Effects of quetiapine on sleep architecture in patients with unipolar or bipolar depression

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Objective: To determine the effect of adjunctive quetiapine therapy on the sleep architecture of patients with bipolar or unipolar depression.

Methods: This is a prospective, single-blind, repeated measures polysomnographic study. Sleep architecture was analyzed by overnight polysomnography, and subjective sleep quality was measured using the Pittsburgh Sleep Quality Index. The Hamilton Rating Scale for Depression, Montgomery Asberg Depression Rating Scale, Young Mania Rating Scale, and Clinical Global Impression-Severity Scale were employed to quantify changes in illness severity with adjunctive quetiapine treatment. Polysomnographs and clinical measures were administered at baseline, after 2–4 days of treatment, and after 21–28 days of quetiapine treatment. The average dose of quetiapine was 155 mg, ranging from 100–200 mg.

Results: Adjunctive quetiapine therapy did not significantly alter sleep efficiency, sleep continuity, or Pittsburgh Sleep Quality Index scores. Respiratory Disturbance Index and percentage of total time in rapid eye movement (REM) sleep significantly decreased and the percentage of total time in non-REM sleep, and duration of Stage 2 and non-REM sleep significantly increased after 2–4 days of quetiapine treatment. Illness severity significantly decreased over time.

Conclusions: Adjunctive quetiapine treatment alters sleep architecture in patients with major depressive disorder or bipolar disorder, which may partially explain its early antidepressant properties. Changes in sleep architecture are more robust and significant within two to four days of starting treatment.

Keywords: quetiapine, sleep architecture, depression, bipolar disorder

Introduction

Quetiapine is an atypical antipsychotic agent and is approved by the United States Food and Drug Administration to treat schizophrenia, major depressive disorder (MDD) and both manic and depressive episodes associated with bipolar disorder. The drug acts as an antagonist at serotonin (5-HT1A and 5-HT2A), dopamine (D1 and D2), histamine (H1), and adrenergic α1 and α2 receptors.1 Results from the BOLDER I and II studies, which were two large, multicenter, randomized, placebo-controlled trials, show that quetiapine is efficacious in the treatment of acute bipolar depression as monotherapy.2,3 These studies led to guidelines recommending quetiapine for use as first-line monotherapy treatment for bipolar depression.4 Use of an atypical antipsychotic as an adjuvant therapy with selective serotonin reuptake inhibitors (SSRIs) has shown benefits in large trials of olanzapine use with fluoxetine.5,6 The use of quetiapine as an adjunctive therapy has been shown to be beneficial in smaller, open-label studies of patients with bipolar depressive episodes.7,8 Large, randomized placebo-controlled...
trials have found the use of quetiapine as monotherapy, or in combination with another antidepressant, to be efficacious in the treatment of MDD.9–11

Patients with MDD and bipolar disorder frequently experience sleep disturbances.12 Poor sleep quality and/or quantity are observed in up to 90% of depressed patients.13 Insomnia is a risk factor for development of major depressive episodes and may precede the onset of depression in those with recurrent illness.14–16 Sleep disturbance is also a risk factor for suicide.17 Studies of sleep architecture using polysomnography (PSG) have demonstrated that sleep in depressed patients tends to be characterized by decreased sleep efficiency, a reduction of slow-wave sleep (SWS), and a disinhibition of rapid eye movement (REM) sleep, manifested by a shortening of REM sleep latency, an increase in REM duration of SWS. If such changes occur and can be related to the improvement of depressive symptomatology, it is suggested that part of quetiapine’s antidepressant effect may be achieved through its restoration of sleep architecture.

Methods
Study design
This was a four-week, single-blind, open-label, repeated measures PSG study of patients with MDD or bipolar disorder currently experiencing a major depressive episode, who received quetiapine fumarate treatment in addition to their current medication regime. Patients were recruited from a single-center, tertiary care mood disorders clinic. The study was approved by the Queen’s University Health Sciences and Affiliated Teaching Hospitals Research Ethics Boards as well as by the Health Canada Therapeutics Products Directorate.

Study population
Patients were recruited from inpatient and outpatient services for the evaluation and treatment of depression. All participants were 18 years of age or older and gave written informed consent. All patients had a Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) diagnosis of bipolar disorder (Type 1, Type 2, or not otherwise specified) or MDD, and were currently experiencing a major depressive episode (Hamilton Depression Rating Scale-17 item [HDRS-17] ≥ 15, Young Mania Rating Scale [YMRS] ≤ 8). Participants with a previous diagnosis of schizophrenia and/or current substance abuse (except caffeine and nicotine) were excluded. Prior antipsychotic use including quetiapine was allowed, but antipsychotics had to have been discontinued at least one week prior to study initiation. Sleep aids, including over-the-counter hypnotics, were discontinued at least one week prior to study initiation, and changes to baseline medications were not allowed in the three weeks prior to participation or during the study. Study participants were withdrawn from the study if they experienced significant side effects or withdrew consent.

Fifteen patients were enrolled in the trial. Four patients voluntarily withdrew from the study before completing a post-baseline PSG, two citing excessive sedation, one a post-menopausal bleed, and one a headache, and thus were not included in the completer analysis population. Therefore, only 11 patients were included in the analysis.

The completer population consisted of nine females and two males, with a mean age of 44.3 (± 9.1) years. Five patients had a diagnosis of MDD and six patients had a diagnosis of bipolar disorder. Ten of 11 patients were taking antidepressants (five venlafaxine, one sertraline, two bupropion, one citalopram, and one a combination of bupropion and venlafaxine). Two patients were taking lithium and topiramate as mood stabilizers. Five patients possibly took sedating medications during the trial; three were taking established regimens of regular benzodiazepines prescribed as anxiolytics (one lorazepam, one clonazepam, and one a combination of oxazepam and lorazepam) and two were taking regular trazodone prescribed as an antidepressant. One patient had

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occasional sleep difficulties surrounding nocturnal priapism
and another patient had obstructive sleep apnea and was being
treated with continuous positive airway pressure.

**Quetiapine treatment**
Quetiapine was given in tablet form and taken at night near
bedtime. An initial dose of 50 mg was given and the dose was
titrated up over the course of the study, with drug tolerance
as the primary influence on titration. The average dose of
quetiapine achieved was 155 mg, ranging from 100–200 mg.
A fourth phase of the study, involving further titration of
quetiapine to a target dose of 600 mg per day and PSG,
PSQI, and mood scales at days 42–48 was optional, and is
not included here due to poor participation (five of 11 patients
of the completer group).

**Clinical assessments**
Patients were assessed at three time points, ie, baseline (before
administration of study medication), and after 2–4 days and
21–28 days of quetiapine treatment. Each clinical assessment
consisted of the HDRS-17, Montgomery Asberg Depression
Rating Scale (MADRS), YMRS, Clinical Global Impression
Severity (CGI-S) scale, and participant-reported PSQI.

**Polysomnomography**
Objective sleep architecture measurements were derived
from PSG data of study participants at defined intervals
throughout the study period. A baseline PSG was taken on
the day before quetiapine administration began, then once
during days 2–4, and once during days 21–28. On each of
the three study nights, sleep PSGs were set up by a quali-
fied technician and recorded using the MediPalm Personal
Recording Device (Braebon Corp., Ogdensburg, NY) while
the patient slept at home. Patients were asked to retire and
rise at their usual time. The standard overnight PSG sleep
study included four electroencephalogram channels (C4-A1,
C3-A2, O2-A1, O1-A2), electro-oculogram (two channels),
submental electromyogram (EMG), pulse oximetry, oronasal
airflow (oronasal thermistor), chest and abdominal movement
(respiratory inductance plethysmography), and tibialis ante-
rior EMG. A position sensor was used to monitor position
continuously (Ultima Body Position Sensor; Braebon Corp.,
Ogdensburg, NY). The overnight sleep routine was applied
starting at around 1900 hours each study night. Recording
began at approximately 2100 hours, and ran for eight hours
continuously or until the participant rose in the morning. One
of two certified PSG analysts, different from the technician
setting up the PSG and blinded to study design and day of
study, scored the sleep record in 30-second segments accord-
ing to the standardized criteria of Rechtschaffen and Kales,25
using Pursuit Advanced Sleep System software (Braebon
Corp., Ogdensburg, NY).

Sleep onset was defined as the beginning of the first
two minutes that were not scored as awake or movement.
Latencies to each sleep stage were calculated to the first two
continuous minutes of the stage. Obstructive apneas and
hypopneas were scored using the criteria from the American
Academy of Sleep Medicine Task Force.26 Events were scored
when a >50% decrease (apnea) in airflow, or clear reduction
(hypopnea) in amplitude of the airflow signal (compared
with stable breathing during the two minutes preceding the
event), occurred associated with an arousal, a greater than 3%
reduction in oxygen saturation (SaO2), or both, and the event
lasted for at least 10 seconds. Arousals were scored based on
American Sleep Disorders Association criteria.27 Arousals
had to be preceded by at least 10 seconds of sleep, have an
electroencephalogram frequency shift to alpha or theta for at
least three seconds and up to 15 seconds, and be associated
with concurrent increased EMG tone in REM sleep. The
respiratory disturbance index (RDI), which included apneas,
hypopneas, and snore arousals for the number of events per
hour of sleep, was calculated. Sleep efficiency (percentage)
was calculated as the total sleep time divided by the total time
in bed, multiplied by 100.

**Statistical analysis**
The completer analysis population was comprised of the
patients who had initiated quetiapine during the trial and
had both a baseline and at least one post-baseline PSG
measurement. Calculation of the sample size was based on
choosing sleep efficiency as the primary outcome measure
and estimating that a 15% improvement in sleep efficiency
would be a clinically meaningful finding in this population. In
the power calculation, we have used baseline sleep efficiency
for depressed population to be 67.4 with a standard deviation
(SD) ± 18.88.28 In order to detect a 15% improvement in sleep
efficiency using one-sided normal distribution paired t-test
analysis with a significance of 0.05 and 80% power, a total of
12 (11.277) patients is required. A sample size of 15 patients
was used to allow for patient drop out.

Statistical analysis of data was done using the SPSS 17.0.1
for PC (SPSS Inc, Chicago, IL). Nonparametric analysis using
the Wilcoxon Signed Rank test for two related samples, com-
paring pre- and post-treatment measures, was used because
sample sizes were small and often not normally distributed
(determined by Kolmogorov-Smirnov analysis). In those
few pairwise comparisons in which both sets of data were normally distributed, additional analysis using two-sided normal distribution paired t-test analysis with a significance of 5% was undertaken. Three of the 11 patients missed their day 21–28 PSG, one of whom had values substituted from their day 42–48 PSG administered during the optional extension period. An attempt to use multiple regression analysis to approximate missed PSG data failed to generate values consistent with prior observed values and, thus, for t-tests, the last observation was carried forward and substituted for missing values.

Results

Sleep efficiency
Quetiapine did not significantly alter sleep efficiency. Mean sleep efficiency (± SD) was 69.8% (± 20.6), 78.4% (± 9.7), and 74.5% (± 17.4) at baseline, and days 2–4, and days 21–28, respectively (P = 0.48 and P = 0.21, Figure 1, Table 1).

Sleep continuity
No significant changes in total sleep time (P = 0.18), number of awakenings (P = 0.72), time in bed (P = 0.66), and latency to sleep onset (P = 0.51) were identified after initiation of quetiapine. A significant fall in the RDI was observed after 2–4 days of quetiapine treatment compared with baseline (P = 0.041). However, RDI then increased and there was no significant difference in RDI after 21–28 days of quetiapine treatment compared with pretreatment initiation (P = 0.86, Table 1).

Sleep architecture

Non-REM sleep
Acute quetiapine treatment significantly altered non-REM sleep stage characteristics, but longer-term treatment did not. The duration of both total Stage 2 sleep (P = 0.016) and total non-REM sleep (P = 0.05), as well as the percentage of total sleep time in non-REM sleep (P = 0.033) significantly increased 2–4 days after treatment initiation, compared with baseline, and then decreased towards baseline values. However, no significant difference in the above sleep measures was found between baseline and 21–28 days after treatment initiation (Table 1).

After 2–4 days of quetiapine treatment, total time in Stage 1 sleep (P = 0.16), percentage of total sleep time in Stage 1 sleep (P = 0.86), percentage of total sleep time in Stage 2 sleep (P = 0.06), percentage of total sleep time in SWS (P = 0.11), and total time in SWS (P = 0.20) were not significantly altered. After 3–4 weeks of treatment, percentage of total sleep time in Stage 1 sleep (P = 0.86), percentage of total sleep time in Stage 2 sleep (P = 0.95), total time in Stage 2 sleep (P = 0.86), percentage of total sleep time in non-REM sleep (P = 0.44), total time in non-REM sleep (P = 0.89), total time in SWS (P = 0.48), and percentage of total sleep time in SWS (P = 1.0) were not significantly altered compared with baseline measurements (Table 1).

REM sleep
Quetiapine initially altered REM sleep stage characteristics, but no significant changes from pretreatment measurements were observed after 21–28 days. The percentage of total sleep time in REM sleep significantly decreased 2–4 days after quetiapine treatment initiation (P = 0.033), although there was no significant difference in percentage of total sleep time in REM sleep between pretreatment and 3–4 weeks post-treatment (P = 0.49, Figure 1, Table 2). After 2–4 days of treatment, there was no significant difference in latency to REM sleep (P = 0.86) and total time in REM sleep (P = 0.18) compared with pretreatment measurements. Three to four weeks of quetiapine treatment did not significantly alter latency to REM sleep (P = 0.59), percentage of total sleep time in REM sleep (P = 0.49), and total time in REM sleep (P = 0.49, Table 1).

Subjective sleep quality
PSQI scores did not significantly change between baseline, 2–4 days, and 21–28 days after initiation of quetiapine treatment, although PSQI scores tended to decrease over time (P > 0.05). After 21–28 days of quetiapine treatment, the
subjective sleep quality subscore of the PSQI was significantly lower than before treatment ($P < 0.05$), indicating that quetiapine significantly improved subjective sleep quality after four weeks. However, there was no significant difference in subjective sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, and sleep dysfunction subscores after 2–4 days or 21–28 days of treatment compared with baseline, although scores declined with the exception of habitual sleep efficiency, which remained unchanged (Table 2).

### Table 2 PSQI scores over one month of quetiapine adjunctive treatment in 11 subjects

<table>
<thead>
<tr>
<th>PSQI sleep questionnaire</th>
<th>Baseline (Mean ± SD)</th>
<th>Days 2–4 (Mean ± SD)</th>
<th>Days 21–28 (Mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjective sleep quality</td>
<td>2.5 ± 0.5</td>
<td>1.9 ± 1.0</td>
<td>1.3 ± 0.9*</td>
</tr>
<tr>
<td>Sleep latency</td>
<td>2.0 ± 1.2</td>
<td>1.5 ± 1.1</td>
<td>1.4 ± 1.2</td>
</tr>
<tr>
<td>Sleep duration</td>
<td>1.2 ± 1.0</td>
<td>1.0 ± 1.1</td>
<td>0.5 ± 0.8</td>
</tr>
<tr>
<td>Habitual sleep efficiency</td>
<td>1.9 ± 1.4</td>
<td>1.0 ± 1.2</td>
<td>0.6 ± 1.0</td>
</tr>
<tr>
<td>Sleep disturbances</td>
<td>1.9 ± 0.6</td>
<td>1.5 ± 0.5</td>
<td>1.6 ± 0.8</td>
</tr>
<tr>
<td>Use of sleep medication</td>
<td>1.2 ± 1.4</td>
<td>1.0 ± 1.3</td>
<td>1.2 ± 1.5</td>
</tr>
<tr>
<td>Daytime dysfunction</td>
<td>2.2 ± 0.6</td>
<td>1.8 ± 0.6</td>
<td>1.7 ± 0.9</td>
</tr>
<tr>
<td>Total score</td>
<td>12.9 ± 4.1</td>
<td>9.7 ± 4.2</td>
<td>8.4 ± 4.9</td>
</tr>
</tbody>
</table>

Mean score ± SD of each item and total score on PSQI subjective sleep scale. PSQI scale was completed by participants at baseline, and after 2–4 days and 21–28 days of quetiapine treatment. *$P < 0.05$ compared with baseline.

#### Mood

Quetiapine significantly improved mood and decreased depressive symptoms. Total MADRS scores significantly declined from baseline to days 2–4 ($P = 0.01$) and to days 21–28 ($P = 0.008$) of quetiapine treatment, to mean scores (± SD) of 28.1 (± 7.0), 22.4 (± 7.9), and 14.1 (± 8.4), respectively (Figure 2). Both HDRS and CGI-S total scores significantly decreased ($P = 0.01$ and $P = 0.02$) from baseline mean scores (± SD) of 22.3 (± 4.4) and 4.5 (± 1.2), respectively, to mean scores of 12.0 (± 5.8) and 3.2 (± 1.7) after 21–28 days of quetiapine treatment (Figures 3 and 4). YMRS mania scores remained low and statistically unchanged over time.

#### Discussion

This study demonstrates that adjunctive quetiapine treatment improves self-reported sleep quality, decreases illness severity, and initially alters sleep architecture in depressed patients. Alterations in sleep architecture are no longer seen after a longer treatment span. Specifically, quetiapine significantly increased total Stage 2 sleep time and total time spent in non-REM sleep, as well as decreased the percentage of total sleep time in REM sleep and the RDI after 2–4 days of treatment. However, these significant effects were not seen after 21–28 days of treatment. Depression significantly improved after 3–4 weeks of treatment. Therefore, it is evident that quetiapine adjunctive treatment in
depressed patients induces changes in sleep architecture that are more robust and significant upon acute treatment and tend to taper off, approaching pretreatment values after 3–4 weeks of treatment. Mood continues to improve over time, with illness severity lowest after 3–4 weeks of treatment. These results emphasize that quetiapine relieves depressive symptoms effectively and rapidly and produces mild sleep benefits, with the exception of slightly increasing the number of awakenings and decreasing the latency to REM sleep.

Improvements in sleep continuity following quetiapine treatment have been observed in individuals who are not depressed. On the first night of treatment, Cohrs et al found that quetiapine significantly increased sleep period time, total sleep time, and sleep efficiency in healthy individuals. Moreover, in an open-label trial of patients with insomnia, total sleep time and sleep efficiency measured by PSG increased, and this increase extended over weeks of quetiapine treatment. To our knowledge, the current study is the first to investigate sleep architecture, as well as observe changes in sleep in depressed patients undergoing quetiapine treatment, and in particular, patients who are resistant to SSRI treatment. It is important to note that pretreatment sleep efficiency values, with a mean of 69.8 ± 20.6%, in this study are comparable with those of other PSG studies in depressed patients (67.4 ± 18.9%), indicating that there was no selection bias regarding the baseline sleep quality of participants in this study.

The effects of atypical antipsychotics on sleep architecture in depressed patients are not well documented. However, similar improvements in sleep following quetiapine treatment are also observed in the few other antipsychotics that have been studied. Adjunctive olanzapine treatment improves sleep continuity as well as increases percentage of sleep time in both non-REM sleep and SWS sleep in treatment-resistant patients with MDD. Risperidone decreases REM sleep and increases Stage 2 sleep in SSRI-resistant depressed patients. This study shows that quetiapine increases non-REM sleep, as does olanzapine, in addition to increasing Stage 2 sleep and decreasing REM sleep, as does risperidone. Quetiapine appears to alter sleep architecture initially in a manner similar to other...
medications in its class; however, unlike treatment with other antipsychotics, these improvements in sleep do not last.

Of particular interest is the finding that quetiapine suppressed REM sleep, as identified by decreased percentage of REM sleep. Depression is associated with REM sleep abnormalities including decreased REM latency, increased REM density, and increased REM time.32,33 It is possible that an initial decrease in REM sleep may be related to acute improvements in mood following quetiapine treatment; however, longer-term improvements in depressive symptomatology are not related to changes in sleep.

The sleep-inducing properties of quetiapine are most likely related to the medication’s receptor-binding profile. Quetiapine is an antagonist at H1 receptors, inducing sleep upon inhibition of histamine synthesis. Histaminergic activity has more recently been implicated in the development of depression. Patients with depression show a decrease in H1 receptor binding, and this decrease is correlated with illness severity.34 Therefore, the modulation of histaminergic activity by quetiapine to induce sleep may be related to the reduction of depressive symptoms in these patients.

The most substantial changes in sleep occurred after 2–4 days of treatment, after which these changes began to decline, yet patients experienced the greatest improvement in mood after 21–28 days of quetiapine treatment. This leads us to conclude that, while psychotropic medications may act to reduce depressive symptoms by improving the sleep of patients with depression or bipolar disorder, sleep improvements are only a part of the medication’s therapeutic action. Improvements in sleep contribute to a therapeutic response, but do not account on their own for the reduction in depressive symptomatology seen after quetiapine treatment.

The main limitations in this study are its open-label design, small sample size, lack of a control group, and a study population of predominantly women. Furthermore, sleep studies such as this one, acquire PSG data at distinct time points which may not be representative of the entire week. This study should be repeated as a randomized, placebo-controlled, double-blind assessment study with a larger sample size.

**Conclusion**

Acute quetiapine adjunctive therapy alters sleep architecture in depressed patients, after which these changes taper off towards baseline levels and are not significantly present after longer-term treatment. This pilot study suggests that further investigation of the effect of quetiapine on sleep architecture is warranted in patients experiencing a major depressive episode.

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