

# Quetiapine Alone and Added to a Mood Stabilizer for Serious Mood Disorders

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**Background:** Use of antipsychotic medication intermittently or over the long term may be necessary in treating patients with bipolar disorder whose symptoms have responded suboptimally to standard mood-stabilizing agents. Quetiapine fumarate is an effective novel antipsychotic with mixed serotonergic (5-HT<sub>2</sub>) and dopaminergic (D<sub>2</sub>) activity. This is an open-label, 12-week prospective study to assess the efficacy and tolerability of quetiapine in the treatment of patients with bipolar and schizoaffective disorder who were suboptimally responsive to mood stabilizers alone.

**Method:** Participants in the study were inpatients or outpatients with a DSM-IV diagnosis of bipolar or schizoaffective disorder. Baseline psychopathology was evaluated with the Brief Psychiatric Rating Scale (BPRS), the Young Mania Rating Scale (YMRS), and the Hamilton Rating Scale for Depression (HAM-D). Involuntary movements were rated with the Simpson-Angus Neurologic Rating Scale. Quetiapine was added on an open-label basis and increased to optimum clinical dosage. Psychopathology and Abnormal Involuntary Movement Scale ratings were repeated weekly for the first 4 weeks and then again at weeks 8 and 12.

**Results:** Ten individuals with bipolar disorder and 10 with schizoaffective disorder received quetiapine therapy. Overall, patients improved, with significant improvement in BPRS ( $p < .001$ ), YMRS ( $p = .043$ ), and HAM-D scores ( $p = .002$ ). Simpson-Angus score also significantly decreased ( $p = .02$ ). Overall, quetiapine was well tolerated by patients in this group with serious mood disorders. The mean  $\pm$  SD quetiapine dose was  $202.9 \pm 124.3$  mg/day (range, 50–400 mg/day). Mean weight gain was 10.9 lb (4.9 kg).

**Conclusion:** Although limited by its small size, open-label design, and relative gender homogeneity, this study suggests that quetiapine therapy may be useful in the treatment of individuals with serious mood disorders who are suboptimally responsive to mood stabilizers alone. These preliminary findings should be explored in larger, controlled trials.

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**B**ipolar disorder is a major public health problem with significant morbidity and mortality.<sup>1</sup> In 1990, the economic burden of bipolar disorder in the United States was estimated to be \$15.5 billion in diminished or lost productivity in work performance alone,<sup>2</sup> while approximately 11% of individuals with bipolar disorder die by suicide.<sup>3</sup> While 1 or more episodes of acute mood disorder are not generally associated with the personality deterioration that occurs in psychotic illnesses such as schizophrenia, many individuals with bipolar disorder experience persistent symptoms and poor outcome.<sup>4</sup> These patients often have severe impairment in functioning and frequent or long hospitalizations and many times require a complex medication regimen with multiple mood stabilizers. Use of antipsychotic medication intermittently or over the long term may also be necessary in treating patients whose symptoms have responded suboptimally to standard mood-stabilizing agents.<sup>5,6</sup> These patients are frequently maintained on chronic neuroleptic treatment,<sup>7</sup> and combining lithium with other medications, including anti-

psychotics, may provide greater prophylaxis in bipolar disorder.<sup>8</sup>

Individuals with schizoaffective disorder have a prominent affective component in addition to chronic psychosis and usually require maintenance antipsychotic medication along with psychotropic medication for affective symptoms. The use of chronic neuroleptic therapy in seriously ill mood disorder patients often creates additional new problems. These patients may be at greater risk of developing tardive dyskinesia (TD) compared with patients with schizophrenia, and often experience other extrapyramidal adverse effects or central nervous system (CNS) side effects associated with conventional neuroleptics such as sedation. Mukherjee et al.<sup>10</sup> reported that up to 73% of patients meeting criteria for bipolar disorder remained on long-term neuroleptic treatment (average = 8.7 years), whereas the prevalence of TD in individuals with bipolar disorder has been reported to range from 19% to 44%.<sup>11–13</sup>

Quetiapine fumarate is an effective novel antipsychotic with mixed serotonergic (5-HT<sub>2</sub>) and dopaminergic (D<sub>2</sub>) activity.<sup>14</sup> Clinically, it appears to be generally well tolerated with a low extrapyramidal adverse effect profile.<sup>15</sup> Given the greater risk of neurologic adverse effects of patients with mood disorder compared with patients with schizophrenia, the novel antipsychotics may prove to be a particularly important therapy for individuals who have significant mood disorder and who require antipsychotic medication. This is an open-label, 12-week prospective study to assess efficacy and tolerability of quetiapine in the treatment of patients with serious mood disorders suboptimally responsive to mood stabilizers alone.

## METHOD

Eligible participants in the study were inpatients or outpatients with a DSM-IV<sup>16</sup> diagnosis of bipolar or schizoaffective disorder at a large, urban Veterans Affairs (VA) Medical Center. All participants had been taking an antipsychotic medication for at least 6 months with documented inability to wean off of neuroleptic treatment. Inability to successfully stop neuroleptic treatment was manifested by clinical worsening with neuroleptic reduction or discontinuation. Participants who were taking mood stabilizers must have been maintained on a stable and therapeutic dosage of the mood stabilizer (lithium or valproic acid). Individuals with significant or acutely worsening medical illness were excluded, as were individuals with significant alcohol or drug use within the previous 3 months. Baseline psychopathology was evaluated with the Brief Psychiatric Rating Scale (BPRS),<sup>17</sup> the Young Mania Rating Scale (YMRS),<sup>18</sup> and the Hamilton Rating Scale for Depression (HAM-D).<sup>19</sup> Involuntary movements were rated at baseline using the Abnormal Involuntary Movement Scale (AIMS)<sup>20</sup> and the Simpson-Angus Neurologic Rating Scale.<sup>21</sup> Subjective response to antipsy-

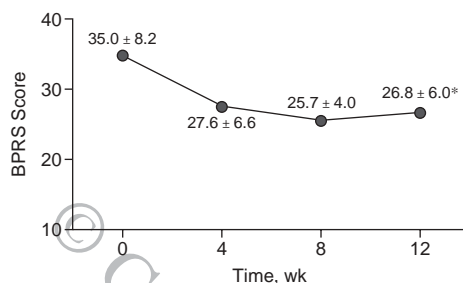
chotic medication was rated with the Drug Attitude Inventory (DAI) developed by Awad.<sup>22</sup> Patients who agreed to study participation and met entry criteria were begun on quetiapine, 25 mg b.i.d., on an add-on, open-label basis. Quetiapine was increased as clinically tolerated to therapeutic dosage (possible range, 25–800 mg/day). Conventional antipsychotic medication was incrementally tapered and eventually discontinued as tolerated during the first 4 weeks of the study. This discontinuation was done at the discretion of the treating psychiatrist on the basis of patient clinical status. Patients were permitted to receive lorazepam, 1 mg orally p.r.n., for sleep or agitation and/or anticholinergic medications if required for acute extrapyramidal symptoms. No other new psychotropic drugs were permitted. Quetiapine therapy was continued for a total of 12 weeks. Psychopathology and abnormal involuntary movement ratings were repeated weekly for the first 4 weeks, then again at weeks 8 and 12 (end of study). Data were analyzed using paired *t* tests comparing baseline psychopathology and abnormal movement scores with endpoint scores. All endpoint scores utilized last observation carried forward (LOCF). This prospective protocol was approved by the local VA Institutional Review Board (Cleveland, Ohio), and appropriate written informed consent was obtained from all study participants.

## RESULTS

Twenty individuals (10 with bipolar disorder and 10 with schizoaffective disorder) received quetiapine therapy. Mean  $\pm$  SD age of the group was  $47.8 \pm 10.2$  years (range, 34–74 years). Not surprisingly, this veteran sample was predominantly male, with 19 men and 1 woman. Racial composition of the group was 14 white individuals (70%) and 6 African American individuals (30%). There were no statistically significant differences between individuals with bipolar disorder and those with schizoaffective disorder in terms of demographic characteristics or baseline psychopathology rating scale scores or movement rating scale scores. Study participants generally had persistent mild-to-moderate psychotic and depressive symptoms at study entry that, by history, had not responded optimally to mood stabilizers alone. Five individuals were maintained on lithium treatment (mean  $\pm$  SD dosage =  $1125 \pm 248.8$  mg/day), and 8 individuals were maintained on valproate treatment (mean  $\pm$  SD dosage =  $1468.8 \pm 471.3$  mg/day). Mean  $\pm$  SD serum levels were  $82.0 \pm 17.0$   $\mu$ g/mL for valproate and  $0.74 \pm 0.15$  mEq/L for lithium. Seven individuals were not taking a mood stabilizer, and no individual was taking more than 1 mood stabilizer.

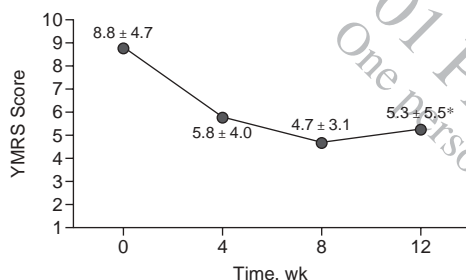
Overall, patients improved on quetiapine therapy, with significant improvement in BPRS score ( $p < .001$ ), YMRS score ( $p = .043$ ), and HAM-D score ( $p = .002$ ). Figures 1 through 3 illustrate changes from baseline to

**Figure 1. Brief Psychiatric Rating Scale (BPRS) Score (mean  $\pm$  SD) for Patients With Serious Mood Disorders on Quetiapine Therapy<sup>a</sup>**



<sup>a</sup>All analyses used last-observation-carried-forward methodology.  
\* $t = 1.7$ ,  $df = 35$ ,  $p < .001$  vs. baseline.

**Figure 2. Young Mania Rating Scale (YMRS) Score (mean  $\pm$  SD) for Patients With Serious Mood Disorders on Quetiapine Therapy<sup>a</sup>**

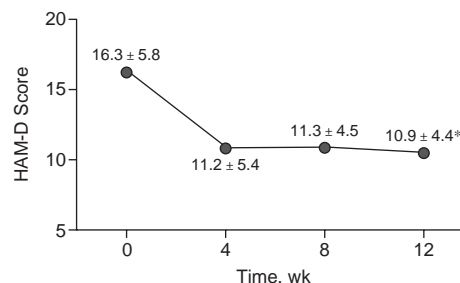


<sup>a</sup>All analyses used last-observation-carried-forward methodology.  
\* $t = 1.7$ ,  $df = 37$ ,  $p = .043$  vs. baseline.

endpoint (using LOCF) on these psychopathology scales. There were no statistically significant differences between the bipolar and schizoaffective groups in response on any scale. There were also no significant differences in treatment response between individuals treated with quetiapine alone and individuals treated with quetiapine in combination with a mood stabilizer. Item analysis of the BPRS suggests that the items evaluating conceptual disorganization and suspiciousness changed the most, whereas the items evaluating guilt feelings, tension, hallucinatory behavior, uncooperativeness, excitement, and disorientation changed the least. However, comparing these items, the amount of change between items was not significant at  $\alpha = .05$ . Mean  $\pm$  SD Simpson-Angus scale score also significantly decreased from a baseline of  $5.5 \pm 4.9$  to an endpoint score of  $1.9 \pm 3.8$  ( $t = 1.7$ ,  $df = 34$ ,  $p = .02$ ). There was no statistically significant change in AIMS score or in DAI score.

Overall, quetiapine was well tolerated by patients in this group with serious mood disorders. Three individuals dropped out within 1 week of beginning the study. These included 1 individual who began abusing alcohol within a

**Figure 3. Hamilton Rating Scale for Depression (HAM-D) Score (mean  $\pm$  SD) for Patients With Serious Mood Disorders on Quetiapine Therapy<sup>a</sup>**



<sup>a</sup>All analyses used last-observation-carried-forward methodology.  
\* $t = 1.7$ ,  $df = 35$ ,  $p = .002$  vs. baseline.

few days after study initiation, 1 individual who was non-compliant with study medication, and 1 individual who reported the development of agitation, which resolved on quetiapine discontinuation. Mean  $\pm$  SD quetiapine dose was  $202.9 \pm 124.3$  mg/day (range, 50–400 mg/day) for the 17 individuals who completed the study and  $178.8 \pm 28.6$  mg/day (range, 50–400 mg/day) for the entire sample. Mean  $\pm$  SD weight gain over the course of the study was  $10.9 \pm 12.9$  lb ( $4.9 \pm 5.8$  kg). Of note were 2 individuals who had nutrition/dietician consultation and follow-up at study entry. These 2 individuals had a small amount of weight loss (3 and 4 lb [1.4 and 1.8 kg], respectively) during the study course.

## DISCUSSION

Long-term or intermittent use of antipsychotic medication may be deemed necessary for some individuals with serious mood disorders when mood or behavioral symptoms have not adequately responded to mood-stabilizer therapy.<sup>5,7</sup> In individuals with persistent mood symptoms and chronic psychosis, the combination of lithium and antipsychotics appears to be more efficacious than an antipsychotic alone.<sup>23</sup> However, the utilization of antipsychotic medication in individuals with chronic, serious mood disorders presents a number of clinical challenges. Some investigators have suggested that neuroleptics may exacerbate postmanic major depressive episodes and induce rapid cycling in some bipolar persons.<sup>24</sup> Additionally, individuals with primary mood disorders may be particularly vulnerable to the development of TD associated with neuroleptic therapy.<sup>25</sup> Other adverse effects, such as sedation, associated with some antipsychotic medications may reduce quality of life. Finally, suboptimal antipsychotic medication response may be associated with persistent behavioral symptoms and long-term functional impairment. The atypical antipsychotic clozapine has been reported to be beneficial, and may have mood-stabilizing

properties, in the treatment of patients with serious mood disorders.<sup>26,27</sup> A recently reported meta-analysis involving primarily retrospective and open-label studies of clozapine suggested that patients with manic or psychotic phases of schizoaffective or bipolar disorder were significantly more likely to respond to clozapine than patients with schizophrenia.<sup>28</sup> The atypical antipsychotic medication olanzapine has been demonstrated to be effective in acute mania,<sup>29</sup> and it has been reported that the atypical antipsychotic risperidone is as effective as lithium or haloperidol in the treatment of acute mania,<sup>30</sup> as well as being effective in adjunctive treatment with mood stabilizers for patients with bipolar and schizoaffective disorder.<sup>31</sup> Published data on the use of quetiapine therapy in serious mood disorders are extremely limited.

Although limited by its small size, open-label design, lack of a control group, and relative gender homogeneity, this study suggests that quetiapine may be a useful agent in the treatment of individuals with serious mood disorders who are suboptimally responsive to mood stabilizers alone. Overall, patients in the study sample did well on quetiapine therapy, with significant improvements in BPRS, YMRS, and HAM-D scores. Improvements were similarly noted by McConville et al.<sup>32</sup> in both positive and negative symptoms in 10 adolescents with psychotic mood disorders (3 individuals with bipolar disorders and 7 individuals with schizoaffective disorder). Most individuals in the study reported here had persistent depressive symptoms. HAM-D improvements were seen here without the addition of antidepressant medication. In a recent report on affective symptoms in individuals with schizophrenia,<sup>33</sup> quetiapine was superior to placebo and haloperidol in improvements in mood symptom items (depressive mood, guilt feelings, somatic concern, and anxiety) on the BPRS.

It must be noted that the results here at 4 weeks reflected a combined effect of quetiapine and neuroleptic, due to the fact that conventional neuroleptic was tapered over the first 4 weeks of the study. It is not clear how the presence of the neuroleptic might have affected dosage of and/or symptom response to the atypical antipsychotic. It is possible that combined therapy may have contributed to the relatively rapid symptom response and may possibly explain the relatively low mean quetiapine dosage in this study (approximately 200 mg/day). The modest quetiapine dosage might also have been due to the use of a concomitant mood stabilizer for most of the patients in this study or to the older age of some of the study participants. However, it is also possible that effective dose of quetiapine required in individuals with mood disorders may be lower than effective doses that have been reported for individuals with schizophrenia.<sup>34</sup> In clinical practice, combination therapy of an antipsychotic plus a mood stabilizer is frequently utilized in the management of serious mood disorders and may enhance clinical outcomes.<sup>35</sup>

Quetiapine was generally well tolerated in this study population, with only 1 dropout due to adverse effect of medication. This finding is consistent with safety and tolerability reports of quetiapine therapy suggesting that most patients, even the elderly, tolerate quetiapine quite well and that incidence of extrapyramidal effects is minimal.<sup>36,37</sup> Kalali et al.<sup>38</sup> reported on 129 patients who received quetiapine therapy and were assessed for patient satisfaction. The majority of individuals (98%) reported being satisfied with their medication treatment, most commonly identifying improved tolerability and improved general well-being compared with previous conventional antipsychotic agents. Quality of life was generally reported to be improved.

There was a mean weight gain of 10.9 lb (4.9 kg) in this trial. This greater-than-expected weight gain may be at least partially due to combined use of quetiapine plus mood-stabilizing medication, both of which may be associated with weight gain. Guille et al.<sup>39</sup> recently reported that individuals with bipolar disorder receiving mood-stabilizing medication plus atypical antipsychotic medication experience weight gain ranging from a mean of 16.1 lb (7.2 kg) with olanzapine to a mean of 7.8 lb (3.5 kg) with risperidone. Guille et al.<sup>39</sup> also reported a trend for less weight gain among patients receiving a novel antipsychotic with lithium than those receiving other mood-stabilizing agents ( $p = .06$ ). Patients receiving prophylactic dietary consultation in the trial presented here did not gain weight.

In conclusion, quetiapine may be beneficial for some individuals with serious mood disorders. These preliminary findings should be explored in larger, controlled trials.

**Drug names:** clozapine (Clozaril and others), haloperidol (Haldol and others), lorazepam (Ativan and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), valproic acid (Depakene and others).

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