Research Article

QUETIAPINE ADJUNCT TO SELECTIVE SEROTONIN REUPTAKE INHIBITORS OR VENLAFAXINE IN PATIENTS WITH MAJOR DEPRESSION, COMORBID ANXIETY, AND RESIDUAL DEPRESSIVE SYMPTOMS: A RANDOMIZED, PLACEBO-CONTROLLED PILOT STUDY

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This double-blind, placebo-controlled study examined the efficacy and tolerability of quetiapine in combination with selective serotonin reuptake inhibitors (SSRIs)/venlafaxine in 58 patients with major depressive disorder, comorbid anxiety symptoms (HAM-A-14 score $\geq$14), and residual depressive symptoms (HAM-D-17 score $\geq$18, CGI-S score $\geq$4). Patients had received an SSRI/venlafaxine (at a predefined therapeutic dose) for $\geq$6 weeks. Overall, 62% (18/29) of quetiapine- and 55% (16/29) of placebo-treated patients completed the study. The mean change in HAM-D and HAM-A total scores from baseline to Week 8 (primary endpoint) was significantly greater with quetiapine (mean dose 182 mg/day) than placebo: −11.2 vs. −5.5 (P = .008) and −12.5 vs. −5.9 (P = .002), respectively. The onset of quetiapine efficacy (HAM-D/HAM-A/CGI-I) was rapid (by Week 1) and continued through to Week 8. Significant differences (P < .05) from baseline to Week 8 were observed between groups in 7/17 HAM-D (including feelings of guilt, suicide) and 6/14 HAM-A items (including tension, cardiovascular symptoms). Response ($\geq$50% decrease in total score) was higher for quetiapine than placebo: HAM-D, 48% vs. 28% (not significant, NS); HAM-A, 62% vs. 28% (P = .02). Remission (total score $\leq$7) was higher for quetiapine than placebo: HAM-D, 31% vs. 17% (NS); HAM-A, 41% vs. 17% (NS). CGI-S, CGI-I, and the Global Assessment Scale showed that quetiapine was significantly more effective than placebo. For quetiapine, adverse events (AEs) were similar to those previously observed; sedation/somnolence/lethargy was the most commonly reported. Here quetiapine was shown to be effective as augmentation of SSRI/venlafaxine therapy in patients with major depression, comorbid anxiety, and residual depressive symptoms, with no unexpected tolerability issues. Further studies are warranted. Depression and Anxiety 24:487–494, 2007.

Key words: *antipsychotic agents; therapeutic use; clinical trial; treatment outcome; depressive disorder, major; anxiety disorders*

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INTRODUCTION

Major depressive disorder with comorbid anxiety is highly prevalent: ≈85% of adults with major depression exhibit significant symptoms of anxiety [Gorman, 1996] and an estimated 58% have a diagnosable anxiety disorder in their lifetime [Kessler et al., 1996]. Comorbid anxiety leads to more severe symptoms, decreased psychosocial functioning, a higher risk of suicide, and a more chronic course compared with major depressive disorder alone [Kessler et al., 1996; Sherbourne and Wells, 1997]. It is also associated with poorer and slower treatment response [Brown et al., 1996; Gorman, 1996].

The selective serotonin reuptake inhibitors (SSRIs) and the serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine are considered first-line treatments for major depressive disorder [CPA and CANMAT, 2001]. Within these classes, individual agents are also indicated for the treatment of anxiety disorders. One of the disadvantages of the SSRIs and SNRIs is that in some patients only a partial response is achieved. Residual symptoms predict recurrence, chronicity, suicidal tendencies, and an increased use of healthcare resources [Judd et al., 2000; O'Leary et al., 2000]. Treatment strategies for patients with major depressive disorder who have not responded to therapy with an SSRI/SNRI include: switching to another antidepressant monotherapy; augmentation with another agent; or combination therapy with another antidepressant agent [Fleck and Horwath, 2005; Kennedy et al., 2001]. Although augmentation or combination therapy is commonly employed in clinical practice, evidence supporting these strategies is limited [Fleck and Horwath, 2005; Dodd et al., 2005; Kennedy et al., 2001]. The benzodiazepines are frequently used to treat sleep and anxiety in addition to SSRI therapy in major depressive disorder and comorbid anxiety; however, cognitive impairment and concerns over the potential for abuse of these agents has limited their use.

The atypical antipsychotics improve the affective symptoms of schizophrenia [Lublin et al., 2005]. In addition, quetiapine monotherapy and olanzapine alone, and in combination with fluoxetine, were effective in studies of bipolar depression [Calabrese et al., 2005; Tohen et al., 2003] and, more recently, quetiapine monotherapy has demonstrated efficacy in the treatment of anxiety symptoms in patients with bipolar I depression [Hirschfeld et al., 2006]. In clinical practice, the atypical antipsychotics are widely used as augmentation therapy in patients with treatment-resistant major depressive disorder [Ostroff and Nelson, 1999; Galynker et al., 2005; Yargic et al., 2004; Pathak et al., 2005; Pitchot and Ansseau, 2001; Papakostas et al., 2005]. Furthermore, there is some indication that atypical antipsychotics have efficacy in the treatment of anxiety symptoms, suggesting their possible clinical utility in major depression and comorbid anxiety [Barnett et al., 2002; Hamner et al., 2003; Adson et al., 2004; Galynker et al., 2005; Schutters et al., 2005; Worthington et al., 2005].

The present study (number D1441C00017) is the first double-blind, placebo-controlled trial of the atypical antipsychotic quetiapine (Seroquel, AstraZeneca Pharmaceuticals), as adjunct to SSRIs or venlafaxine for the treatment of patients with major depressive disorder and comorbid anxiety symptoms, with residual depressive symptoms. The primary aim was to determine the efficacy of quetiapine in this patient population, with the secondary aim of assessing its safety and tolerability when used in combination with SSRIs or venlafaxine.

MATERIALS AND METHODS

PATIENTS

Adults (18–65 years of age) were eligible to participate if they had a DSM-IV [APA, 2000] diagnosis of major depression; a 17-item Hamilton Depression Scale (HAM-D) [Hamilton, 1960] score of $\geq$18; a Clinical Global Impression of Severity (CGI-S) [NIMH, 1970] score of $\geq$4 (moderately ill); and a 14-item Hamilton Anxiety Scale (HAM-A) [Hamilton, 1959] score of $\geq$14. These criteria for residual depressive and comorbid anxiety symptoms had to be met both at screening and baseline. In addition, all patients had been treated for their current episode of major depressive disorder with a single SSRI/venlafaxine at a therapeutic dose [Bauer et al., 2002] for at least 6 weeks. Exclusion criteria included: a DSM-IV diagnosis of substance abuse or dependence within 6 months of screening, and patients who received an antipsychotic or benzodiazepine 7 days prior to entering the study, or a potent cytochrome P450 inhibitor or inducer 14 days prior to entering the study. Patients who were pregnant, breastfeeding, or at risk of suicide in the investigator's opinion were also excluded.

The study was performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients and local institutional review board/ethics committee approval was obtained.

STUDY DESIGN

This was an 8-week, double-blind, randomized, placebo-controlled study conducted in a single center in Canada. Patients were recruited via referral from a family physician, Penticton Regional Hospital, or Penticton Mental Health Center. Patients were randomized to receive either quetiapine or placebo for 8 weeks. Patients continued to receive the same SSRI/venlafaxine at the same dose that they were taking prior to study start. Study medication was taken at night and the initial dose was 50 mg/day; patients received this for 7 days. The dose was then escalated to 100 mg/day for 7 days, then 200 mg/day for 7 days, and then at the investigator's discretion (using tolerability and

response) to a maximum of 600 mg/day. Patients unable to tolerate 200 mg/day of study medication were withdrawn from the study. Before withdrawal due to lack of efficacy, patients were required to have tried a minimum of 400 mg/day of study medication. However, patients were free to withdraw from the study at any time. During the study, other anxiolytic or antidepressant agents (other than the single-agent SSRI/venlafaxine therapy) were not permitted. Patients already receiving hypnotics (for the treatment of insomnia) were permitted to continue taking them; benzodiazepines were not permitted.

EVALUATIONS

The clinician administered the HAM-D, HAM-A, CGI, and Global Assessment Scale (GAS) [Endicott et al., 1976] at baseline and at Weeks 1, 2, 4, 6, and 8. For HAM-D and HAM-A, the proportion of responders (a 50% or greater reduction in Week 8 scores from baseline) and remitters (a Week 8 score of 7 or lower) were recorded. The patient-administered short-form Drug Attitude Inventory (DAI-10) scale [Hogan et al., 1983] was used to assess patient attitude to study treatment at Weeks 1, 2, 4, 6, and 8.

Patients' vital signs were recorded at all study visits. Body weight, ECG, and laboratory tests were recorded at baseline and Week 8. Adverse events (AEs) were monitored throughout the study and the frequency and type recorded.

STATISTICAL ANALYSIS

A sample size of $\approx$20–25 completers per arm was expected to show an effect size that was 80–90% of the standard deviation (*SD*) of change between the active and placebo groups when using the *t*-test and a two-tailed alpha of 0.05 and beta of 0.20. Approximately 60 patients would need to be randomized to achieve the target sample size, i.e., a completion rate of 66–83%. The null hypothesis was that augmentation therapy with quetiapine would not be different to augmentation with placebo. The primary endpoint was mean change from baseline to endpoint in HAM-D and HAM-A total scores (last observation carried forward [LOCF] analysis).

The intent-to-treat (ITT) population (any randomized patient who received at least one dose of study medication) was used in all statistical analyses. The mean differences between treatments for all continuous efficacy measures were assessed using the two-sample *t*-test and *P*-values were calculated. For responders and remitters, differences in the proportion in each arm were reported and the associated 95% confidence intervals (CIs) and *P*-values calculated using the standard comparison of two independent proportions. LOCF analyses are reported for the above measures. For the DAI-10, means for placebo and quetiapine using observed data at each timepoint and *P*-values for treatment differences were calculated using the two-sample *t*-test.

A two-sample *t*-test was used to compare the mean change in laboratory measures between the two treatment arms.

Nonprotocolled analyses. Simpler statistical methodology (two-sample *t*-tests) for the primary efficacy endpoint was used rather than the planned analysis of covariance (ANCOVA) for repeated measures because the latter makes assumptions about the shape of the trajectories over time, making comparison of the treatment effects problematic. Treatment effect on individual HAM-D and HAM-A scores and the time course of sedation/somnolence/lethargy were analyzed post hoc. Linear models (ANCOVA) were used retrospectively to assess the difference between the two groups in mean change from baseline to Week 8 for weight and serum triglyceride concentration, adjusting for their baseline values.

RESULTS

PATIENTS

A total of 73 patients were screened; 58 patients met the inclusion/exclusion criteria and were enrolled in the study, with 29 patients randomized to each treatment group. Eighteen quetiapine-treated patients (62%) and 16 placebo-treated patients (55%) completed the study. In the quetiapine group, the reasons for discontinuation were: AEs (eight patients: six due to sedation/somnolence/lethargy; one due to weight gain and fatigue; one due to increased appetite, increased irritability, and sedation/somnolence/lethargy); consent withdrawal (two patients); and protocol violation (one patient). For placebo-treated patients the main reason for discontinuation was lack of efficacy (nine patients); an additional two patients discontinued due to AEs (one due to sedation/somnolence/lethargy; one due to increased irritability) and two patients were lost to follow-up.

In general, the treatment groups were similar in terms of baseline characteristics (Table 1). However, the mean body weight of patients in the placebo group was 7 kg higher than in the quetiapine group. The mean venlafaxine dose was higher in the placebo group than in the quetiapine group. The majority of patients (52%) received citalopram as their concomitant antidepressant.

EFFICACY

Patients in the quetiapine group received a mean (*SD*) dose of 182 (69) mg/day.

Quetiapine statistically significantly improved symptoms of depression and anxiety compared with placebo as demonstrated by the mean change from baseline at Week 8 on both the HAM-D and HAM-A scales (Fig. 1). The mean (95% CI) treatment difference between quetiapine and placebo was 5.7 (1.5, 9.8) for

TABLE 1. Baseline characteristics

	Quetiapine ($n = 29$)	Placebo ($n = 29$)
Proportion of men (%)	35	41
Age, mean (SD) (years)	44 (10)	45 (12)
Bodyweight, mean (SD) (kg)		
All patients/ completers[a]	84 (23)/82.2 (25.8)	91 (25)/88.3 (17.7)
SSRI/SNRI therapy		
Number (%) receiving		
Citalopram	14 (48%)	16 (55%)
Paroxetine	5 (17%)	6 (21%)
Venlafaxine	7 (24%)	4 (14%)
Fluoxetine	2 (7%)	3 (10%)
Sertraline	1 (3%)	0 (0%)
Mean (SD) dose (mg/day) of		
Citalopram	51.4 (10.3)	50.0 (9.9)
Paroxetine	46.0 (8.9)	46.7 (10.3)
Venlafaxine	278.6 (71.3)	356.3 (112.5)
Fluoxetine	50.0 (14.1)	50.0 (10.0)
Sertraline	200	—
Efficacy measures		
Mean (SD) scores		
HAM-D	23.4 (3.0)	23.2 (2.2)
HAM-A	22.6 (4.5)	22.6 (3.9)
CGI-S	4.1 (0.3)	4.1 (0.3)
GAS	53.5 (4.0)	53.3 (3.9)

SD, standard deviation.
[a]Data only for those patients with a Week 8 body weight measurement.

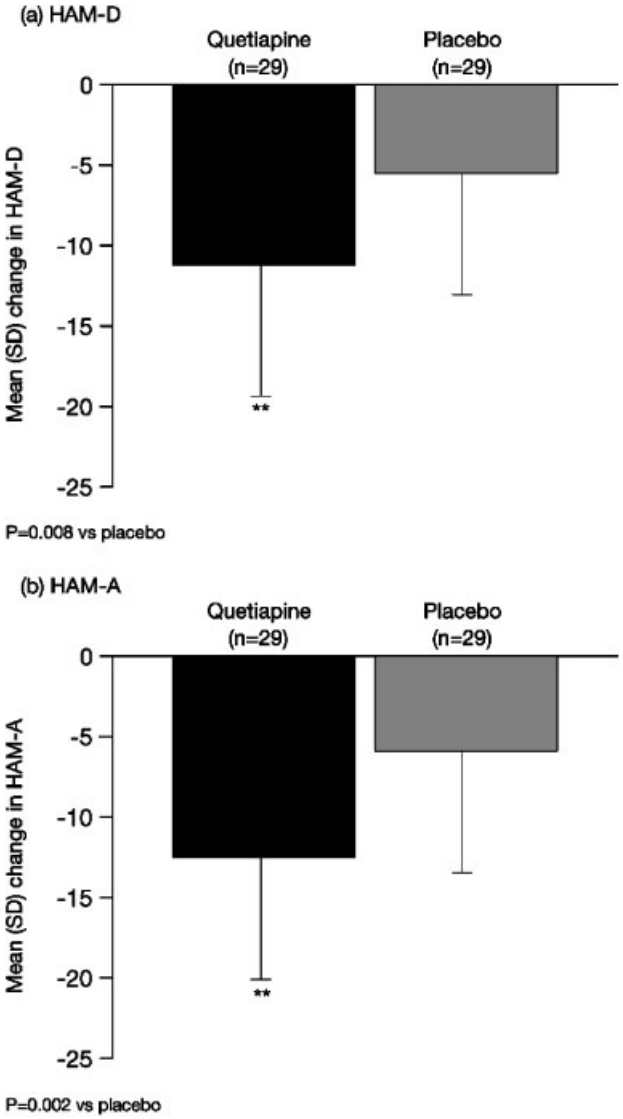

Figure 1. Mean change from baseline at Week 8 in (a) HAM-D and (b) HAM-A total scores (LOCF analysis).

HAM-D and 6.6 (2.6, 10.6) for HAM-A. The effect of quetiapine was statistically significant versus placebo as early as Week 1 and continued throughout the study (Fig. 2). Quetiapine was effective across many of the individual symptoms of depression and anxiety on the HAM-D and HAM-A scales. Statistically significant differences from baseline to Week 8 were observed between the two treatment groups in 7/17 individual HAM-D items: depressed mood; suicide; feelings of guilt; insomnia (early, middle, and late); and anxiety-somatic. For HAM-A, statistically significant differences from baseline to Week 8 were observed between the two treatment groups in 6/14 items: anxious mood; tension; insomnia; depressed mood; cardiovascular symptoms; and respiratory symptoms.

Approximately twice as many patients responded to quetiapine treatment compared with placebo. The HAM-D response rates were 48% and 28%, respectively. The HAM-A response rates were 62% and 28%, respectively, and the combined response rates (HAM-D and HAM-A reduction of $\geq 50\%$) were 48% and 24%, respectively. The proportion of patients who were classed as remitters was higher for quetiapine than placebo: HAM-D remitters, 31% vs. 17%; HAM-A remitters, 41% vs. 17%; HAM-D and HAM-A remitters, 28% vs. 17%. With the exception of the HAM-A response rate ($P = .02$), none of the treatment differences in response and remission rates were statistically significant. Mean (95% CI) differences between quetiapine and placebo for the percentage of patients achieving response or remission were: HAM-D response, 20% (−7, 49); HAM-A response, 34% (7, 62); HAM-D and HAM-A combined response, 24% (−3, 52); HAM-D remission, 14% (−11, 39); HAM-A remission, 24% (−2, 50); HAM-D and HAM-A combined remission, 11% (−14, 35).

All other efficacy assessments showed that quetiapine was statistically significantly more effective than placebo. For the final CGI-I score, the mean difference between quetiapine and placebo groups was −1.0 (95% CI: −1.8, −0.3; $P = .008$). The improvement in CGI-I score in the quetiapine group was statistically significantly greater than placebo from Week 1 through to

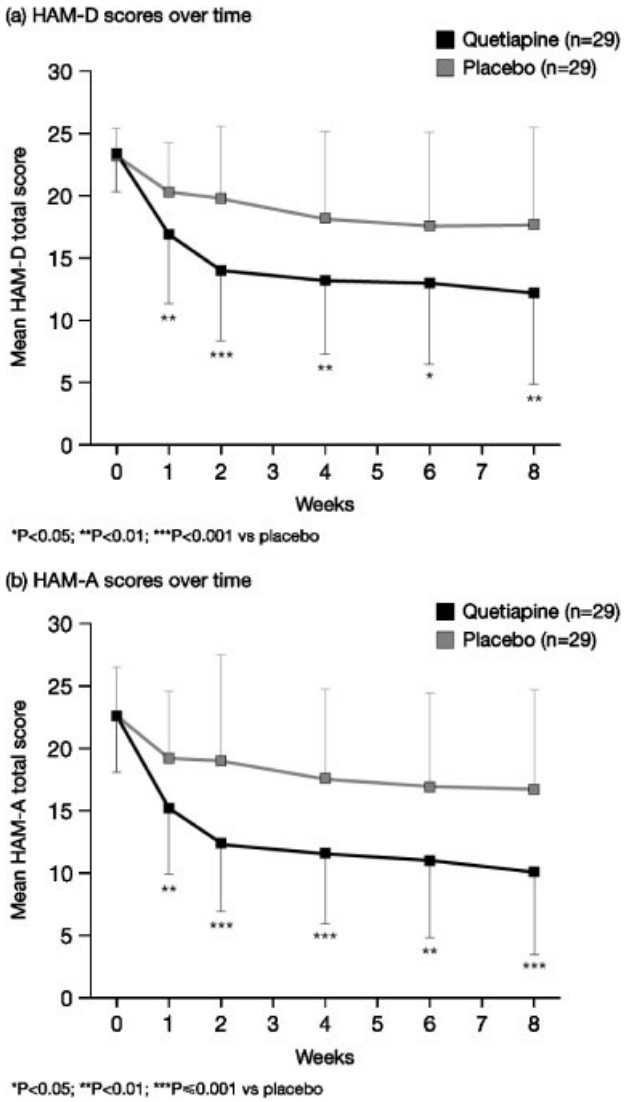

Figure 2. Mean (*SD*) total scores over time for (a) HAM-D and (b) HAM-A. *P*-values are for the difference between quetiapine and placebo in the intent-to-treat population (LOCF analysis).

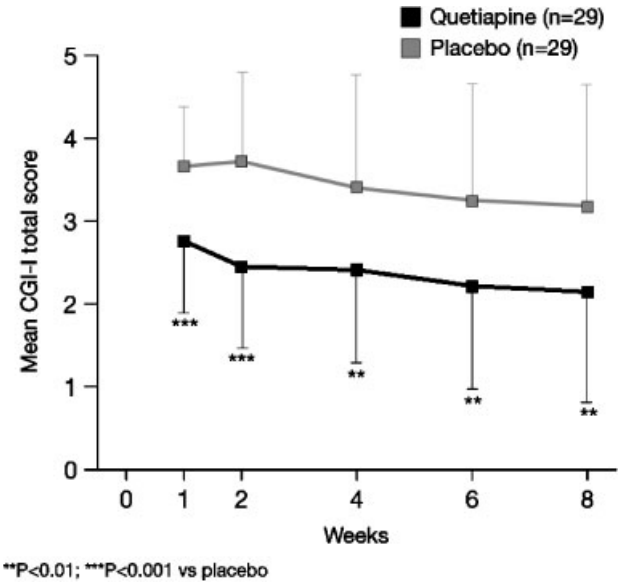

Figure 3. Mean (*SD*) CGI-I scores over time in both treatment groups. *P*-values are for the difference between quetiapine and placebo in the intent-to-treat population (LOCF analysis).

Week 8 (Fig. 3). For the CGI-S score, a statistically significantly greater improvement from baseline to Week 8 was observed for quetiapine compared with placebo: mean difference −0.9 (95% CI: −1.5, −0.2; $P = .01$). For the GAS score, the mean difference between quetiapine and placebo from baseline to Week 8 was 11.0 (95% CI: 4.1, 17.9; $P = .002$).

Patients in the quetiapine group had a more positive attitude toward medication, as indicated by the DAI-10 scores, although differences in this measure were not statistically significant.

SAFETY AND TOLERABILITY

No serious AEs were reported. Most AEs were transient and mild to moderate in intensity. Sedation/somnolence/lethargy was the most commonly reported AE in both groups (Table 2) and was most often mild to moderate in intensity. From examining trajectories of sedation/somnolence/lethargy over time (data not shown), it appears that the incidence of sedation/somnolence/lethargy decreases over time. During the study, one quetiapine-treated and two placebo-treated patients received zopiclone for the treatment of insomnia.

An increase in body weight between baseline and Week 8 was recorded for 12 quetiapine-treated and 5 placebo-treated patients. At Week 8, 4/18 (22%) quetiapine-treated and 0/14 placebo-treated patients gained over 7% in weight. At Week 8, the mean weight increase was +2.36 kg in the quetiapine group and −0.29 kg in the placebo group; after adjustment for baseline weight imbalance, the mean difference between groups was not statistically significant (2.1 kg; 95% CI: −0.6, 4.8; $P = .13$).

There were no clinically significant differences between treatment groups with regard to changes in laboratory assessments from baseline to Week 8.

DISCUSSION

The addition of quetiapine to SSRI/venlafaxine therapy led to a rapid reduction in symptoms of depression and anxiety in patients with major depressive disorder, comorbid anxiety, and residual depressive symptoms. This is the first double-blind, placebo-controlled study of quetiapine as an adjunct to an SSRI/venlafaxine in this patient population. The results demonstrate that quetiapine was effective at reducing symptoms of depression and anxiety as

TABLE 2. Number of patients reporting an adverse event (AE)

	Quetiapine ($n = 29$)	Placebo ($n = 29$)
Sedation/ somnolence/lethargy	25	14
Dry mouth	13	4
Increased weight[a]	10	3
Dizziness	6	7
Headache	4	8
Irritability/restlessness	4	5
Increased appetite	5	6
Insomnia	0	9
Pain	3	4
Flu-like symptoms	2	3
Dysuria	3	1
Constipation	4	0
Anxiety	0	3
Nausea	1	3
Increased dreaming/ nightmares	4	0
Other[b]	12	12

[a]Based on patient's perception.
[b]Includes AEs reported by two or fewer patients in either treatment group.

measured by the HAM-D and HAM-A. Furthermore, the onset of action was rapid: statistically significant differences between quetiapine and placebo in HAM-D and HAM-A total scores were seen as early as Week 1 and persisted through to Week 8. Moreover, quetiapine was effective across a number of core symptoms of depression and anxiety, as shown by the improvements in individual HAM-D and HAM-A item scores. These data indicate that the antidepressant and anxiolytic effects of quetiapine are not simply due to its beneficial effects on sleep. Quetiapine efficacy was also demonstrated by all secondary efficacy measures (CGI-S, CGI-I, GAS).

Response and remission rates were approximately 2-fold higher in the quetiapine group compared with placebo, but, with the exception of the HAM-A response rates, there were no statistically significant treatment differences; however, the study was not powered to detect treatment differences in these parameters. The number needed to treat (NNT) to achieve remission was calculated as 7 for depression symptoms and 4 for anxiety symptoms.

The efficacy results are supported by previous studies with quetiapine. A single-blind study in patients with major depression and associated anxiety demonstrated the efficacy of quetiapine in combination with the SSRI paroxetine [Yargic et al., 2004]. An 8-week study in patients with treatment-resistant major depression showed that augmenting antidepressant treatment with quetiapine improved HAM-D scores significantly more than augmentation with lithium ($P<.01$) [Doree et al., 2004]. Quetiapine was also shown to be effective in the treatment of depression and anxiety symptoms in patients with anxiety disorders [Hamner et al., 2003; Denys et al., 2004; Adson et al., 2004; Schutters et al., 2005].

Although limited, study data with other atypical antipsychotics as augmentation therapy in patients with major depression suggest that they may have utility in this role [Rapaport et al., 2003; Papakostas et al., 2004, 2005; Simon and Nemeroff, 2005; Shelton et al., 2005]. Aripiprazole, risperidone, and ziprasidone augmentation therapy were effective in three separate open-label studies in patients ($n = 12$, 33, and 20, respectively) with treatment-resistant depression [Papakostas et al., 2004, 2005; Rapaport et al., 2003]. There is also some evidence for the efficacy of olanzapine in combination with fluoxetine in this population [Shelton et al., 2005].

In the present study the effect of quetiapine was observed across a range of depression and anxiety symptoms. Results from a recent study of quetiapine monotherapy in patients with bipolar depression also demonstrated its efficacy against a broad range of depression and anxiety symptoms [Calabrese et al., 2005; Macfadden et al., 2004], reinforcing the concept that quetiapine exhibits antidepressant and anxiolytic effects that are independent of its positive effects on sleep.

There are currently no direct comparative studies of the atypical antipsychotics in major depression; however, there are differences in their binding profiles and it is believed that quetiapine—with its broad spectrum of rapid D_2 dissociation kinetics, lower D_2 receptor occupancy, $5HT_{1A}$ partial agonist effects, and $5HT_{2A}$ antagonism—may be particularly effective as an antidepressant.

The AEs reported here are consistent with the expected tolerability profile of quetiapine and most AEs were mild to moderate in intensity and transient in nature. The most commonly reported AE with quetiapine was sedation/somnolence/lethargy, but in those patients who continued treatment this side effect was also transient. The somnolent effects of quetiapine are due to its high affinity for H_1 receptors, and the transient nature of this side effect is likely to reflect rapid tolerance to its interaction with these receptors [Goldstein et al., 2005]. Tolerance to sedation associated with quetiapine has been observed in clinical practice and sedation/somnolence generally decreases over time. Patients need to be educated regarding sedation so that it does not adversely affect adherence to medication.

Increases in weight occurred more frequently in the quetiapine group, but there was no significant difference between quetiapine and placebo for the mean weight gain. It is possible that the degree of weight gain is dependent on the SSRI/SNRI combination, but patient numbers do not allow any definitive conclusions to be drawn from the results of the current study. Further investigation to determine the optimum combination is warranted.

In summary, quetiapine as an adjunct to an SSRI/SNRI was effective in reducing symptoms of major depressive disorder and comorbid anxiety in patients

who had residual depressive symptoms despite having received treatment with an SSRI/SNRI. The onset of action was rapid (by Week 1) and quetiapine was effective across a number of symptoms of depression and anxiety. In general, the combination of an SSRI/SNRI plus quetiapine was well tolerated in this patient population, with no unexpected tolerability issues. This was a short-term, pilot study and its main limitation was the small sample size. The data presented here indicate that quetiapine may be useful for the augmentation of SSRI/SNRI therapy in patients with major depressive disorder, comorbid anxiety, and residual depressive symptoms. Further investigation of these positive results in larger, longer-term, double-blind studies is warranted.

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