Research Article

QUETIAPINE IS EFFECTIVE AGAINST ANXIETY AND DEPRESSIVE SYMPTOMS IN LONG-TERM TREATMENT OF PATIENTS WITH SCHIZOPHRENIA

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This analysis of data from the open-label extension (OLE) phases of three randomized clinical trials of quetiapine in patients with schizophrenia (n = 415) was undertaken to investigate whether the initial improvements in anxiety and depressive symptoms were maintained during long-term treatment. The mean (95% confidence interval [CI]) change from the acute phase baseline in the Factor I score of the Brief Psychiatric Rating Scale (BPRS), which includes somatic concern, anxiety, guilt feelings, and depression, was calculated at the OLE baseline and at various time points up to 156 weeks. After 6 weeks of treatment with quetiapine during the acute phase, the mean (95% CI) change in the BPRS Factor I score was −1.13 (−1.23, −1.04) and after 156 weeks, it was −1.33 (−1.78, −0.87). Therefore, the efficacy of quetiapine for the treatment of anxiety and depressive symptoms is maintained in long-term treatment. Depression and Anxiety 20:44–47, 2004. *© 2004 Wiley-Liss, Inc.*

Key words: *psychiatry; antipsychotic agents; behavioral symptoms; clinical trials; treatment efficacy*

INTRODUCTION

The therapeutic management of schizophrenia continues to represent a considerable challenge, particularly with regard to patient compliance. As the treatment options for schizophrenia have developed, expectations have shifted from the primary goal of controlling positive symptoms, to a more comprehensive approach. The aim is now to provide relief across all symptomatic domains of schizophrenia (positive, negative, cognitive, mood), prevent relapse and, importantly, to improve compliance with treatment over time [Kane, 2001]. The introduction of atypical antipsychotics has helped clinicians in meeting these treatment expectations.

Quetiapine is one such atypical antipsychotic, with results from three double-blind placebo-controlled trials showing efficacy in the short-term treatment of positive and negative symptoms [Arvanitis et al., 1997; Borison et al., 1996; Small et al., 1997]. It has also been shown to be efficacious in reducing cognitive impairment [Purdon et al., 2001] and in improving affective symptoms [De Nayer et al., 2003; Purdon et al., 2001]. Furthermore, its effectiveness in the treatment of schizophrenia has been shown to be maintained in long-term usage [Tandon, 2003].

One factor that impacts considerably upon treatment compliance is patients' quality of life; changes in anxiety and depression correlate with individual changes over time in subjective quality of life [Priebe et al., 2000]. Although typical neuroleptics also alleviate symptoms of anxiety and depression, they are generally less well tolerated than newer atypical

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antipsychotics. This study focuses on affective and anxiety symptoms associated with schizophrenia, and employs a post hoc analysis to examine whether the initial improvements in anxiety and depressive symptoms are maintained during long-term treatment with quetiapine.

PATIENTS AND METHODS

STUDY DESIGN AND PATIENT POPULATION

This study consisted of an analysis of data from the open-label extension (OLE) phases of three randomized, clinical trials of quetiapine in patients with schizophrenia [Arvanitis et al., 1997; Copolov et al., 2000; King et al., 1998]. The three studies each included a double-blind (acute) phase of 6 weeks duration comprising the following quetiapine dose groups: five fixed-dose quetiapine groups (75, 150, 300, 600, and 750 mg/day) [Arvanitis et al., 1997]; three fixed-dose quetiapine groups (450 mg/day given in two or three divided doses daily, and 50 mg/day given twice daily) [King et al., 1998]; and flexible dosing up to a maximum of 800 mg/day, depending on an individual's clinical response and tolerance [Copolov et al., 2000]. After completion of the acute phase, patients were eligible to continue open-label treatment with flexible-dose quetiapine for up to 4 years, on a compassionate need basis. The present analysis included only patients who completed the 6-week acute phase, continued into the OLE phase and had a mean dose of quetiapine between 150–750 mg/day.

EFFICACY ASSESSMENT

Anxiety and depressive symptoms were assessed using the score on Factor I of the Brief Psychiatric Rating Scale (BPRS), which includes the following BPRS items: somatic concern; anxiety; guilt feelings, and depression. The mean (95% confidence interval [CI]) change in BPRS Factor I score from the acute phase baseline was calculated at the OLE baseline and at various time points up to Week 156 of the OLE phase, using each patient's baseline score and an observed cases (OC) approach.

RESULTS

Four hundred fifteen patients were included in this analysis and their demographic characteristics are shown in Table 1, along with the characteristics of subgroups of patients completing 24, 52, 104, and 156 weeks of treatment. There were twice as many men than women, which reflects the populations of the three trials on which this analysis is based and the higher incidence of schizophrenia in men than in women in the general population. At the OLE baseline,

TABLE 1. Patient demographics

		Patients completing various timepoints (weeks)			
Demographic variable	Patients entering OLE	24	52	104	156
Total patients	415	173	96	47	33
Geady, *n* (%)					
Male	278 (67.0)	115 (66.5)	63 (65.6)	25 (53.2)	17 (51.5)
Female	137 (33.0)	58 (33.5)	33 (34.4)	22 (46.8)	16 (48.5)
Age, *n* (%)[a]					
<40 years	263 (63.4)	112 (64.7)	65 (67.7)	30 (63.8)	23 (69.7)
40≤64 years	151 (36.4)	60 (34.7)	30 (31.3)	16 (34.0)	9 (27.3)
≥65 years	1 (02)	1.0 (.6)	1 (1.0)	1 (2.1)	1 (3.0)
Ethnic origin, *n* (%)					
White	376 (90.6)	159 (91.9)	89 (92.7)	44 (93.6)	31 (93.9)
Black	21 (5.1)	8 (4.6)	4 (4.2)	2 (4.3)	1 (3.0)
Asian/Oriental	5 (1.2)	2 (1.2)	1 (1.0)	1 (2.1)	1 (3.0)
Hispanic	9 (2.2)	2 (1.2)	1 (1.0)	–	–
Other	4 (1.0)	2 (1.2)	1 (1.0)	–	–
DSM schizophrenia subtype, *n* (%)					
Catatonic	11 (2.7)	3 (1.7)	–	–	–
Disorganised	44 (10.6)	15 (8.7)	9 (9.4)	4 (8.5)	2 (6.1)
Paranoid	271 (65.3)	115 (66.5)	67 (69.8)	35 (74.5)	24 (72.7)
Undifferentiated	89 (21.5)	40 (23.1)	20 (20.8)	8 (17.0)	7 (21.2)
Mean quetiapine dose, mg/day	490.7	448.0	451.0	434.3	432.1

[a]At first exposure to quetiapine during this study.

the mean (95% CI) change from acute phase baseline in BPRS Factor I score for all evaluable patients was −1.13 (−1.23, −1.04). After 52 weeks, the mean (95% CI) change from acute phase baseline was −1.53 (−1.73, −1.34) ($n = 96$) and after 156 weeks, it was −1.33 (−1.78, −0.87) ($n = 33$). It can be seen that the improvement effect in anxiety and depressive symptoms, which was seen after 6 weeks of treatment with quetiapine, was also seen during the OLE phase, compared with acute phase baseline (Fig. 1). Therefore, the efficacy of quetiapine for the treatment of anxiety and depressive symptoms is maintained in long-term treatment.

Analysis of those patients who completed 156 weeks of treatment confirmed the results based on all evaluable patients (Fig. 1). The scores at the same time points as those who completed the study for those who withdrew are included for comparison in Table 2.

DISCUSSION

These results provide evidence that the initial improvement effects in depressive symptoms and anxiety in patients with schizophrenia are maintained throughout long-term treatment with quetiapine. This is of considerable significance in light of findings that anxiety and depression are among factors shown to correlate negatively with adherence to treatment [Young et al., 1986], with patients' initial subjective experience during antipsychotic therapy being a major predictor of compliance [Naber and Karow, 2001]. The impact of poorly controlled affective symptoms on patients' quality of life was investigated in a study conducted by Huppert et al. [2001]. This showed that more severe depressive symptoms, as measured using the BPRS, were associated with lower general life satisfaction and lower satisfaction with daily living, finances, health and social life. Also, higher anxiety scores on the BPRS correlated with less satisfaction with global quality of life, daily activities, family, health, and social relationships, despite controlling for positive symptoms, negative symptoms, or depressive symptoms, and that no other symptoms of schizophrenia were as strongly associated with subjective quality of life [Huppert et al., 2001].

Previous experience with typical neuroleptics suggests that these agents alleviate symptoms of anxiety and depression in schizophrenia [Budden, 1979;

TABLE 2. Mean BPRS Factor I score for patients who continued into the OLE phase, split by those who withdrew and those who completed 156 weeks of quetiapine treatment

	Mean Factor I score	
	Withdrawn (n)[a]	Completed (n)
Acute phase start	2.26 (382)	2.01 (33)
OLE baseline	1.13 (382)	.84 (33)
Week 24	1.13 (140)	.67 (33)
Week 52	0.93 (64)	.54 (33)
Week 104	0.95 (14)	.67 (33)
Week 156	n/a (–)	.68 (33)

[a]Scores represent the last observed value for patients who withdrew from the study before Week 156.
n/a = not applicable.

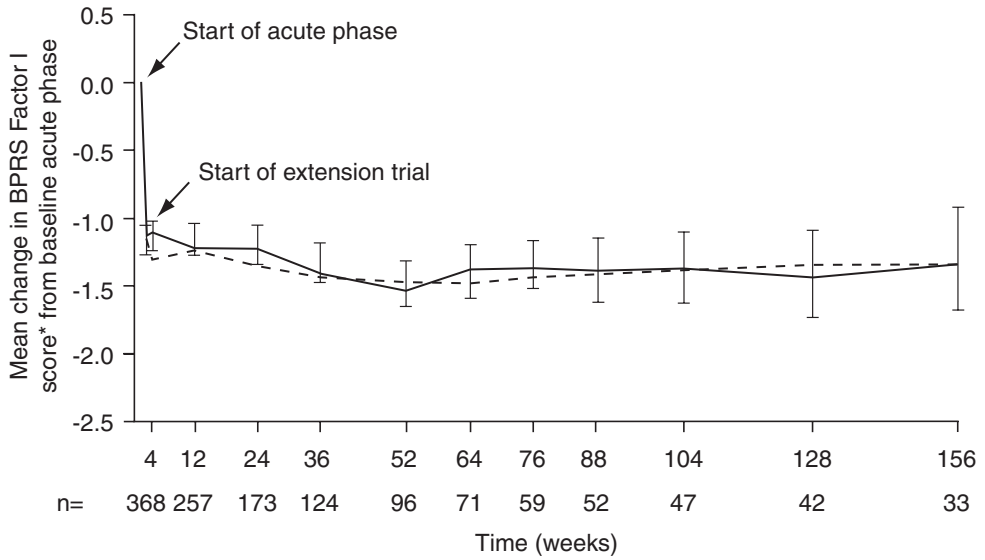

Fig. 1. Mean (95% CI) change from acute phase baseline in BPRS Factor I score during OLE treatment using an observed cases (OC) approach. The dashed line represents the mean change in score from acute phase baseline for the 33 completers. Quetiapine (150–750 mg/day) mean daily dose. Open-label extension data from three acute phase studies. *Includes somatic concern, anxiety, guilt feelings, and depression.

Dufresne et al., 1993]. More recently, data from short-term trials have also demonstrated that quetiapine and other atypical antipsychotics are effective in treating anxiety and depressive symptoms, although differences exist between individual agents [Azorin et al., 2001; Conley and Mahmoud, 2001; De Nayer et al., 2003; Purdon et al., 2001]. For example, greater reductions in the severity of anxiety and depressive symptoms were demonstrated with risperidone compared with olanzapine among patients completing an 8-week, double-blind study in 377 patients with schizophrenia or schizoaffective disorder [Conley and Mahmoud, 2001].

Formal clinical trial data to support the long-term efficacy of the atypical antipsychotics in the treatment of anxiety and depressive symptoms are lacking. A possible explanation for this is that there are limitations of such long-term analyses, one of which is that patients are invariably lost to follow-up, or withdraw from treatment for various reasons. Because the OLE treatment phase had less rigorous objectives than the acute phase of each of the three trials, patients were not monitored as frequently in the present study, and it is considered that they were therefore more likely to discontinue treatment.

In summary, it would seem that quetiapine is effective in improving anxiety and depressive symptoms associated with schizophrenia. Although data to show that this effect is maintained with long-term therapy are limited, it is apparent from the results of short-term studies that there are differences in efficacy between the various atypical antipsychotics. The results from the present analysis indicate that the improvement effect of quetiapine in anxiety and depressive symptoms is maintained in the long-term treatment of patients with schizophrenia; this may therefore impact favorably upon patient compliance with antipsychotic treatment.

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