuation in patients treated with OLZ. Longer treatment duration (or a lower rate of study discontinuation) is associated with greater improvements in overall functioning.[46] In addition, previous work has shown that functional improvement tends to follow the reduction in symptoms.[47] Thus, although the relative treatment durations were adequate for both QUE- and OLZ-treated patients to achieve significant improvement in negative symptoms and in other symptom domains, the shorter treatment duration for the QUE treatment group (as a whole) may not have been adequate for significant improvement in functioning.

Of interest, the greater rate of discontinuations observed in the QUE treatment group was attributed primarily to poor response or worsening of symptoms, a category that included worsening of psychosis as well as other psychiatric-related conditions, such as depression and anxiety. This finding may underlie, to some extent, the lack of improvement in positive symptoms that was observed in the QUE treatment group. Furthermore, it highlights the importance of maintaining adequate control of patients' psychiatric symptoms, that is, for patients to achieve maximal benefits in functioning, they must stay in treatment, and in the present study, this continuity appeared to require adequate control of positive symptoms.

In addition, the tolerability of an antipsychotic medication can affect outcome measures by impacting a patient's willingness to stay on medication.[48] Very few differences in tolerability were observed between the 2 treatment groups with monitoring up to 6 months of treatment. In fact, no adverse events were significantly greater with OLZ, despite greater exposure to medication treatment. Both groups demonstrated an increase in body weight with no between-group differences, although the average increase in weight was relatively small ($\sim$1 kg). However, patients were already overweight to obese at the beginning of the study (average BMI, $\geq$30), reducing the likelihood of further weight gain.[49] In the CATIE trial,[43] patients in the OLZ-treatment group gained more weight than those treated with QUE, suggesting that weight gain observed during antipsychotics treatment may well reflect the patient population studied. Overall, results of this study showed no clinically relevant differences in tolerability for patients treated with OLZ or QUE.

LIMITATIONS

Current findings need to be evaluated in the context of the study's limitations. First, this study selected patients with prominent negative symptoms and poor functioning. Therefore, the findings are primarily generalizable to that population. Second, the study used LOCF analyses, per

protocol. Using this statistical approach may bias results when there are treatment group differences in dropout rates-as was the case in the present study. It is important to note, however, that the only group difference in study discontinuation rates was the result of a poor symptom response, suggesting that had these QUE-treated patients remained in the study, their outcomes might not have improved much. Although a completers analysis may help address this concern, it would also introduce bias by ignoring the outcomes of poor responders to each treatment group.

A number of differences in psychopathology and overall functioning were noted between the 2 treatment groups in favor of OLZ, although the current analyses were not powered specifically for these secondary measures, and no adjustment was made for multiple comparisons. Further study would be useful to replicate and evaluate the clinical relevance of these secondary findings.

Another potential study limitation may be dosing strategies. Although dosing of OLZ and QUE followed guidelines provided in each product's label and are relatively consistent with doses recently reported in the treatment of chronic schizophrenia (OLZ[50–52] and QUE[25,50,53]), recent dosing recommendations have suggested a more rapid titration schedule for QUE.[54,55] Review of the survival curves of early study discontinuation did not reveal a treatment difference in the proportion of patients discontinuing the study during the 2-week titration period, although the potential impact of a slower versus accelerated titration rate on subsequent responses in patients who are flexibly dosed is unclear. It is not possible in the current study to determine the effects of titration on treatment outcomes. Moreover, there have been some speculations that higher doses of QUE may produce better outcomes,[56] but the available data do not support this claim.[57] The flexible dose design of the current study does not allow determination of a dose response relationship. Further exploration of the dose response of QUE will be useful.

CONCLUSIONS

Among patients with schizophrenia or schizoaffective disorder with prominent negative symptoms and poor functioning, negative symptoms improved significantly after treatment with OLZ or QUE. Olanzapine therapy was associated with greater benefit for positive symptoms, global psychopathology, and overall level of functioning than QUE therapy, although support for these differential outcomes will require subsequent confirmation.

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