Quetiapine in Anorexia Nervosa Patients: An Open Label Outpatient Pilot Study

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ABSTRACT

Objectives: The main objective of the study was to determine whether quetiapine was effective in reducing scores on the positive and negative syndrome scale (PANSS) in anorexia nervosa (AN) patients. Secondary objectives included determining whether quetiapine was effective in reducing symptoms of anxiety and depression. In addition, the effect on weight was determined.

Method: In an open label design, 19 patients with AN but without schizophrenia or schizoaffective disorder were given 150–300 mg quetiapine daily over a 10 week period. Results were analyzed using last observation carried forward (LOCF).

Results: Fourteen patients completed the study and all but one of the 5 patients who dropped out returned for an early termination visit. Scores on the total, general psychopathology, and depression scales of the PANSS declined significantly ($p = .024$, .010, .0005, respectively) at LOCF. There were improvements in several measures of anxiety, depression, and obsessive compulsive symptoms. Mean weight gain was modest at 1.6 lbs (0.73 kg). Adverse events were generally mild and no patients discontinued due to adverse events

Conclusion: Quetiapine was well-tolerated and patients had significant improvements in several subscales of the PANSS as well as decreases in measures of anxiety and depression.

Keywords: anorexia nervosa; quetiapine

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Introduction

Anorexia nervosa (AN) is a serious psychiatric disorder that affects about 1 in 200 women and 1 in 2,000 men in the United States.[1] It has a high premature mortality rate: it is estimated that 10–18% of untreated patients have died after 20 years of illness.[2,3] Those who survive often have a severely impaired quality of life[4] and major physiological complications. For example, even among patients ill for relatively brief periods (1 year or less), many have osteoporosis which may persist a lifetime.[5] The treatment of anorexia nervosa is difficult, time-consuming, and expensive. Inpatient hospitalization is common to treat the physical and emotional aspects of the illness and relapse often occurs. The cost of treatment is higher than for schizophrenia; the yearly cost of treatment for anorexia nervosa has been estimated at $6,045 compared to $4,824 for schizophrenia.[6]

There is some evidence that some patients with anorexia nervosa have psychotic symptoms that are similar to those seen in patients with schizophrenia.[7] For example, anorexia nervosa patients have a body image disturbance (that is, they see themselves as larger than they are in reality), which is a misperception. Many patients have the fixed false belief that they are "fat" when actually semistarved; this belief is unresponsive to reassurance or logic and thus meets the criteria for a delusion. Cognitive distortions are common[8] and may represent a thought disorder. Neurocognitive abnormalities have been identified including abnormalities in verbal learning and executive functioning.[9] Although these perceptual abnormalities are not identical to those seen in schizophrenia, there are some similiarities. Computed tomography and magnetic resonance imaging scans of the brain reveal enlarged cerebral ventricles in at least one third of patients[10]; furthermore, decreases in white and gray matter have been identified in some patients.[11] These brain abnormalities do not always resolve with weight restoration.

Atypical antipsychotic medications, such as olanzapine, are being used to facilitate weight gain and

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to treat other symptoms of anorexia nervosa including anxiety and affective symptoms.[12–14] In a study reported by our group[15] we found that a modest weight gain was accompanied by statistically significant decreases in total scores on the Positive and Negative Syndrome Scale (PANSS) which is a well-validated scale typically used to assess severity of psychotic symptoms in patients with schizophrenia.[16] The PANSS has seven scales that measure "positive" symptoms of schizophrenia (delusions, conceptual disorganization, hallucinatory behavior, excitement and grandiosity, suspiciousness and hostility); seven scales that measure "negative" symptoms (blunted affect, emotional withdrawal, poor rapport, apathetic social withdrawal, difficulty in abstract thinking, lack of spontaneity, stereotyped thinking); and six scales that measure general psychopathology. Quetiapine, another atypical antipsychotic, has been shown to decrease psychotic symptoms, has antidepressant and antianxiety effects, and is well-tolerated.

The primary objective of this study was to determine whether 150–300 mg of quetiapine daily was effective in decreasing scores of the positive and negative syndrome scale (PANSS) over a 10 week period in 19 patients with anorexia nervosa. Secondary objectives were to determine whether there were changes in other symptoms associated with anorexia nervosa as measured by the Eating Disorder Inventory-2 (EDI-2), Yale Brown Cornell-Eating Disorder Scale (YBC-EDS), Hamilton Depression Scale (HAM-D), Spielberger State Trait Anxiety Inventory (STAI), and Clinical Global Improvement Scale (CGI-I). Improvement in symptoms measured by these scales might result in patients being able to agree to and tolerate needed weight gain. An additional secondary objective was to determine whether there were changes in serum leptin levels since leptin levels are known to be low in underweight AN patients and to increase with weight restoration.[17]

Method

This was an open-label efficacy and safety pilot study of quetiapine 150–300 mg daily of 19 patients with AN. Inclusion criteria included the following: diagnosis of anorexia nervosa, (either restricting or binge eating subtype) according to DSM-IV-TR[18] criteria; age 14–65 years; females and males; and weight at least 15% but no more than 25% below ideal body weight. Exclusion criteria were: current or past history of schizophrenia or schizoaffective disorder and physiological complications deemed by the principal investigator to pose a risk to the patient's participation. Candidates for the study were asked to read the informed consent form approved by the University of South Florida Institutional Review Board; after having questions answered, patients who chose to sign the informed consent form entered the study. There were two phases in the study: a screening phase and a 10 week treatment phase. During the screening phase, patients were assessed for eligibility, a physical examination was performed, laboratory tests were performed (including complete blood count, electrolytes, and metabolic panel), and an electrocardiogram (ECG) was obtained. A battery of tests to assess movement disorders was completed including the Abnormal Involuntary Movement Scale,[19] the Barnes Akathisia Scale,[20] and the Simpson-Angus Scale.[21] All psychotropic drugs were discontinued for five half-lives. Subjects on fluoxetine had to be off this medication for 28 days before entering the next phase. The M.I.N.I Plus,[22] a semistructured interview, was administered to ensure that subjects did not met criteria for either schizophrenia or schizoaffective disorder and to confirm the diagnosis of AN made by clinical interview.

On Day 1 of the treatment phase, before the first administration of study medication, the PANSS,[23] the EDI-2,[24] the Yale Brown Cornell-Eating Disorder Scale,[25] the HAM-D,[26] the STAI,[27] and the Severity of Illness subscale of the Clinical Global Impression[19] were completed. Quetiapine was then titrated upward to each subject's maximum tolerated dose using the following titration schedule: Day 1, quetiapine 50 mg; Day 2, 50 mg bid; Day 3, 100 mg bid; and Day 4 (onward), 150 mg bid. Subjects had to achieve a minimum dose of 150 mg/day to remain in the study.

During the 10 weeks of the treatment phase of the study, patients were seen weekly to assess symptoms, vital signs, weight, monitor for adverse events, and to administer the battery of movement scales. At Week 1, 3, 5, and 10, laboratory tests and an ECG were repeated. At Week 5 and 10, the PANSS, EDI-2, HAM-D, YBC-EDS, and STAI were repeated. The severity of illness and global improvement severity and improvement scales were completed weekly. Weekly study visits were conducted and were typically 15–30 min in length. The physician had access to key assessment measures, commented on progress or lack of progress, inquired about possible side effects, elicited information about compliance to the medication regime, and if asked, provided psychoeducation about AN. The interviews were conducted using the consensus guidelines described by Mitchell et al.[28] No patients received psychotherapy (including cognitive behavioral therapy) or any other psychiatric treatment during the study.

Original source data were collected in clinical research files and entered into an Excel database. StatView soft-

ware was used for analyses. For all statistical tests, p values of .05 or lower were considered statistically significant. Two-tailed paired t tests were used to compare group means when variables were compared over time. The primary method of analysis was by an intent-to-treat analysis in which the last observation was carried forward (LOCF) to Week 10 and utilized in the analysis. To further assess the PANSS data, the group was divided into those who gained weight and those who did not gain weight at Week 10 LOCF; then paired t tests were used to compare changes within groups on various PANSS scores. Although there were multiple comparisons, no correction was made for this because this was an exploratory study.

Results

Patient Description

Twenty patients signed informed consent and 19 completed the screening phase, began quetiapine, and returned for at least one postbaseline visit. The patient who did not begin the treatment phase was judged too ill to participate. One patient dropped out after Visit 2 and did not return for an early termination visit and four patients discontinued the study before Week 10 but returned for an early termination visit. Nineteen patients received medication and were evaluated at least once, following study drug administration. Among the five patients who dropped out, one gave no reason and the other four gave the following reasons: one decided to seek other treatment, one was afraid she would gain weight on the medication, one decided the study medication was not working, and one moved out of the area.

The mean age of patients at screening was 26.8 years (SD = 11.2 years) with a range from 14 to 48 years, six patients were between 14 and 18 years. All but one patient were female. Twelve patients had anorexia nervosa, restricting subtype and eight had anorexia nervosa, binge purge subtype. Mean weight at baseline was 99 pounds (range: 76–132 lbs) and mean height was 64.75 (range: 60.7–73.0 inches) inches; mean body mass index (BMI) was 16.6; (range: 13–17.54).

PANSS Scores

There were statistically significant deceases in total mean PANSS scores from 56.2 at baseline to 48.4 at Week 10 LOCF ($t = 2.483$; $p = .024$). In addition, there were statistically significant decreases from baseline to Week 10 LOCF in two additional PANSS subscales: PANSS general psychopathology mean scores decreased from 31.1 at baseline to 26.3 at Week 10 LOCF ($t = 2.903$; $p = .010$); and the PANSS depression subscale scores decreased from 10.9 at baseline to 8.0 at Week 10 LOCF ($t = 4.306$; $p = .0005$). There were no statistically significant differences between baseline and Week 10 LOCF for the PANSS positive or PANSS negative subscales.

Eating Disorder Inventory-2

The mean total EDI-2 scores decreased significantly when compared between baseline and Week 10 LOCF ($t = 2.990$; $p = .008$) (**Fig. 1**). There were also statistically significant decreases in scores on most subscales including the drive for thinness subscale ($t = 2.820$; $p = .012$); the bulimia subscale ($t = 2.299$; $p = .034$); the body dissatisfaction subscale ($p = 2.470$; $p = .024$); the ineffectiveness subscale ($t = 2.730$; $p = .014$); the interoceptive awareness subscale ($t = 2.917$; $p = .010$); and the maturity fears subscale ($t = 2.231$; $p = .039$). There were no significant changes in the subscales of perfectionism and interpersonal distrust. Among the provisional subscales, there were significant decreases in the impulse regulation subscale ($t = 2.948$; $p = .009$) and the social insecurity subscale ($t = 2.438$; $p = .026$) but not on the asceticism subscale ($t = 0.061$; $p = .952$).

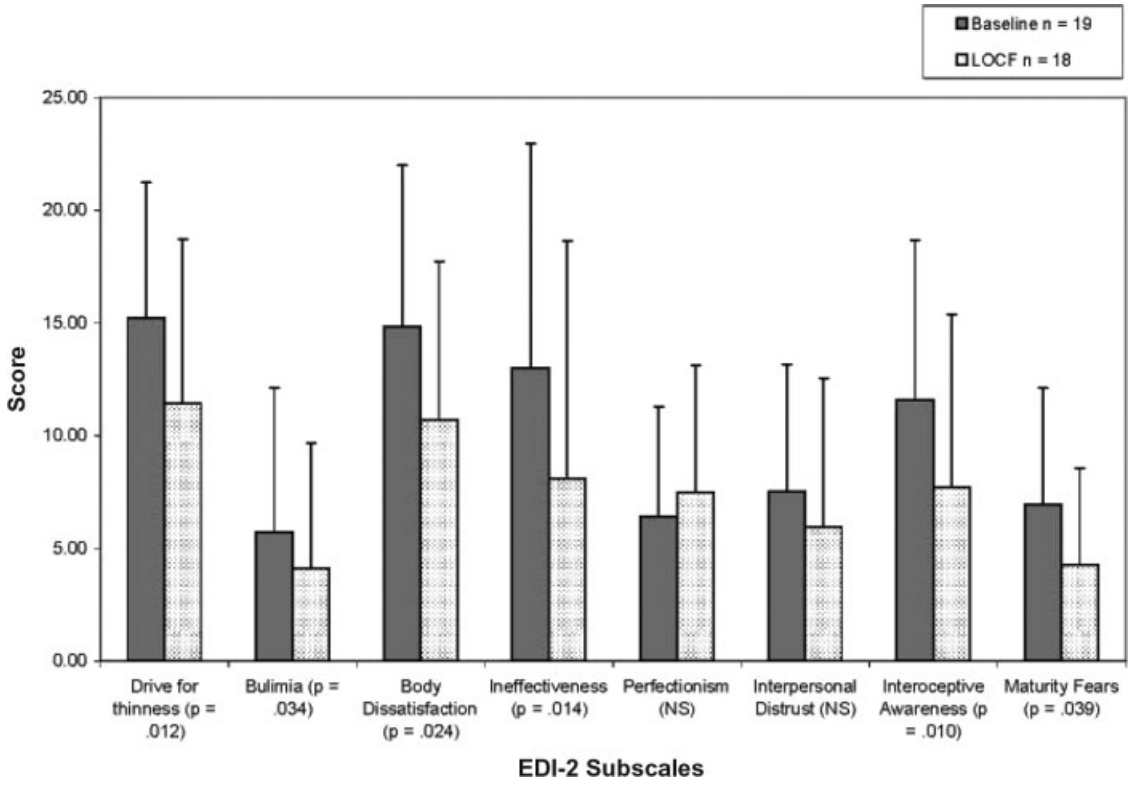
Yale Brown-Cornell-Eating Disorder Scale

This clinician-administered scale assesses obsessions and compulsions related to eating disorder symptoms. The number of hours devoted daily to preoccupations (obsessions) and rituals (compulsions) are determined, and the interference of these preoccupations and rituals with social or work-related functions is then rated on a four-point scale. There were reductions in the number of hours devoted to both obsessions and compulsions when baseline scores were compared to the Week 10 LOCF; however, only the decrease in preoccupation time reached statistical significance {mean obsession time decreased from 3.2 daily hours to 2.5 daily hours ($t = 3.117$; $p = .006$) and mean ritual time decreased from 2.7 daily hours to 2.3 hours (not statistically significant, $t = 1.304$; $p = .210$)}. There were statistically significant reductions in the items measuring interference in daily activities due to preoccupations ($t = 3.828$, $p = .001$) and rituals ($t = 2.297$, $p = .035$).

Depression and Anxiety Measures

Mean scores on the Hamilton depression scale decreased from 24.8 (SD = 11.9) at baseline to 12.8

FIGURE 1. There were significant decreases in mean total scores on the EDI-2 when baseline scores were compared to Week 10 LOCF. In addition, there were significant decreases in all the standard subscales except for the perfectionism and interpersonal distrust subscales.



(SD = 11.2) at Week 10 LOCF; this difference was statistically significant ($t = 4.841$, $p = .000$). HAM-D scores in the range of 0 to 13 indicate no clinical depression; 14–18 subclinical depression; 19–25 mild depression; 26–32 moderate depression; 33–39 moderate to severe depression; and ≥40 severe depression.

Mean scores on the STAI-trait scale decreased from 56.2 (SD = 18.4) at baseline to 48.2 (SD = 18.1) at Week 10 LOCF; this change was statistically significant ($t = 3.644$; $p = .002$). Mean scores on the STAI-state scale decreased from 49.3 (SD = 19.6) to 42.2 (SD = 17.1); this difference was also statistically significant ($t = 3.811$; $p = .001$).

Clinical Global Severity and Clinical Global Improvement Scales

All patients were initially judged to be markedly ill or severely ill at baseline with a statistically significant improvement at Week 10 LOCF ($t = 2.397$; $p = .028$) but clinically this was a very modest change from a severity score at baseline of 5.4 and at Week 10 LOCF 4.8. Mean scores on the clinical global improvement scale at Week 10 LOCF were 3.1 indicating minimal improvement from baseline.

Weight Change and Relationship to PANSS Scores

The mean weight gain from baseline to Week 10 LOCF was 1.6 lbs. The difference between mean weight at baseline and mean weight at Week 10 LOCF was not statistically significant. The range of weight change was a loss of 5.5 lbs (2.5 kg) and a gain of 16.0 lbs (7.3 kg). Nine patients gained weight (mean 5.3 lbs [2.4 kg], SD = 4.6 [2.1 kg]); seven patients lost weight (mean loss was 2.4 lbs [1.1 kg], SD = 1.8 [0.8 kg]); and two patients maintained the same weight. One patient gained to ideal body weight. When results of mean changes in PANSS scores were assessed according to whether or not weight was gained, patients who gained weight had statistically significant improvements on the total PANSS scores, and the general psychopathology subscale scores but those patients who did not gain had no statistically significant differences on these scales when baseline was compared to Week 10 LOCF. Also, although the difference between the PANSS positive subscale scores and the PANSS Thought Disturbance subscale scores were not statistically significant when the entire group was considered in the analyses, the patients who gained weight had a mean statistically significant improvement in both these scales compared

to those who had not gained (PANSS positive subscale scores $t = 2.748$, $p = .025$ for the group that gained weight and $t = 0.104$, $p = .920$ for those who did not gain; PANSS Thought Disturbance subscale scores $t = 2.935$, $p = .019$ for the group that gained weight and $t = -894$, $p = .397$ for those who did not gain). Changes in various other scales were compared between the group that gained and the group that lost weight and no notable differences were found.

Leptin

Serum leptin levels were obtained in patients at screening and at completion or early termination for 17 subjects. Leptin levels increased from a mean of 3.6 ng/ml at baseline to a mean of 5.6 ng/ml at Week 10 LOCF; this was statistically significant ($t = -2.364$; $p = .031$).

Adverse Events

The most common adverse events were dizziness,[8] joint/muscle pain,[7] lightheadedness,[4] sleepiness,[4] constipation,[4] paresthesias,[4] headaches,[4] lethargy,[3] dry mouth,[3] and upper respiratory infections.[3] All adverse events were considered mild and only possibly related to the study medication. It was often difficult to determine whether an adverse event was related to the physiological complications of the anorexia nervosa, or was a side effect of the study medication. For example, four subjects experienced lightheadedness; this may have been related to either the study medication or the semi-starvation associated with the anorexia nervosa. No patients discontinued participation in the study due to adverse events.

Conclusion

After 10 weeks of treatment with quetiapine, there were significant decreases in the total PANSS scores as well as the general psychopathology and depression subscales of the PANSS. There were statistically significant and clinically meaningful improvements in most subscales of the eating disorder inventory-2, significant decreases in anxiety and depression as measured by the STAI and HAM-D, and significant reduction in hours devoted to obsessions about food, weight, and dieting. Plasma leptin levels increased during the study. Adverse events were generally mild and lightheadedness and transient sedation (sleepiness and lethargy) were the most commonly reported adverse events. No patients discontinued from the study due to adverse events.

Although none of the patients in this study qualified for a diagnosis of schizophrenia, schizoaffective disorder, or bipolar disorder, the mean baseline PANSS scores were quite high with a mean of 56.2 and a range from 44 to 79; seven patients had total scores of 60 or above. Scores over 60 are frequently seen in patients who qualify for studies of patients with schizophrenia. The mean baseline score on the positive subscale of the PANSS was 11.6; about 13% of patients with schizophrenia score in this range[23]; items on this scale include questions about delusions, hallucinations, excitement, and suspiciousness. The mean baseline scores on the general psychopathology subscale of the PANSS for this group of AN patients was 31.1; 17% of patients with schizophrenia score in this range.[23]

Although mean weight gain from baseline to last observation carried forward was modest and not statistically significant, nearly half the patients did gain weight, and among these nine patients, the mean weight gain was 5.3 lbs (2.4 kg). Also, one of these patients gained to ideal body weight. Interestingly, when the PANSS data were analyzed separately for those patients who gained weight compared with those who did not gain weight, there were significant differences only for those who gained weight but not for those who did not gain weight. It is unclear if this means that patients who had significant improvements in the PANSS were more likely to gain weight or if improvement in weight resulted in improvement in the PANSS.

Some findings in this study are similar to those reported in an earlier study with olanzapine[15] although the mean weight gain with quetiapine was less. However, in both studies there were significant declines in total PANSS scores and among the groups that gained weight, compared to the groups that did not gain weight, and there were improvements in certain scales of the PANSS that measure symptoms of psychosis. It is possible that weight gain per se results in improvement in psychotic symptoms in this patient population, but since there was no statistically significant difference in PANSS scores at Day 1 among patients who subsequently gained or lost, another explanation seems more likely. Among other groups of patients treated with atypical antipsychotics (e.g., patients with schizophrenia), olanzapine results in greater weight gain than quetiapine. In one large European study, after 6 months, olanzapine resulted in a weight gain of 2.4 kg (5.3 lbs) compared to quetiapine that resulted in a weight gain of 0.6 kg (1.31 lbs); this difference was statistically significant.[29]

Another finding that is similar to the study with olanzapine is that there were significant improve-

ments in anxiety (including obsessive compulsive symptoms) and depression. Also, many symptoms that are part of anorexia nervosa that are measured by the EDI-2 improved during the 10 weeks on quetiapine. It may be that psychological symptoms do not underlie the difficulty gaining weight and it may be that olanzapine has a more potent effect on weight via a number of different mechanisms.

In summary, in this study, there were improvements in PANSS scores, in several measures of anxiety and depression, and in symptoms of anorexia nervosa measured by the EDI-2. There were multiple limitations to the study including open treatment, nonblind assessment, short-term duration of the trial, and a high dropout rate. Also the risk of extrapyramidal side effects must be considered. Although mean weight gain was not clinically significant for the entire group, nearly half gained a modest amount of weight and one patient gained to ideal body weight. Patients with AN have multiple symptoms including anxiety, depression, obsessions, and compulsions. Reduction in those symptoms might make weight gain easier. An important next step in understanding the possible value of quetiapine in the treatment of patients with anorexia nervosa is a double-blind, randomized placebo-controlled trial.

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