

# Quetiapine for insomnia: A review of the literature

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**P**opulation-based estimates have indicated that as many as 30% of adults have symptoms of insomnia, and 10% experience daytime impairment or stress due to their insomnia.<sup>1</sup> Insomnia can result in decreased quality of life, decreased work productivity, increased risk of accidents (e.g., motor vehicle accidents, work-related accidents), and increased health care utilization.<sup>1,2</sup> People with insomnia are more likely to be absent from work and to use more health care resources compared with people without insomnia, resulting in increased costs to both patients and society.<sup>3,4</sup>

Insomnia is often chronic in nature. In a population-based study of 388 adults with insomnia, 74% reported having insomnia for at least one year, and 46% continued to have insomnia after three years.<sup>5</sup> The chronic nature of insomnia implies the potential for long-term drug therapy, particularly with sedative hypnotics, a controversial topic beyond the scope of this article.<sup>6</sup>

Insomnia is frequently associated with psychiatric disorders. Estimates report that as many as 40% of patients with insomnia have a

**Purpose.** The safety and efficacy of quetiapine for the treatment of insomnia in adults are reviewed.

**Summary.** Quetiapine was developed for the treatment of psychiatric disorders, but its antagonism of histamine H<sub>1</sub>- and serotonin type 2A receptors has the added effect of causing sedation. As such, quetiapine is widely used off-label as a treatment for insomnia. Due to quetiapine's potential adverse effects, guidelines for the treatment of insomnia have recommended the drug's use only in patients with specific comorbid psychiatric disorders. The use of quetiapine for the treatment of insomnia in the absence of comorbid conditions has been evaluated in only two clinical trials of 31 patients in total, and very few studies have evaluated quetiapine use in patients with insomnia and other comorbidities. No trials have been conducted comparing quetiapine with an

active control (e.g., zolpidem); the data that exist compare quetiapine to a placebo or there is no comparison and all patients are treated with quetiapine. Very few studies have evaluated quetiapine's efficacy in the treatment of insomnia using sleep objective testing, another limitation of the available data on quetiapine.

**Conclusion.** Robust studies evaluating the safety and efficacy of quetiapine for the treatment of insomnia are lacking. Given its limited efficacy data, its adverse-effect profile, and the availability of agents approved by the Food and Drug Administration for the treatment of insomnia, quetiapine's benefit in the treatment of insomnia has not been proven to outweigh potential risks, even in patients with a comorbid labeled indication for quetiapine.

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concomitant psychiatric disorder.<sup>1</sup> The comorbid psychiatric disorder most commonly associated with insomnia is depression, but insomnia has also been associated with anxiety, substance abuse, and posttraumatic stress disorder.<sup>1-4,7-9</sup> Insomnia can be either a cause or a consequence of an underlying psychiatric disorder;

as such, insomnia in the presence of a psychiatric disorder should be considered a comorbid condition.<sup>7</sup> Common mechanisms are thought to underlie insomnia and psychiatric disorders, suggesting that, while a person may be predisposed to both, it might be possible to treat both conditions with the same treatment.<sup>1-4,8,9</sup>

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### Rationale for and prevalence of quetiapine use for insomnia

Quetiapine is a dibenzothiazepine derivative with Food and Drug Administration (FDA)-approved labeling for the treatment of schizophrenia and acute manic, depressive, or mixed episodes of bipolar I disorder; maintenance treatment of bipolar I disorder in combination with lithium or divalproex; and adjunctive treatment of major depressive disorder.<sup>10,11</sup> Quetiapine has also been used for the off-label treatment of anxiety disorders, dementia, autism, refractory obsessive-compulsive disorder, delirium, and insomnia.<sup>12,13</sup> It exhibits a strong affinity for antagonism at histamine H<sub>1</sub>-receptors, similar to that of diphenhydramine, amitriptyline, mirtazapine, and doxepin, and has a moderate affinity for serotonin type 2A (5-HT<sub>2A</sub>) receptors.<sup>14</sup> Antagonism at these receptor sites is thought to be the primary mechanism behind quetiapine's sedative properties.<sup>14</sup> Due to quetiapine's potential adverse effects (e.g., orthostatic hypotension, weight gain, hyperlipidemia, hyperglycemia), guidelines for the treatment of insomnia have recommended the drug's use only in patients who have a comorbid psychiatric disorder and in those "who may benefit from the primary action of [the drug] as well as from the sedating effect."<sup>15</sup>

Despite the recommendation to limit its use to individuals with a comorbid psychiatric disorder, the medical literature has reported widespread use of quetiapine for

the treatment of insomnia, particularly in prison and military populations, with significant cost implications. A recent study of low-dose quetiapine use (<100 mg daily) in the New Jersey prison population highlighted the frequency of the drug's use for insomnia as well as the expense of brand-name quetiapine (Seroquel, AstraZeneca).<sup>16</sup> At the beginning of the study, as many as 12 patients per psychiatrist were taking low-dose quetiapine for insomnia. The average wholesale price was \$4.50 per tablet of quetiapine (50 or 100 mg) compared with \$0.05 per tablet of hydroxyzine hydrochloride (100 mg), making quetiapine 90 times more expensive than hydroxyzine, another agent used to treat insomnia.<sup>16</sup>

A retrospective chart review of 692 soldiers treated with quetiapine at Madigan Army Medical Center in Tacoma, Washington, revealed that the most common indications for quetiapine use were insomnia (57%) and anxiety (20%).<sup>17</sup> Further, only 9.4% of soldiers were prescribed quetiapine for an FDA-approved indication. According to the Associated Press, the Pentagon and the Department of Veterans Affairs spent \$8.6 million and \$125.4 million on quetiapine in 2009, respectively.<sup>18</sup> Information on the use of quetiapine in the general population is more elusive; however, off-label use is frequent. In 2002, quetiapine was sixth on the list of the top 16 drugs used to treat insomnia.<sup>19</sup> Quetiapine became available in generic form in March 2012 but is still considerably costly, approximately \$6–\$7 per tablet for 50- and 100-mg tablets.<sup>20</sup>

This article examines the safety and efficacy of quetiapine use for the treatment of insomnia.

### Literature review

A literature search was performed using PubMed and MEDLINE (1950–April 2013) with the search terms *quetiapine* and *insomnia*. The

search was limited to clinical trials, human studies, and studies written in English. Of the 25 studies identified using these criteria, 13 were included in this review. Twelve studies were excluded because the enrolled participants did not have a diagnosis of insomnia at baseline.

**Outpatient insomnia management.** Cohrs et al.<sup>21</sup> performed a randomized, double-blind, placebo-controlled crossover study to examine the effects of quetiapine on the polysomnographic sleep structure and subjective sleep quality of 14 healthy men (mean age, 27 years old). Each participant was studied three times for three consecutive nights four days apart. No treatment was administered on night 0. On nights 1 and 2, participants received placebo, quetiapine 25 mg, or quetiapine 100 mg orally one hour before sleep. Participants slept in standard sleep laboratory conditions on night 1; on night 2, acoustic stress was applied. Compared with placebo, quetiapine improved sleep latency, total sleep time, and sleep efficiency ( $p < 0.01$ ,  $p < 0.001$ , and  $p < 0.001$ , respectively) compared with placebo. Specific polysomnographic data are provided in Table 1. Similar findings were noted in the subjective sleep quality scores and time scores on the visual analog scale and sleep questionnaires. The number of awakenings experienced was fewer in participants randomized to quetiapine versus placebo but was not significantly different ( $p = 0.10$ ). Overall, quetiapine was well tolerated. Two volunteers withdrew from the study after experiencing orthostatic hypotension after receiving 100 mg of quetiapine; these participants were not included in the data analysis. The other adverse effect of note was periodic leg movement, which was most prevalent in the individuals who received quetiapine 100 mg. This study was limited by its small sample size and the fact that subjects took quetiapine for only two nights.

**Insomnia disorder.** To date, two published studies have evaluated the use of quetiapine specifically for the treatment of insomnia. In an open-label pilot study by Wiegand et al.,<sup>22</sup> 18 adults with insomnia (demographics not reported) were treated with quetiapine 25 mg orally at bedtime. The dosage of quetiapine was increased to 50 mg in 7 patients and to 75 mg in 1 patient. Patients experienced improvement in sleep parameters after two weeks and continued to show improvements at six weeks

based on both objective and subjective data (Tables 1 and 2). Total sleep time and sleep efficiency evaluated by polysomnography were significantly improved at weeks 2 and 6 ( $p = 0.05$ ). Similarly, the Pittsburgh Sleep Quality Index (PSQI) score and subscores were statistically improved at both weeks 2 and 6 (Table 1). The most frequently reported adverse effects were dry mouth and transient morning hangover effects. Importantly, quetiapine promoted sleep in these patients at dosages well below those

used for the treatment of psychiatric disorders.

Tassniyom et al.<sup>23</sup> conducted a small, randomized, double-blind, placebo-controlled trial in 16 Thai adults with a diagnosis of insomnia based on criteria established by the *Diagnostic and Statistical Manual, 4th edition, Text Revision (DSM-IV-TR)*. Participants' mean age was 46 years, and the majority were women. Patients were excluded if they had comorbid psychiatric conditions or were already receiving medications

Table 1.  
**Subjective Evaluations of Quetiapine for Insomnia<sup>a</sup>**

Ref.	Intervention	Evaluation	Findings
22	Quetiapine 25–75 mg daily	PSQI	Quetiapine showed statistical improvement ( $p = 0.00$ ) on the total score and subscale scores of sleep quality, total sleep time, and sleep efficiency at weeks 2 and 6.
23	Quetiapine 25 mg daily	VAS	Sleep satisfaction scores improved for both groups and were not statistically different ( $p = 0.505$ ).
24	Quetiapine 315 ± 109 mg daily	HAM-D Insomnia Subscale	Quetiapine significantly ( $p < 0.001$ ) improved items 4–6 compared to placebo.
25	Quetiapine 25–100 mg daily	MADRS Insomnia	Quetiapine plus fluoxetine improved the mean insomnia score sooner ( $p \leq 0.01$ for the first, second, and third follow-up visits) compared with the fluoxetine plus placebo group.
26	Quetiapine 300 or 600 mg daily	PSQI	Both doses of quetiapine showed statistical improvement ( $p < 0.001$ ) at days 29 and 57 compared to placebo.
27	Quetiapine 300 or 600 mg daily vs. paroxetine 20 mg daily	MADRS Insomnia	Both doses of quetiapine showed statistical improvement ( $p < 0.05$ ) on item 4 (reduced sleep) compared to paroxetine.
28	Quetiapine 12.5–50 mg daily	PSQI	PSQI improved in 11 patients and was reduced by $3.9 \pm 3.8$ points ( $p < 0.01$ ).
29	Quetiapine 25–100 mg daily	ISI	For 5 of 6 patients, the ISI score moved from moderate insomnia to absence of insomnia at week 1 and was maintained through week 6.
30	Quetiapine 25–225 mg daily	SSQ	75% improvement in global score; greatest improvements in overall quality of sleep and sleep latency.
31	Quetiapine 50–750 mg daily vs. olanzapine 2.5–20 mg daily, risperidone 1–12 mg daily, and perospirone 4–48 mg <sup>b</sup> daily	PSQI	A significant time effect for total score occurred after 8 weeks in both middle-aged and elderly patients, regardless of drug ( $p = 0.008$ ).
33	Quetiapine 340 mg (mean) daily	PSQI	Most improved quality of sleep occurred in the patients in the upper quetiapine quartile (>360-mg mean daily dose). The strongest reduction in daytime sedation was observed in patients receiving the highest quetiapine doses.

<sup>a</sup>PSQI = Pittsburgh Sleep Quality Index, VAS = visual analog scale, HAM-D = Hamilton Rating Scale for Depression, MADRS = Montgomery-Åsberg Depression Rating Scale, ISI = Insomnia Severity Index scale, SSQ = Spiegel Sleep Questionnaire.

<sup>b</sup>Not available in the United States.

known to cause sedation. Patients received either placebo or quetiapine 25 mg orally nightly for two weeks. A total of 13 participants (6 in the placebo group, 7 in the quetiapine group) completed the study. One person in the quetiapine group withdrew after being diagnosed with vertigo, and 2 participants in the placebo group withdrew citing lack of efficacy; all 3 individuals withdrew before receiving the intervention. Both the quetiapine and placebo groups experienced increased total sleep time (by 125 and 72 minutes, respectively), decreased sleep latency (by 96 and 24 minutes, respectively), and improved sleep satisfaction based on visual analog scale scores, but none of the differences between groups were significant ( $p > 0.05$ ) (Tables 1 and 2). Adverse effects were observed only in the quetiapine group and included dry lips, dry tongue, and daytime drowsiness. The authors acknowledged that the small sample size rendered the study underpowered and that the duration

of the study may have been too short to determine if there was a difference between quetiapine and placebo with regard to improvement in sleep.

None of the aforementioned studies reported on changes in metabolic variables (e.g., weight, waist circumference, fasting glucose concentration, lipid profile). This was likely not done due to the small sample sizes, short durations, and relatively healthy populations evaluated.

**Major depressive disorder.** Šagud et al.<sup>24</sup> conducted a prospective, open-label, noncomparative, flexible-dose study to evaluate the efficacy of quetiapine add-on therapy in 14 patients with major depressive disorder (defined using *DSM-IV* criteria) who were refractory to previous therapy. The mean age of patients was 53 years, and the majority were men. Quetiapine 50 mg was added to patients' current antidepressant regimen at bedtime, with dosage increases in increments of 50 mg; the mean  $\pm$  S.D. bedtime dose in study patients was  $315 \pm 109$  mg. The primary ef-

ficacy outcome was improvement in the Hamilton Rating Scale for Depression (HAM-D) score, which included an evaluation of the subscale for insomnia (items 4–6). The insomnia subscale scores improved over baseline by week 2, and this effect was maintained through week 20 (Table 1). Of the 14 patients studied, 3 experienced hypotension and 2 had daytime sedation, all of which were noted to be mild and transient in nature. Four patients were noted to have hyperlipidemia at baseline, but no metabolic outcomes (e.g., change in lipid values) were reported. The authors concluded that quetiapine alleviated insomnia, a common and severe symptom of depression, in patients enrolled in this study and this was perceived as a beneficial effect.

Garakani et al.<sup>25</sup> evaluated the ability of quetiapine to augment fluoxetine therapy over eight weeks in 114 patients with major depressive disorder, as defined by *DSM-IV* criteria. A total of 51 men (mean age, 41 years) and 64 women (mean

**Table 2.**  
**Objective Evaluations of Quetiapine for Insomnia via Polysomnography or Actigraphy**

Ref. and Intervention	Mean $\pm$ S.D.			No. Occurrences $\pm$ S.D.	
	Sleep Latency, min	Total Sleep Time, min	Sleep Efficiency, %	Awakenings	Periodic Leg Movements
21					
Quetiapine 25 mg daily	12.2 $\pm$ 6.1 <sup>a,b</sup>	439.9 $\pm$ 20.5 <sup>c</sup>	91.8 $\pm$ 4.2 <sup>c</sup>	27 $\pm$ 7.7	62.2 $\pm$ 78.1
Quetiapine 100 mg daily	13.3 $\pm$ 8.5 <sup>a,b</sup>	441.4 $\pm$ 23.4 <sup>c</sup>	92.0 $\pm$ 4.8 <sup>c</sup>	24.9 $\pm$ 10.1	138.4 $\pm$ 153.8 <sup>c</sup>
Placebo	22.8 $\pm$ 18.4 <sup>b</sup>	411.4 $\pm$ 37.7	85.8 $\pm$ 7.9	30.0 $\pm$ 11.3	41.2 $\pm$ 63.2
22					
Quetiapine 25–75 mg daily	24.2 $\pm$ 19.0	395.6 $\pm$ 62.3 <sup>d</sup>	89.9 $\pm$ 8.2 <sup>d</sup>	... <sup>e</sup>	...
23					
Quetiapine 25 mg daily	66.5 $\pm$ 51.2	347.5 $\pm$ 100.9	...	...	...
Placebo	47.4 $\pm$ 30.4	361.9 $\pm$ 85.4	...	...	...
32					
Quetiapine 340 mg (mean) daily	15.6 $\pm$ 18.1 <sup>f</sup>	432 $\pm$ 66	82.7 $\pm$ 9.1 <sup>f</sup>	...	...
No therapy (control)	24.5 $\pm$ 30.2	390 $\pm$ 54	77.0 $\pm$ 7.9	...	...

<sup>a</sup> $p < 0.005$  compared with placebo.

<sup>b</sup>Sleep stage 2.

<sup>c</sup> $p < 0.001$  compared with placebo.

<sup>d</sup> $p < 0.05$  compared with baseline.

<sup>e</sup>Not evaluated.

<sup>f</sup> $p < 0.05$  at week 4 compared with control.

age, 42 years) participated in this randomized, double-blind, placebo-controlled trial. The study allowed for flexible dosing of quetiapine (starting dosage of 25 mg daily adjusted in 25-mg increments every third day to a maximum of 100 mg daily); the mean dosage was 47.3 mg daily. Quetiapine and placebo were administered in the evening. All patients received concurrent fluoxetine 20–40 mg daily. The main outcome measure was the Montgomery-Åsberg Depression Rating Scale (MADRS) score, with a focus on the sleep item. Patients were defined as having insomnia at baseline if they scored 4 or greater on the reduced sleep question of the MADRS. Overall, there was no difference in response on the MADRS or a difference in remission rates between groups; however, patients who had insomnia at baseline in the quetiapine plus fluoxetine group experienced improvements in sleep and anxiety. The insomnia scores of patients in the quetiapine plus fluoxetine group improved quicker than those in the placebo plus fluoxetine group (Table 1). The mean  $\pm$  S.D. weight change from baseline to weeks 8 and 9 of treatment was not statistically different between groups ( $-0.853 \pm 2.79$  kg in the placebo group and  $-0.204 \pm 2.404$  kg in the quetiapine plus fluoxetine group,  $p$  not reported). The most common patient-reported adverse effects in both groups were gastrointestinal symptoms (nausea, diarrhea, constipation), dizziness, and sedation; sedation was significantly more common in the quetiapine plus fluoxetine group ( $p = 0.006$ ).

**Bipolar depression.** Endicott et al.<sup>26</sup> performed a secondary analysis on data from the BOLDER (BipOLAR DEpRession) I and II trials to evaluate the effects of quetiapine monotherapy on quality of life and sleep in patients with bipolar I and II depressive episodes. The BOLDER I and II trials were randomized, double-blind, placebo-controlled

studies that randomized 1051 patients who were experiencing a major depressive episode of bipolar I or II disorder (as defined by *DSM-IV* criteria) to monotherapy with fixed-dose quetiapine 300 or 600 mg daily or placebo for eight weeks. The majority of patients were women, and the mean age was approximately 38 years. Data on the quality of sleep from the BOLDER I trial ( $n = 511$ ) were analyzed. Improvements in PSQI scores for both dosages of quetiapine at days 29 and 57 were significant compared with placebo ( $p < 0.001$ ) (Table 1). Although quantitative data were not reported, the most substantial benefits appear to have been in sleep quality and total sleep time. The improvements in PSQI scores correlated with improvements in depression and anxiety symptoms, measured using the MADRS, HAM-D, Hamilton Rating Scale for Anxiety, and the Clinical Global Impression scale. The most common adverse events in the quetiapine groups included dry mouth, sedation, and somnolence. Fewer than 4% of patients in each quetiapine group reported insomnia as an adverse event. Patients in the quetiapine groups were more likely to report weight gain as an adverse effect (2.9% in the 300-mg group, 5.7% in the 600-mg group) compared with placebo (1.2%). It should be noted that patients in the quetiapine groups weighed more at baseline than those in the placebo group (mean weights of 87.0, 85.6, and 83.4 kg in the 300-mg, 600-mg, and placebo groups, respectively).

Similar to the BOLDER I and II studies, the EMBOLDEN II (Efficacy of Monotherapy Seroquel in BipOLAR Depression II) trial conducted by McElroy et al.<sup>27</sup> randomized 740 patients with bipolar I or II disorder and a major depressive episode (as defined by *DSM-IV* criteria) to quetiapine 300 mg daily, quetiapine 600 mg daily, paroxetine 20 mg daily, or placebo for eight weeks. The

majority of patients were women, and the mean age was approximately 39 years. Both dosages of quetiapine produced significant improvements in sleep compared with placebo; the same was not true of paroxetine (Table 1). As in the BOLDER I study, the most common patient-reported adverse effects of quetiapine were dry mouth, somnolence, and sedation. In the EMBOLDEN II study, 9–11.3% of patients in the quetiapine groups experienced clinically significant weight gain (greater than 7% of their baseline weight) compared with those receiving paroxetine (3.3%) or placebo (4.1%). The only statistically significant change in weight from baseline compared with placebo occurred in the quetiapine 600-mg group (mean  $\pm$  S.D. weight change from baseline of  $1.7 \pm 0.23$  kg,  $p < 0.001$ ). More patients in the quetiapine groups experienced clinically relevant increases in cholesterol values, with 14.2–14.7% of quetiapine-treated patients having a triglyceride concentration of  $\geq 200$  mg/dL at the end of the study; however, 13% of patients in the placebo group also had significant increases in cholesterol values. A small percentage of patients in the quetiapine groups (3–5.6%) and in the paroxetine group (4.3%) had clinically significant increases in fasting blood glucose (concentrations of  $\geq 126$  mg/dL).

Although the use of quetiapine in these populations with insomnia and concurrent unipolar or bipolar depression was shown to be effective for improving sleep, it is unknown whether the insomnia improved because the depression improved or if the insomnia improved independently of the depression.

**Parkinson's disease.** Juri et al.<sup>28</sup> studied 14 patients (11 men and 3 women) with nonpsychotic Parkinson's disease who received quetiapine for 12 weeks for the treatment of insomnia. This was an open-label study that allowed for dosage adjustments based on response; at the end of 12 weeks,

the mean daily quetiapine dose was 31.9 mg (range, 12.5–50 mg). Total PSQI and its subscale scores improved significantly over baseline ( $p < 0.01$ ), with the largest improvement seen in sleep latency (reduced from a mean  $\pm$  S.D. time of  $82 \pm 65.4$  minutes to  $28.6 \pm 22.7$  minutes). Two patients with restless legs syndrome at baseline discontinued treatment with quetiapine due to worsening of these symptoms.

**Breast cancer.** Pasquini et al.<sup>29</sup> studied 6 women with localized breast cancer (TNM Stage I–IIIA) who were receiving tamoxifen 20 mg daily and had a diagnosis of substance-induced sleep disorder. At baseline, the 6 participants had been taking daily tamoxifen for at least three months. Quetiapine treatment for insomnia was started at 25 mg nightly and could be increased in 25-mg increments to a maximum daily dose of 100 mg. Five of the 6 women showed improvements in insomnia at week 1 that persisted to week 6 based on the Insomnia Severity Index scale. Two women reported weight gain (not quantified), and 1 reported dizziness at the six-week follow-up visit. Interestingly, 2 of the 6 women had previously taken a benzodiazepine and 1 had taken mirtazapine for insomnia. Although the conclusions regarding the efficacy of quetiapine for insomnia were positive, it is difficult to draw generalized conclusions from a small study with such a specific patient population.

**Addictive conditions.** Terán et al.<sup>30</sup> reviewed the charts of 52 patients with polysubstance abuse who had insomnia as their primary withdrawal symptom and were treated with quetiapine for insomnia. The majority of patients ( $n = 31$ ) were started on quetiapine in the inpatient setting; the remaining patients ( $n = 21$ ) started quetiapine as outpatients. All had been followed for 60 days in the outpatient setting. Quetiapine was initiated at 50–100 mg daily, and the dosage was adjusted based

on response. At the end of 60 days, the mean dosage was 62.35 mg daily (range, 25–225 mg) at bedtime. Patients were assessed using the Spiegel Sleep Questionnaire and demonstrated a 75% improvement in the global score over baseline ( $p < 0.001$ ). The greatest improvements occurred in overall quality of sleep and sleep latency. Benzodiazepine use was also evaluated and had decreased from 83% at baseline to 22.6% at 60 days. No patients discontinued therapy due to adverse effects, the most common of which was dry mouth (34.6%). Metabolic effects were not reported.

**Inpatient management of insomnia.** **Schizophrenia.** Yamashita et al.<sup>31</sup> stratified 86 inpatient adults into two groups, elderly (older than 65 years) and middle-aged (43–64 years), and randomized these patients to switch from their baseline antipsychotic to one of four atypical antipsychotics, which included quetiapine (13 in the elderly group, 12 in the middle-aged group). These patients were admitted to an inpatient psychiatric hospital in Japan. Antipsychotic dosages were allowed to vary; the mean quetiapine dosages at the end of the study were 409.6 mg daily in the elderly group and 541.7 mg daily in the middle-aged group. Sleep was assessed via the PSQI at baseline and at eight weeks after the medication switch. PSQI scores were reported for all patients (not stratified by antipsychotic) and showed a significantly improved time effect for total PSQI score and number of minutes spent in bed ( $p < 0.05$ ). A logistic regression analysis found that the use of quetiapine (as well as the use of olanzapine and risperidone) was a predictor of improvement on the PSQI. The authors noted that 1 patient in the elderly group who was treated with quetiapine dropped out because of a hip fracture; otherwise, safety concerns regarding quetiapine were not reported.

**Major depressive disorder.** The effects of quetiapine as an adjunct to

antidepressant therapy on daytime sleepiness and quality of sleep were evaluated over four weeks in 27 adult patients admitted for the treatment of a major depressive episode.<sup>32,33</sup> During the treatment period, the mean daily quetiapine dose was 340 mg. Actigraphy data from the first and last seven nights (10:00 p.m. to 6:00 a.m.) were used to objectively assess sleep quality. There were no significant differences found in the patients between weeks 1 and 4. Actigraphic data were also collected for 27 matched controls due to a lack of normative actigraphic data. Compared with study patients, patients in the control group at week 4 had significantly longer sleep latency ( $p = 0.03$ ), lower sleep efficiency ( $p = 0.01$ ), and shorter sleep time ( $p = 0.02$ ).<sup>32</sup> A PSQI score was collected at baseline and weekly for study patients. Both the total PSQI score and the PSQI daytime sleepiness subscore showed significant improvement over baseline for all four weeks ( $p < 0.001$ ). The largest improvement in sleep quality occurred in the patients receiving the highest dose of quetiapine ( $>364$  mg daily).<sup>33</sup> There were no recorded instances of adverse metabolic or clinical effects or significant weight gain ( $\geq 10\%$  of baseline weight) over the four-week study.<sup>33</sup>

Similar to the studies that evaluated quetiapine for the treatment of insomnia in outpatient adults with unipolar or bipolar depression, it is unknown whether the insomnia improved because the psychiatric disorder improved or the insomnia improved independent of the psychiatric disorder.

### Safety of quetiapine for insomnia

The two studies that evaluated the use of quetiapine specifically for the treatment of insomnia in the absence of comorbid conditions found that the drug was generally well tolerated at a dosage of 25–75 mg nightly for two to six weeks.<sup>22,23</sup> In each study,

the adverse effects most commonly cited by patients in the quetiapine groups were dry mouth and daytime sedation, which are consistent with the common adverse effects noted in the drug's prescribing information.<sup>10,11,22,23</sup> Adverse-effect data from the small, short-duration trials of quetiapine for insomnia showed the drug to be well tolerated, but it is unknown if this would hold true for longer durations of use in a larger number of patients. Recent safety reviews of quetiapine dosages of less than 300 mg per day have noted that the drug can cause harmful adverse effects.<sup>34-36</sup> Low-dose quetiapine ( $\leq 200$  mg) at bedtime used for insomnia has been shown to cause significant increases in weight ( $p = 0.037$ ) and body mass index ( $p = 0.048$ ).<sup>34</sup> The American Diabetes Association consensus development conference cautions that any medication that causes substantial weight gain could put a person at risk for developing diabetes mellitus.<sup>37</sup> The data are mixed on whether diabetes or dyslipidemia is caused by quetiapine use, but the same consensus position statement recommends that patients treated with second-generation antipsychotics, such as quetiapine, have their weight, waist circumference, blood pressure, fasting glucose concentration, and fasting lipid panel routinely monitored.<sup>37</sup>

Although the causality is questionable, nonmetabolic adverse effects that have been associated with low-dose quetiapine include restless legs syndrome and periodic limb movements in sleep, daytime sedation, dry mouth, akathisia, and fatal hepatotoxicity.<sup>21-23,36</sup> Tardive dyskinesia has also been associated with quetiapine use. While the risk of developing tardive dyskinesia is typically associated with increasing dosages and longer treatment durations of therapy, it can occur with low dosages and during short treatment courses, such as those used to treat insomnia.<sup>10,11,13</sup> Postmarketing

reports have also demonstrated the tendency for quetiapine to induce Q-Tc-interval prolongation, particularly in patients taking concomitant drugs known to prolong the Q-T interval (e.g., amiodarone, methadone) and in patients with underlying conditions known to predispose someone to Q-Tc-interval prolongation (e.g., electrolyte imbalance, heart failure).<sup>10,11,13</sup> The obvious adverse effect of sedation exists with quetiapine use, but, in the case of insomnia treatment, sedation is a desired effect.

### Discussion

Quetiapine was developed for the treatment of psychiatric disorders, but its antagonism of the H<sub>1</sub>- and 5-HT<sub>2A</sub> receptors has the added effect of causing sedation. As such, quetiapine is widely used as a treatment for insomnia. However, before a practitioner recommends or prescribes quetiapine for the treatment of insomnia, several issues should be considered.

First, robust studies evaluating the safety and efficacy of quetiapine for the treatment of insomnia are lacking. There are a limited number of studies, some of which evaluated niche populations whose data would not be generalizable to the general population. The use of quetiapine for the treatment of insomnia in the absence of comorbid conditions has been evaluated in only two clinical trials of 31 patients in total.<sup>22,23</sup> Quetiapine studies in patients with insomnia and other comorbidities are not much more prevalent; the four trials included in this review that included patients with unipolar or bipolar depression evaluated just 1379 patients.<sup>24-27</sup> This is not a large number of patients, given the high prevalence of insomnia and the high prevalence of quetiapine prescribing.<sup>1,38</sup> Very few of the studies evaluated sleep using objective testing, which is another limitation of the available data on quetiapine. Polysomnographic testing was performed

and sleep outcomes were statistically analyzed in healthy volunteers and patients with primary insomnia, respectively, in two studies<sup>21,22</sup>; such testing and analysis were not conducted in the four studies evaluating the use of quetiapine for insomnia in patients with unipolar or bipolar depression.<sup>24-27</sup> In addition, no trials comparing quetiapine with an active control (e.g., zolpidem) have been conducted; the data that exist compare quetiapine to a placebo or there is no comparison and all patients are treated with quetiapine. This type of comparative data would be helpful to determine the true efficacy of quetiapine in treating insomnia, particularly in patients with a psychiatric comorbidity. The limited number of trials combined with small sample sizes, short durations, variable populations (e.g., Parkinson disease, breast cancer), and predominantly subjective evaluations (e.g., questionnaires) do not lend confidence to the concept that quetiapine is a proven safe and effective treatment modality for insomnia.

Second, quetiapine has gained a reputation as a drug of misuse and abuse. Quetiapine has been referred to as several street names, including "quell," "Susie Q," and "baby heroin."<sup>39</sup> Case reports of quetiapine abuse have described patients who have misused the drug orally, intranasally, and intravenously (achieved by crushing quetiapine tablets).<sup>40</sup> Quetiapine has also been mixed with illicit drugs, such as cocaine ("Q-ball") or marijuana ("Maq-ball").<sup>40</sup> It should be noted, however, that most reports of quetiapine abuse have occurred among prison inmates or in inpatient psychiatric settings in patients with a history of substance abuse, so the abuse potential may not be generalizable to the overall population of people with insomnia.<sup>41</sup> The implications for abuse by people using the drug for insomnia are unknown. Quetiapine is not a controlled substance but, based on

reports of abuse, may have the potential to be misused in a patient desperate for sleep.

Finally, off-label use of quetiapine for the treatment of insomnia has medical-legal implications. Based on its known H<sub>1</sub>-receptor antagonistic properties, the use of quetiapine for insomnia could be considered “evidence-based off-label use”; nonetheless, such use is not supported by the FDA-approved labeling for the drug.<sup>42</sup> Because quetiapine has the potential to cause serious adverse effects, including increased risk of death in elderly patients; increased risk of suicidal thinking and behavior in children, adolescents, and young adults; cardiac dysrhythmias; and metabolic dysfunctions (e.g., significant weight gain, hyperglycemia, hyperlipidemia), patients could pursue litigation against a prescribing physician, a dispensing pharmacy, or a drug manufacturer if harmed by quetiapine used for an off-label indication.

## Conclusion

Robust studies evaluating the safety and efficacy of quetiapine for the treatment of insomnia are lacking. Given its limited efficacy data, its adverse-effect profile, and the availability of agents approved by FDA for the treatment of insomnia, quetiapine’s benefit in the treatment of insomnia has not been proven to outweigh potential risks, even in patients with a comorbid labeled indication for quetiapine.

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