Brief Report

PRELIMINARY EXPERIENCE WITH ADJUNCTIVE QUETIAPINE IN PATIENTS RECEIVING SELECTIVE SEROTONIN REUPTAKE INHIBITORS

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Treatment of depression and anxiety disorders with selective serotonin reuptake inhibitors (SSRIs) has been shown by numerous studies to be generally effective. Less well understood is how clinically to address the residual anxiety symptoms a significant minority of such patients treated with SSRIs continue to experience. We assessed quetiapine as adjunctive therapy to SSRIs for patients with anxiety symptoms complicating a depressive or anxiety disorder. Patients receiving a stable dosage of an SSRI for at least 6 weeks who also had persistent anxiety symptoms (Hamilton Anxiety scale [HAM-A] $\geq$16), were enrolled in a 9-week, open-label, variable dose study. Changes in clinical status were assessed with the Hamilton Depression Rating Scale (HAM-D), HAM-A, and State Anxiety Inventory (SAI). Statistically and clinically significant reductions of $\geq$50% in the HAM-D and HAM-A occurred by the second week of treatment in 10 of the 11 patients. These improvements continued throughout the study along with a significant improvement on the SAI scale. The most frequent side effects reported were mild dry mouth, constipation, and transient drowsiness with dose escalation. The results provide evidence that quetiapine may be an effective adjunctive treatment for recalcitrant anxiety symptoms in individuals treated with SSRIs for either anxiety or depressive disorders. Given the open-label design of the trial, more rigorous studies are clearly indicated. Depression and Anxiety 19:121–126, 2004. © 2004 Wiley-Liss, Inc.

Key words: *anxiety; clinical trial; depression; quetiapine; SSRIs*

The lifetime prevalence in the general population of anxiety disorders is as high as 25% and approaches 20% for depression [Kessler et al., 1994]. Anxiety disorders and depression commonly occur in the same individual, and when anxiety disorders complicate a depressive episode, there is often increased morbidity and a more prolonged course of illness [Tylee et al., 1999]. Anxiety disorders, particularly generalized anxiety disorder (GAD) and panic disorder, rarely exist in isolation. It is estimated that patients with GAD have another Axis I condition (most often depression) in about 90% of cases [Noyes, 2001]. Because of this comorbidity, most clinicians use an antidepressant for patients presenting with a mixture of depressive and anxiety symptoms. Although the selective serotonin reuptake inhibitors (SSRIs) have become the first-line therapies for depression, these agents do not always give adequate symptom relief in patients with comorbid anxiety. Moreover, several of the SSRIs have Federal Food and Drug Administration indications for one or more of the anxiety disorders. Adjunctive benzodiazepines are also used in these patients and continue to be commonly prescribed [Stahl, 2002]. However, because of sedation, cognitive impairment, and habituation, alternative therapies are often sought

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[Gorman, 2002]. Buspirone has also been used but its efficacy does not start until many weeks after initiation of dosing, and it is generally ineffective in patients previously exposed to benzodiazepines [Strand et al., 1990].

Recently, clinicians have been using adjunctive treatment to aim for remission of a disorder rather than just improvement. Accordingly, traditional antipsychotic medications have been used for many years in the treatment of anxiety and depression; however, side effects and risk of tardive dyskinesia (TD) have limited their usefulness in patients with these conditions [Thase, 2002]. Atypical neuroleptics, with a lower incidence of extrapyramidal side effects (EPS) and TD, have been used successfully in areas other than schizophrenia and mania [Adityanjee and Schulz, 2002]. Recently conducted studies have demonstrated their promise in treating depressive illness as well [Shelton et al., 2001]. Owing to its relative lack of EPS and low potential for prolactin elevation or significant weight gain, quetiapine appears to be an ideal neuroleptic to investigate in patients with residual anxiety and depression despite SSRI treatment [Goldstein, 1999].

We assessed the short-term efficacy of quetiapine in a group of anxious patients (study entry required a Hamilton Anxiety scale [Ham-A] of ≥ 16) who were taking an SSRI for an episode of anxiety and/or depression. We sought to study a group of patients with residual anxiety commonly encountered in clinical practice rather than a discrete *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition* (DSM-IV; American Psychiatric Association, 1994] category. We hypothesized that quetiapine would be a well-tolerated and effective adjunctive treatment in this patient population.

PATIENTS AND METHODS

This was a 9-week, open-label, flexible-dosed study. Patients were recruited through bulletin-board postings, a newspaper advertisement, and referrals from our outpatient psychiatry clinic. The University of Minnesota Institutional Review Board approved the study and all patients provided written informed consent before study entry.

We used the following inclusion criteria: (a) aged ≥ 18 years; (b) currently being treated with an SSRI at a dose of at least fluoxetine 20 mg/day, paroxetine 20 mg/day, sertraline 50 mg/day, or citalopram 20 mg/day for at least 6 weeks; (c) DSM-IV diagnosis of unipolar depression or dysthymia and/or GAD, panic, or specific phobia; and (d) HAM-A score ≥ 16 and State Anxiety Inventory (SAI) score ≥ 40. Potential subjects were enrolled into the study receiving the SSRI dose with which they presented; i.e., we made no effort to optimize the dose of the initial medication (see minimum doses for inclusion).

Patients were excluded from the study when any of the following criteria were met: (a) thought disorder or cognitive problems that would interfere with informed consent; (b) history of significant renal, hepatic, respiratory, cardiovascular, or cerebral vascular disease; (c) significant risk of suicide; (d) significant psychoactive use disorder within the previous 6 months; (e) use of benzodiazepines (except for lorazepam, which was permitted on an as-needed basis up to 3 mg/day but not used for more than 2 of 3 days); and (f) women who were pregnant or nursing, or of child bearing age, not using an adequate method of birth control.

Initial evaluation consisted of a complete psychiatric assessment including medication history, Hamilton Depression Rating Scale (HAM-D; 24-item), HAM-A (17-item), Mini International Neurological Inventory (MINI), SAI, and physical examination. Neither blood tests nor electrocardiograms were obtained except in one subject who was also taking a tricyclic. At baseline and at visits 4 and 9 weeks after starting medication, patients were assessed for abnormal motor movements with the Simpson–Angus Scale and the Barnes Akathisia Rating Scale. Follow-up visits for medication management, side-effect monitoring, blood pressure, pulse and weight, and administration of the HAM-A, HAM-D, and SAI were scheduled 1, 2, 3, 4, 5, 7, and 9 weeks after starting medication.

The starting dosage of quetiapine was 25 mg/day at bedtime. The dosage was increased as needed in 25-mg increments every two to three doses. Patients were allowed to increase the amount of drug to a maximum of 100 mg in the morning and 200 mg at bedtime (300 mg/day). Titration of drug dose was allowed for the first 3 weeks of the study and then held constant for the last 6 weeks. Each patient, in consultation with the study physician, determined the dosage of quetiapine used based on efficacy and tolerability.

Descriptive statistics were calculated and a series of matched pairs *t* tests were conducted in which baseline data and terminal data were compared. In one instance in which a patient withdrew from the study prematurely, the method of last observation carried forward was employed.

RESULTS

Eleven patients were enrolled; a summary of Axis I diagnoses, type of SSRI being used, and approximate duration of SSRI treatment at study entry is presented in Table 1. GAD is the most common diagnosis and seven patients had comorbid major depressive disorder or dysthymia. Paroxetine was the most commonly used SSRI, followed by citalopram and fluoxetine. Ten patients completed the study; one patient withdrew at 4 weeks because of his perception that he wasn't "sick enough" to be in the study (being much improved at that point). Table 2 presents patient demographics and baseline values of the three primary outcome measures.

TABLE 1. Diagnoses and medications of study subjects at enrollment

Subject no.	Diagnosis	Length of time on SSRI	SSRI	Daily dose	Baseline EPS scores*	Maximum EPS scores
001	Dysthymia, GAD	2 yr	Fluoxetine	20 mg	0,0	0,0
002	GAD, panic d/o	2 yr	Citalopram	40 mg	0,0	0,0
003	MDD, panic d/o, GAD	3.5 yr	Citalopram	40 mg	0,0	0,0
004	MDD, GAD	3 yr	Paroxetine	20 mg	0,0	0,0
005	Panic d/o,	6 mo	Fluoxetine	60 mg	0,0	0,0
006	Panic d/o, MDD, SAD, GAD	5 mo	Paroxetine	20 mg	0,0	2,0
007	MDD, specific phobia, SAD	7 yr	Fluoxetine	40 mg	0,0	0,0
008	GAD	5 yr	Sertraline	100 mg	0,0	0,0
009	MDD, GAD, panic d/o	3 mo	Paroextine	40 mg	0,0	0,0
010	GAD	4 mo	Paroxetine	20 mg	0,0	0,0
011	MDD, GAD, SAD	2 mo	Citalopram	40 mg	0,0	0,0

*Measured by Simpson–Angus Scale and Barnes Akathisia Rating Scale.
GAD = generalized anxiety disorder; MDD = major depressive disorder; SAD = social anxiety disorder; d/o = disorder.

TABLE 2. Subject demographics at baseline

Demographic	Value
Patients (*n*)	11
Gender distribution	4 M/7 F
Age, yr ($\pm sd$)	48.8 ± 10.59
Mean HAM-A score (± 1 *sd*)	24.6 ± 7.10
Mean HAM-D score (± 1 *sd*)	20.0 ± 5.72
Mean SAI score	51.36 ± 9.37

HAM-A = Hamilton Anxiety Scale; HAM-D = Hamilton Depression Scale; SAI = State Anxiety Inventory.

The mean quetiapine dosage attained by the third week (and maintained to the study end point at 9 weeks) was 180 mg/day, with a range of 0–100 mg in the morning and 25–200 mg at bedtime. None of the patients required lorazepam for anxiety during the study.

Clinically relevant reductions in the mean HAM-A, HAM-D, and SAI scores from baseline were seen as early as 1 week after dosing. In addition, 91% of patients had $\geq 50\%$ mean reductions from baseline in both HAM-A and HAM-D scores (-18.63 and -14.63, respectively) by week 2. Sustained improvement in symptoms over the 9-week treatment period was evident on all three primary outcome measures. HAM-A scores decreased from a mean of 24.45 (± 7.1) at baseline to 5.82 (± 3.84) at study conclusion (Figure 1). HAM-D scores decreased from 20.27 (± 5.5) at study entry to 5.64 (± 3.32) at the final visit (Figure 2). SAI scores decreased from 51 (± 9.37) at entry to 30 (± 6.19) at study end (Figure 3). Mean changes from baseline of all measures were highly significant (t values > 7; $P < .0001$).

Analysis of specific items on the Ham-A revealed $\geq 50\%$ reduction by week 2 on medication of "anxious mood, tension, cardiovascular, respiratory, and behavior at interview" questions. Similar reductions were seen in the Ham-D on questions regarding "depressed mood, feelings of guilt, early and middle insomnia, work and activities, agitation, anxiety-psychic." Tables 3 and 4 present data on individual subjects' scores for the Ham-A and Ham-D for baseline, after 2 weeks with quetiapine, and at the conclusion of the study.

Clinical adverse effects were transient and mild and typically occurred during dose escalation. There were no serious adverse events and no patient discontinued owing to an adverse event. Transient drowsiness was a common side effect during the dose-escalation period; 7 of 11 patients reported this side effect within the first 3 weeks of the trial. Three patients (27%) reported severe drowsiness after dose escalation. Both transient mild dry mouth and constipation were reported in 64% of patients; however, none of these side effects led to discontinuation from the trial. Individual side effects are summarized in Table 5. There were no clinically relevant changes in the Barnes Akathisia or Simpson-Angus scales. However, on one visit a patient scored a two-point elevation in the Barnes Akathisia Rating Scale. The mean baseline weight of all patients was 191 lb (range 145–259 lb) and the mean terminal weight was 195 lb (range 148–263 lb). During this 9-week trial, one patient gained 22 lb; however, this degree of weight gain was notably the exception.

DISCUSSION

Addition of quetiapine to a stable dose of an SSRI resulted in a significant improvement of symptoms as measured by the primary outcome measures of depression and anxiety. Improvement of symptoms was evident by the first week and was sustained and progressive for the duration of the trial. Patients achieved marked reductions of their anxiety and depression symptoms as evidenced by mean scores of < 6 on both the HAM-A and HAM-D scores at the end of the trial. Mean improvements from baseline on these rating scales were 18.63 on HAM-A and 14.63 on HAM-D. Quetiapine was generally safe and well

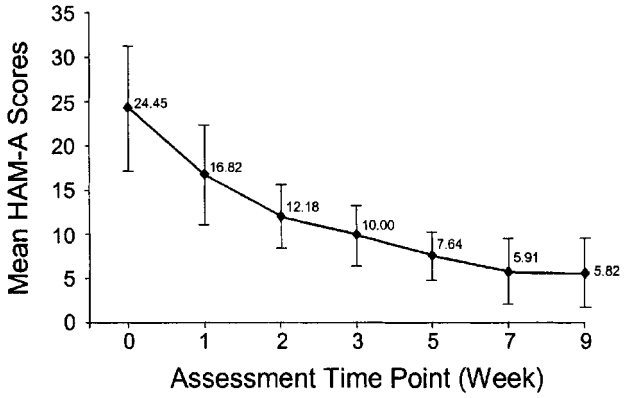

Figure 1. Change in mean HAM-A scores during 9-week adjunctive therapy with quetiapine in the treatment of depression complicated by anxiety. N = 11; baseline (mean ± *sd*) = 2.45 ± 7.10; baseline range = 16–35; terminal (mean ± *sd*) = 5.82 ± 3.84; terminal range = 1–12; *t* = 8.423; *df* = 10; *P* < .0001).

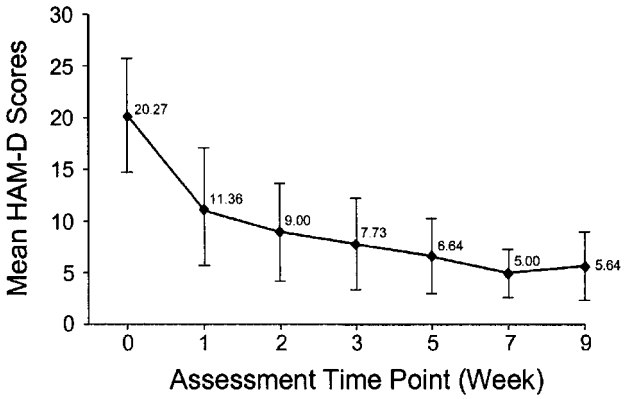

Figure 2. Change in mean HAM-D scores during 9-week adjunctive therapy with quetiapine in the treatment of depression complicated by anxiety. N = 11; baseline (mean ± *sd*) = 20.27 ± 5.50; baseline range = 14–30; terminal (mean ± *sd*) = 5.64 ± 3.32; terminal range = 2–11; *t* = 7.122; *df* = 10; *P* < .0001.

tolerated, and the adverse events were similar to those previously reported with quetiapine.

The results of this study further support the safety and efficacy of atypical neuroleptics in augmenting the effects of antidepressants. Quetiapine may be a better-tolerated agent than other atypicals for this purpose because of less potential for prolactin elevation, EPS, and weight gain [Brecher and Melvin, 2000; Kapur and Remington, 2001; Maguire, 2002]. The SSRIs have been associated with EPS and akathisia [Leo, 1996] but there did not appear to be an additive effect on EPS when the SSRIs were used with an antipsychotic in this trial. This lack of EPS when the two agents are used in combination is in accord with another trial that used this combination [Shelton et al., 2001]. Quetiapine

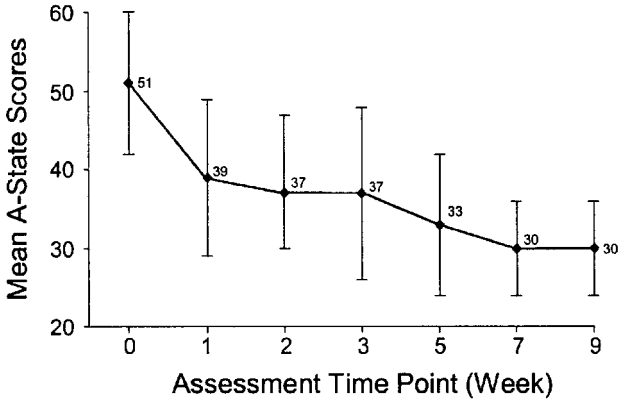

Figure 3. Change in mean patient-rated SAI scores during 9-week adjunctive therapy with quetiapine in the treatment of depression complicated by anxiety. N = 11; baseline (mean ± *sd*) = 51.36 ± 9.37; baseline range = 31–70; terminal (mean ± *sd*) = 29.64 ± 6.19; terminal range = 21–38; *t* = 7.100; *df* = 10; *P* < .0001.

TABLE 3. Individual subjects; Hamilton Anxiety Rating Scales

	Ham-A scores		
Subject no.	Baseline	Week 2 of medication	Termination visit
1	16	6	6
2	18	11	12
3	35	18	11
4	29	10	5
5	21	10	2
6	33	15	11
7	33	16	3
8	18	14	5
9	26	15	3
10	17	10	5
11	23	9	1

TABLE 4. Individual subjects' Hamilton Depression Rating Scale scores

	Ham-D score		
Subject no.	Baseline	Week 2 of medication	Termination visit
1	17	9	9
2	16	11	10
3	23	18	11
4	23	8	6
5	14	5	3
6	30	10	6
7	19	3	2
8	15	13	4
9	28	14	2
10	15	6	7
11	23	2	2

TABLE 5. Individual side effects: subjective reports at each visit

	Week on medication					
Subject no.	1	2	3	5	7	9
1	Mild dry-mouth	Moderate dry-mouth				
2	Severe sedation with dose increase	Moderate constipation	Moderate constipation	Moderate sedation	Moderate sedation	Moderate sedation
3	Mild dry-mouth, constipation	Mild dry-mouth, constipation	Mild dry-mouth, constipation	Mild dry-mouth, constipation	Mild dry-mouth, constipation, insomnia (2 d)	Mild dry-mouth
4	Moderate dry-mouth	Moderate dry-mouth, constipation, mild bloating	Moderate dry-mouth	Moderate dry-mouth	Moderate dry-mouth, sedation	Moderate dry-mouth, sedation
5	Mild dry-mouth, sedation	Mild dry-mouth, sedation	Mild dry-mouth	Mild dry-mouth	Mild dry-mouth	Mild dry-mouth
6	Mild constipation	Mild gas, bloating		Mild dry-mouth and sedation	Mild dry-mouth and sedation	Mild dry-mouth and sedation
7		Mild sedation	Mild sedation			
8	Mild headache	Mod. sedation		Mild headache		Mild headache
9	Moderate dry-mouth, mild sedation, constipation	Moderate dry-mouth	Moderate dry-mouth	Moderate dry-mouth	Moderate dry-mouth, mild sedation, constipation	Mod dry-mouth
10	Mild dry-mouth, constipation	Mild dry-mouth, constipation	Mild sedation, dry-mouth, constipation	Mild dry-mouth, constipation	Mild dry-mouth, constipation	Severe weight gain, mild sedation
11	Mild sedation	Mild sedation	Mild sedation	Mild sedation	Mild sedation	Mild sedation

does not appear to inhibit cytochrome P450-mediated oxidative metabolism [Prior, 2003], so it is unlikely that it caused changes in serum levels of the SSRIs.

This study stands as an effectiveness trial of an adjunctive treatment for anxious or depressed patients with recalcitrant residual symptoms following a standard SSRI treatment protocol. This can be contrasted with the more typical efficacy drug trial in which patients with either an anxiety disorder or a depressive disorder (but not both) undergo a trial of a (would-be) first-line treatment (e.g., an SSRI) with a primary focus of moving the patient from a state of meeting diagnostic criteria to a state of not meeting diagnostic criteria. In the current study, we attempted to capture a common real-world sample of clinic patients experiencing difficulty in the anxiety–depression spectrum most similar to the mixed anxiety-depressive disorder diagnostic category found in the appendix of the DSM-IV [p. 780, American Psychiatric Association, 1994], who, although benefiting by SSRIs, were not in a state of recovery. We feel that, given the ongoing discussion regarding the importance of performing more clinically relevant clinical trials [Mitchell et al., 2001; Thase, 2001], this is one of the strengths of the present research.

The study has several limitations. The study design required a minimum of 6 weeks with an SSRI. It is conceivable that further treatment and/or higher doses of the SSRI would have led to symptom relief. However, subjects received typical doses of SSRIs, and the early and significant response to the quetiapine supports the efficacy of the adjunctive treatment. Also, most subjects had been treated with SSRIs for ≥ 6 months. However, we made no attempt to optimize the dose of the SSRI before the study began. Unfortunately, our data do not allow us to determine whether this approach would have led to significant improvement in subjects' presenting symptoms. Second, the small number of patients, along with the open-label design, requires that our results be seen as a pilot study that could lead to further investigation. Similarly, this was a short-term trial that did not assess the potential for side effects that might emerge with longer treatment. Antipsychotics are potent medications that have shown utility when used in recalcitrant cases. However, this was not a study of treatment-resistant patients. These preliminary findings should not be interpreted to condone casual use in patients suffering from mood and anxiety disorders. On the other hand, these findings point to the possible utility of obtaining increased symptom reduction in patients receiving stable doses of various SSRI drugs.

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