

# Off-label use of atypical antipsychotic agents for treatment of insomnia

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## ABSTRACT

Despite limited supporting evidence, off-label uses of atypical or second generation antipsychotics (particularly olanzapine, quetiapine, and risperidone) are not uncommon. The off-label use of these agents for the treatment of insomnia is the focus of this review. While atypical antipsychotics are associated with a lower risk of tardive dyskinesia, extrapyramidal side effects, and more favorable effects on cognitive deficits and negative symptomatology in schizophrenic patients compared to typical or first generation antipsychotic agents, they are not without risks. Metabolic adverse effects are particularly problematic with atypical antipsychotics, even at doses lower than those used to treat FDA-approved indications. The receptor affinity profiles of most atypical antipsychotic agents promote sedation. The level of H<sub>1</sub>-histamine receptor blockade is believed to be most associated with somnolence and sedation. Several studies evaluating the safety and efficacy of the atypical antipsychotics quetiapine, olanzapine, and risperidone for the treatment of insomnia were identified and are summarized in this article.

## KEYWORDS

atypical antipsychotic, second-generation antipsychotic, insomnia

## INTRODUCTION/BACKGROUND

There are ten atypical or second generation antipsychotic agents currently marketed in the United States: aripiprazole (Abilify), asenapine (Saphris), clozapine (Clozaril), iloperidone (Fanapt), lurasidone (Latuda), olanzapine (Zyprexa), paliperidone (Invega), quetiapine (Seroquel), risperidone (Risperdal), and ziprasidone (Geodon). These agents are all FDA approved for the treatment of schizophrenia, with some atypical antipsychotics obtaining additional FDA approval for other psychiatric conditions including autism spectrum disorders, bipolar I disorder (acute manic and/or mixed episodes, maintenance), and as adjunctive treatment of major depressive disorder.<sup>1</sup> All of the atypical antipsychotics are antagonists at the dopamine 2 (D<sub>2</sub>) and serotonin type 2 (5-HT<sub>2A</sub>) receptors, but differ considerably with respect to activity at other central nervous system receptor systems. Because of these differences in receptor activity, adverse effects associated with atypical antipsychotics can vary and can include weight gain, dyslipidemia, glucose dysregulation, sedation, akathisia, and an increased risk of death in elderly patients with dementia.<sup>1</sup> Compared to typical antipsychotic agents, atypical antipsychotics are associated with a lower risk of extrapyramidal side effects and more favorable effects on cognitive deficits and negative symptomatology in schizophrenic patients.<sup>1</sup> Results of a recently published meta-analysis and an Agency for Healthcare Research and Quality Comparative Effectiveness Review (AHRQ CER) indicate that the off-label use (use without FDA approval for the indication) of some atypical antipsychotics (most commonly

olanzapine, quetiapine, and risperidone) has increased significantly.<sup>2,3</sup> The off-label use of these agents includes treatment of ADHD, anxiety disorders, dementia in the elderly, depression, eating disorders, insomnia, personality disorders, and substance abuse disorders. Despite the fact that very few of these off-label uses are supported by large, high-quality, randomized clinical trials, it is estimated that between 1995 and 2008, off-label use of atypical antipsychotics doubled with approximately 60% of prescriptions for these agents being for off-label use in 2008.<sup>4</sup> These data are based on the results of a survey of a random sample of physicians, the majority (>80%) of which practice in an outpatient office setting. To date, no trials evaluating the off-label use of asenapine, iloperidone, lurasidone, or paliperidone have been reported in the literature.<sup>1,2</sup> Due to its side effect profile and mandatory laboratory monitoring for agranulocytosis, the use of clozapine has been nearly exclusive for schizophrenia. This article will provide an overview of the evidence regarding the safety and efficacy of off-label use of atypical antipsychotics agents for the treatment of insomnia due to various causes.

Many people with insomnia complain about difficulty falling asleep and, as a result, sleep onset (the transition from waking to sleep) has long been the focus of both pharmacologic and non-pharmacologic treatment interventions.<sup>5</sup> Sleep maintenance (staying asleep) can also be a significant problem. Total sleep time (TST) reflects the amount of actual sleep time (rapid eye movement [REM] and non-REM) from sleep onset to final awakening and wake after sleep onset (WASO) is a measure of the total amount of time spent awake in bed

after sleep onset. In studies evaluating the outcomes of treatments of sleep disturbances, insomnia is often defined by a sleep-onset latency (SL) and/or WASO that is greater than 30 minutes, a sleep efficiency (TST divided by the total amount of time spent in bed with the intent to sleep) of less than 85%, or a TST of less than 6.5 hours. Polysomnographic (PSG) assessment can be used to evaluate objective sleep measures and patient-completed sleep diaries and rating scales can be used to assess subjective measures of sleep quality.<sup>5</sup>

### Atypical Antipsychotics and Sedation

When used for the treatment of schizophrenia or bipolar disorder, the positive effects of atypical antipsychotic medications on sleep architecture are well documented.<sup>6-10</sup> The sedative effects of atypical antipsychotics vary (Table 1) and appear to be dose-related and primarily based on the level of H<sub>1</sub>-receptor antagonism.<sup>7,11</sup> Histamine receptors are believed to be involved in regulating circadian rhythms and the sleep-wake cycle. H<sub>1</sub>-receptor blockade can lead to an increase in somnolence and sedation as well as changes in sleep architecture, specifically a decrease in REM sleep and wakefulness, and an increase in slow wave sleep (SWS).<sup>8</sup> In addition, antagonism at the alpha 1 (α<sub>1</sub>)-adrenergic, 5-HT<sub>2</sub>, and cholinergic (muscarinic) receptors can lead to sedation.<sup>9</sup> Dopamine plays an important role in the regulation of the sleep-wake cycle and the dopamine uptake system is involved in the pharmacological control of electroencephalography arousal.<sup>9</sup> Tolerance to the sedating effects of atypical antipsychotics can develop with long-term use; however, some patients can continue to experience sedative effects.<sup>7</sup>

**Table 1. Comparison of the sedative effects of atypical antipsychotic agents<sup>6,7,8</sup>**

Generic (Brand)	Sedation
Aripiprazole (Abilify)	+
Asenapine (Saphris)	+ / ++
Clozapine (Clozaril)	+++
Iloperidone (Fanapt)	+
Lurasidone (Latuda)	++
Olanzapine (Zyprexa)	++
Paliperidone (Invega)	+
Quetiapine (Seroquel; Seroquel XR)	++
Risperidone (Risperdal)	+
Ziprasidone (Geodon)	+

+ low/mild; ++ moderate; +++ high/marked

A literature search using Medline (1946 to Aug week 3 2012) and EMBASE (1980 to 2013 week 35) was performed using each individual atypical antipsychotic agent (except clozapine) and the terms insomnia or sleep.

With limits of human, English language, and clinical trials applied, studies evaluating atypical antipsychotic agents for the off-label treatment of various causes of insomnia were identified as follows: eight evaluating quetiapine, three evaluating olanzapine, one evaluating risperidone, and one comparing olanzapine and risperidone for the treatment of paradoxical insomnia. No studies evaluating the use of aripiprazole, asenapine, iloperidone, lurasidone, paliperidone, or ziprasidone for the treatment of insomnia were found.

### Quetiapine

At doses ranging from 300 mg to 800 mg daily, quetiapine is FDA approved for the treatment of schizophrenia in adults and adolescents (13 to 17 years), bipolar mania in adults and children (10 to 17 years), and bipolar depression in adults.<sup>1,13</sup> The extended-release formulation of quetiapine (quetiapine XR), is also FDA approved as adjunctive therapy to antidepressants for the treatment of major depressive disorder.<sup>1,13</sup> While the sedative properties of quetiapine are proposed to be related to its antagonistic effects at 5-HT<sub>2A</sub>, H<sub>1</sub>, and α<sub>1</sub>- and α<sub>2</sub>-receptors, its affinity for the H<sub>1</sub>-receptor is much higher than for any other receptors.<sup>7,12,13</sup> Quetiapine has no appreciable affinity for cholinergic receptors (particularly at doses less than 500 mg/day) or for the benzodiazepine-specific site on the gamma-aminobutyric acid-benzodiazepine receptor complex.<sup>13</sup> As a result of its sedating properties, quetiapine is the most commonly evaluated atypical antipsychotic, at doses ranging from 25 mg to 200 mg, for the treatment of insomnia.

Most adverse effects observed with quetiapine have been reported during treatment of bipolar mania or schizophrenia with doses ranging from 150 to 800 mg daily. Common side effects at these doses include weight gain, drowsiness, increased cholesterol and triglyceride levels, xerostomia, dizziness, orthostatic hypotension, and constipation.<sup>13</sup> Rare, but potentially fatal adverse effects associated with doses of quetiapine used to treat bipolar mania or schizophrenia include QTc prolongation and neuroleptic malignant syndrome. Quetiapine is also known to have abuse potential.<sup>14</sup> Case reports indicate that quetiapine abuse is most common in forensic and inpatient psychiatric settings and is associated with intranasal and intravenous administration and a prior history of substance abuse (particularly benzodiazepines). While the mechanism for the reinforcement of this abuse is unknown, it has been hypothesized to be related to quetiapine's H<sub>1</sub>- and α<sub>1</sub>-receptor antagonism and possibly an additive effect with other substances of abuse.<sup>14</sup> Limited data concerning the adverse effects of

low dose quetiapine are available but the information available indicates that the use of quetiapine as a sedative, even at low doses, is not without risk.

One prospective, double-blind, randomized, crossover study evaluated the effects of quetiapine 25 mg or 100 mg versus placebo on PSG sleep structure and subjective sleep quality in 14 healthy males (18 to 65 years).<sup>15</sup> Each subject was studied in a sleep laboratory for three sessions; each session consisted of 3 consecutive nights (an adaptation night followed by 2 nights on medication taken 1 hour before bedtime) separated by a 4 day washout period. The first night on medication consisted of monitored undisturbed sleep and during the second night on medication, the study participants were exposed to acoustic stimuli in order to evaluate sleep under stressful conditions. During each 3-night session, PSG recordings were performed nightly and participants completed subjective sleep rating questionnaires each morning. Compared with placebo, the treatment effect of two doses of both 25 mg and 100 mg of quetiapine significantly increased PSG measures of sleep period time (SPT, time from sleep onset to final awakening), TST (SPT minus time spent awake), sleep efficiency, and percentage of stage 2 sleep under both undisturbed and acoustic stress sleep conditions ( $p < 0.001$ ). In addition, both doses significantly decreased SL to sleep stage 1 and 2 ( $p < 0.01$ ) and percentage of time awake ( $p < 0.005$ ). A significant increase in periodic leg movement ( $p < 0.001$ ) and a reduction in percentage REM ( $p < 0.001$ ) were observed only with the quetiapine 100 mg dose. Similarly, when compared with placebo, the treatment effect of two doses of both quetiapine 25 mg and 100 mg significantly increased subjective sleep time ( $p < 0.005$ ) and sleep quality ( $p < 0.0001$ ), and significantly decreased psychosomatic complaints ( $p < 0.01$ ) on subjects' self-ratings. Only quetiapine 100 mg significantly increased exhaustion in the evening ( $p < 0.01$ ) and reduced the number of awakenings ( $p < 0.01$ ) versus placebo on subjective sleep ratings. Two subjects not included in the final analysis, described by the authors as being of Asian descent and of slim stature, were withdrawn from the study due to symptomatic orthostatic hypotension following administration of the first 100 mg dose of quetiapine.<sup>15</sup>

An open pilot study evaluated the effects of low-dose quetiapine administered over a 6-week period in 18 patients with primary insomnia.<sup>16</sup> Following a 1-week washout period, 25 mg quetiapine at bedtime was started with an increase to 50 mg in 7 patients and 75 mg in one patient during the study period. At weeks 2 and 6,

objective sleep parameters were measured by PSG, subjective sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI) and sleep diaries, and a neuropsychological test battery was used to assess cognitive effects. Compared to baseline values, TST and sleep efficiency, as measured by PSG, were significantly improved with low-dose quetiapine at week 2 ( $p = 0.001$  and  $p = 0.01$ , respectively) and at week 6 ( $p = 0.03$  and  $p = 0.02$ , respectively). Sleep onset latency, REM sleep latency, and slow wave sleep were not improved at week 2 or week 6 of treatment. All subjective sleep quality measures (sleep quality, TST, sleep efficiency) were significantly improved compared to baseline at week 2 and week 6 ( $p = 0.00$  for all measures). The authors note that based on the fact that improvement of sleep quality after 2 weeks of quetiapine continued or further improved after another 4 weeks, there was no evidence of development of tolerance to the sleep-promoting effects of quetiapine. Most neuropsychological test variables showed improvements from baseline to the end of the study, with no test variables showing a decline. While the incidence and severity were not provided, the most commonly reported adverse effects were dry mouth and transient hangover effects in the morning.<sup>16</sup>

In a randomized, double-blind, placebo-controlled study performed at a teaching hospital in Thailand, 16 patients (aged 25 to 62 years) meeting DSM-IV-TR criteria for primary insomnia were randomized based on strictly applied inclusion and exclusion criteria to receive quetiapine 25 mg or placebo nightly for two weeks.<sup>17</sup> The primary outcomes evaluated were TST, SL, daytime alertness and functioning, and sleep satisfaction (scored on a visual analog scale); side effects were recorded as secondary outcomes. Patients were asked to record a sleep diary for one week prior to randomization and two weeks after initiation of treatment. A total of 13 patients (placebo  $n = 6$ ; quetiapine 25 mg  $n = 7$ ) completed the 2 week double-blind treatment period. Of the 3 patients who did not complete the study, one patient in the quetiapine group was discontinued secondary to the development of vertigo prior to starting treatment and two patients in the placebo group discontinued due to lack of efficacy. There were no statistically significant differences in patient baseline demographic characteristics between the two treatment groups. However, baseline sleep characteristics were more severe in the quetiapine group compared to the placebo group: baseline TST 222.55 and 289.64 minutes, respectively; baseline SL 162.65 and 71.16 minutes, respectively. Following the 2 week treatment period, TST increased by 124.92 minutes in the quetiapine group and 72.24 minutes

in the placebo group, resulting in TSTs that were not statistically significantly different between the two groups ( $p=0.193$ ). Time to SL was decreased by 96.16 minutes and 23.72 minutes in the quetiapine and placebo group, respectively. However, there was no statistical significance in post-treatment SL between the groups ( $p=0.07$ ). Similarly, no statistically significant differences in sleep quality and daytime functioning or sleep satisfaction between the two groups were observed following treatment. Despite the fact that no statistically significant improvements were found in the primary sleep outcomes, the authors of the study point out that an increase in TST of 2 hours and a decrease in SL of 90 minutes seen after 2 weeks of quetiapine 25 mg may be clinically significant and may improve the quality of life in patients with insomnia. Adverse effects reported in the quetiapine group included dry lips, dry tongue, and daytime drowsiness; no adverse effects were reported in the placebo group.<sup>17</sup>

Doses of quetiapine ranging from 12.5 mg to 50 mg in the evening (mean dose of 31.9 mg) were evaluated in a 12 week open-label trial that enrolled patients with Parkinson's disease ( $n=14$ ) prescribed levodopa (average dose of 1325 mg/day) and experiencing frequent insomnia with no associated psychotic symptoms.<sup>18</sup> At baseline and months 1, 2, and 3 following the initiation of quetiapine, the severity of insomnia was assessed using the PSQI, daytime sleepiness was evaluated with the Epworth Sleep Scale (ESS), and motor performance was evaluated using the motor section of the Unified Parkinson's Disease Rating Scale. The ESS score was significantly decreased by 4.3 +/- 3.7 points ( $p < 0.01$ ) and patients experienced a significant decrease in SL (82 +/- 65.4 vs. 28.6 +/- 22.7 minutes,  $p < 0.05$ ) from baseline. No significant changes in motor scores were found. Two patients withdrew due to restless leg syndrome which subsided after the quetiapine was discontinued and two patients reported experiencing increased daytime sleepiness.<sup>18</sup>

A retrospective chart review of patients with substance abuse disorders experiencing insomnia due to withdrawal and treated with 25 mg to 225 mg quetiapine (mean dose 62.35 mg +/- 35.90; median dose 50 mg) at bedtime found significant improvement in sleep parameters ( $p < 0.001$ ) as measured by changes in the global and individual item Speigel Sleep Questionnaire (SSQ) scores.<sup>19</sup> The greatest improvement in the global SSQ score occurred in the first week of quetiapine treatment and "overall sleep quality" and "time to fall asleep" were noted as the greatest improvements for individual SSQ items evaluated. In addition, benzodiazepine use decreased from 83% at

baseline to 22% at the end of the 60 day follow-up period. The most commonly reported adverse event was xerostomia ( $n=18$ ). However, no patients discontinued due to adverse events.<sup>19</sup>

A case series describing 6 women with localized breast cancer experiencing tamoxifen-related insomnia without depression reported improvement in the Insomnia Severity Index (ISI) scale scores in 5 patients as soon as one week following the start of quetiapine 25 mg 1 hour before bedtime.<sup>20</sup> Based on therapeutic response and tolerance, doses of quetiapine were titrated upward in 25 mg increments to a maximum dose of 100 mg. One patient received 25 mg, two patients were titrated to 50 mg, one patient was titrated to 75 mg, and two patients (one of whom was a non-responder) were titrated to 100 mg of quetiapine at bedtime. In the 5 women who experienced rapid improvement in their insomnia, baseline ISI scores indicated moderate insomnia and ISI scores at week 1 indicated an absence of insomnia; response was maintained during the 6 weeks of quetiapine use. The one non-responder continued to experience moderate insomnia. Two patients reported weight gain and one patient reported experiencing dizziness.<sup>20</sup>

A prospective 6 week open-label study examined sleep data from a previously published study of quetiapine in combat veterans meeting DSM-IV criteria for PTSD ( $n=20$ ).<sup>21</sup> Following no changes in medication for a one month period, quetiapine was started at 25 mg at bedtime and titrated up to 300 mg based on clinical response and tolerability (average dose 100 +/- 70 mg daily). Changes in sleep disturbance outcomes were measured using the PSQI and the sleep-disturbance PTSD-specific addendum (PSQI-A). Significant improvements on PSQI measures at week 6 compared to baseline included subjective sleep quality ( $p < 0.001$ ), SL ( $p=0.006$ ), sleep duration ( $p=0.002$ ), and sleep disturbances ( $p=0.034$ ). Significant decreases in episodes of terror and acting out dreams ( $p=0.04$  and  $p=0.013$ , respectively) as measured by the PSQI-A were found. Sedation was the most frequent side effect reported ( $n=7$ ) and led to discontinuation by one patient whose back pain was exacerbated by increased sleep.<sup>21</sup>

In addition to the adverse effects associated with the use of quetiapine for the treatment of insomnia noted in the previously discussed studies, two retrospective chart reviews provide additional information.<sup>22,23</sup> Primary outcome variables of changes in weight, body mass index (BMI), and waist circumference were evaluated in a retrospective chart review of 43 psychiatric patients (19 to

65 years of age; mean baseline BMI 31 kg/m<sup>2</sup>) prescribed  $\leq$ 200 mg quetiapine at bedtime for insomnia for a mean duration of 11 months. Mean weight gain and BMI significantly increased (2.22 kg,  $p=0.037$  and 0.8 kg/m<sup>2</sup>,  $p=0.048$ ), and increases in waist circumference were not statistically significant. It is important to note that in addition to the quetiapine, all of the patients were receiving at least one additional psychotropic medication, with 22 patients receiving another atypical antipsychotic (11 received risperidone, 6 received aripiprazole, 3 received ziprasidone, and 2 received olanzapine).<sup>22</sup> A second retrospective chart review examined the effects of low-dose ( $\leq$ 100 mg daily) quetiapine on weight gain in adult military healthcare beneficiaries.<sup>23</sup> Exclusion criteria included receipt of quetiapine at a total daily dose above 100 mg at any time during the study period, duration of quetiapine use for less than 1 month, and concurrent use of other antipsychotics (either first or second generation). Compared with baseline, weight gain increased linearly over a 12 month period with a statistically significant increase in all months except months 1 and 3. At month 6 the mean weight gain was 2.52 kg ( $p<0.001$ ) and 4.8 kg at month 12 ( $p<0.001$ ).<sup>23</sup> Furthermore, published case reports on the use of low-dose quetiapine for the treatment of insomnia describe adverse events that include fatal hepatotoxicity in a 77-year-old-female receiving 12.5 mg twice daily for agitation and insomnia, restless leg syndrome in a 68-year-old female receiving 100 mg daily, and two cases of the development of akathisia (one in a 43-year-old female receiving 50 mg at bedtime; one in a 27-year-old female receiving 25 mg at bedtime).<sup>24,25,26</sup>

### Olanzapine

At doses of 5 to 20 mg /day, olanzapine is FDA approved for the treatment of schizophrenia and bipolar I disorder (mixed or manic episodes) in adults, as well as depressive episodes associated with bipolar I disorder and treatment resistant depression in adults when used in combination with fluoxetine.<sup>27</sup> Olanzapine's antagonist activity at 5-HT<sub>2A/2C</sub>, H<sub>1</sub>, muscarinic, and  $\alpha_1$  receptors is believed to play a role in its sedative properties.<sup>28,29</sup> While serious cardiovascular complications associated with olanzapine are infrequent, significant weight gain, dyslipidemia, and glucose dysregulation are commonly associated with this atypical antipsychotic.<sup>27</sup> As with quetiapine, tardive dyskinesia and extrapyramidal adverse effects are uncommon with olanzapine. The most common adverse reaction observed in placebo-controlled trials of olanzapine is somnolence and olanzapine has been shown to affect sleep architecture.<sup>27-29</sup>

Compared to placebo, significant increases in TST ( $p<0.01$ ), sleep efficiency ( $p<0.01$ ), SWS( $p<0.05$ ), and percent REM sleep ( $p<0.05$ ) and decreases in wake time ( $p<0.01$ ) were observed in a randomized, double-blind, placebo-controlled, cross-over, clinical trial evaluating the effects of a single morning dose of olanzapine 5 mg on objective and subjective sleep variables in 17 healthy volunteers.<sup>28</sup> A second randomized, placebo-controlled, double-blind, cross-over study compared placebo, olanzapine 5 mg and 10 mg in 9 healthy male patients (age range 33 to 60 years; mean age 45.3 years).<sup>29</sup> Single oral doses of olanzapine or placebo were administered 4 hours before bedtime over 3 nights, with each treatment separated by 7 to 14 days. Home-based PSG sleep recordings indicated that compared to placebo, olanzapine 5 mg and 10 mg produced significant increases in actual sleep time ( $p<0.005$  and  $p<0.05$ , respectively), sleep efficiency ( $p<0.005$  and  $p<0.05$ , respectively), and SWS ( $p<0.005$ , both doses); significant increases in subjective sleep quality were also observed ( $p<0.05$ , both doses). Olanzapine 10 mg was significantly better than olanzapine 5mg at decreasing sleep latency ( $p<0.05$ ) and only the 10 mg dose was significantly better than placebo at decreasing REM sleep ( $p<0.005$ ) and increasing REM latency ( $p<0.005$ ).<sup>29</sup>

Olanzapine, in doses ranging from 2.5 mg to 10 mg, was evaluated in a case series that included 9 patients with chronic insomnia secondary to various causes.<sup>3,30</sup> Eight of the nine patients experienced improved sleep parameters (measured by PSG) that included improved SL ( $n=3$ ), a "feeling of good sleep" ( $n=2$ ), an increase in TST ( $n=3$ ), a decrease in nightmares ( $n=1$ ), and unspecified improvement ( $n=3$ ). Five of the eight patients received olanzapine as monotherapy. One patient experienced no improvement in sleep.<sup>3,30</sup>

The effects of olanzapine were evaluated over a 3 week period in 12 patients experiencing insomnia and major depressive disorder unresponsive to therapy with therapeutic doses of citalopram, fluoxetine, paroxetine, sertraline, or venlafaxine.<sup>31</sup> Olanzapine was started at 2.5 mg nightly and increased to a maximum of 10 mg, as needed (mean dose 4.8 mg). Sleep parameters were measured using home PSG recordings at baseline, on night one of olanzapine treatment, and at the completion of the 3 week study period. In addition, after each of the 3 study nights, patients were asked to subjectively evaluate sleep quality based on "how well they had slept" using a 5 point scale where 1 indicated "much better than usual" and 5 indicated "much worse than usual". The addition of a nightly dose of olanzapine significantly improved actual

sleep time ( $p < 0.001$  night 1,  $p < 0.01$  at 3 weeks), sleep efficiency ( $p < 0.001$  night 1 and at 3 weeks), total WASO ( $p < 0.01$  night 1 and at 3 weeks), and subjective sleep quality ( $p < 0.01$  night 1,  $p < 0.05$  at 3 weeks). Significant improvements in SWS ( $p < 0.01$ ) and SL ( $p < 0.05$ ) were seen after 3 weeks of olanzapine treatment. Adverse effects were not reported in this study, but the authors do note patients reported olanzapine as being highly sedating and were unable to maintain a consistent morning rising time for the second and third PSG recordings. Weight was not measured.<sup>31</sup>

### Risperidone

Risperidone is approved for the treatment of schizophrenia in adults (4 to 16 mg/day) and adolescents (0.5 to 6 mg/day), bipolar mania in adults (1 to 6 mg/day), children and adolescents (1 to 6 mg/day), and for irritability associated with autistic disorder (0.5 to 3 mg/day).<sup>32</sup> Adverse effects commonly experienced in patients treated with risperidone include metabolic changes (hyperglycemia, dyslipidemia, and weight gain), sedation, and dizziness. Due to high affinity for the  $D_2$  receptor, risperidone has the highest rate of extrapyramidal adverse effects and hyperprolactinemia compared to other atypical antipsychotics. Risperidone possesses affinity for  $5HT_{2A}$ ,  $D_2$ ,  $\alpha_1$ ,  $\alpha_2$ , and  $H_1$  receptors, and no affinity for muscarinic receptors.<sup>3,32</sup> While the  $H_1$  blockade of risperidone is less than that of olanzapine, the effects of risperidone on sleep parameters in schizophrenic patients has been demonstrated.<sup>7</sup> Compared to placebo, a single morning dose of risperidone 1 mg administered to healthy volunteers resulted in significant decreases in wake time ( $p < 0.05$ ) and increases in stage 2 sleep ( $p < 0.01$ ).<sup>28</sup>

The efficacy and safety of risperidone (mean dose 1.49 mg/day) was evaluated for the treatment of sleep-wake cycle disturbances in 321 patients with dementia in an open-label, 12-week, observational, prospective study.<sup>33</sup> Use of antipsychotic medications must have been discontinued within 15 days of enrollment and any patient previously treated with risperidone was excluded. Patients or caregivers evaluated sleep-wake cycle disturbances at week 12 using a newly developed sleep-patterns questionnaire. After 12 weeks of risperidone, significant improvements were reported in sleep quality (11.6% vs. 85.6% providing a rating of quite good or very good), total night sleep hours (5.5 vs. 7.1 hours), hours spent awake in bed at night (2.3 vs. 1.2 hours), and number of nightly awakenings (3.6 vs. 1.8) compared to baseline ( $p < 0.01$ ). In addition, when compared to baseline, the percentage of patients reporting insomnia

(40% vs. 8.4%), daytime somnolence (63.3% vs. 27.7%), and interferences with daytime activities (83.7% vs. 38.5%) due to sleep-wake cycle disturbances was significantly decreased at week 12 ( $p < 0.01$ ). The number of patients who did not require use of sleep meds increased from 25.8% at baseline to 46.6% after week 12 ( $p < 0.01$ ). Six patients reported adverse effects that included somnolence ( $n = 3$ ), sialorrhea ( $n = 2$ ), agitation ( $n = 1$ ), headache ( $n = 1$ ), abnormal vision ( $n = 1$ ), paresthesia ( $n = 1$ ) and asthenia ( $n = 1$ ).<sup>33</sup>

An open-label, cross-sectional study comparing olanzapine 10 mg and risperidone 4 mg was conducted in patients experiencing paradoxical insomnia.<sup>34</sup> Patients with paradoxical insomnia (also known as sleep state misperception) complain of difficulties initiating and maintaining sleep despite PSG recordings that indicate good sleep efficiency and quality and in the absence of any medical or psychiatric disorders that could be causing the sleep complaints.<sup>35</sup> Following a 2 week washout period for any sedative-hypnotic agents, 30 patients diagnosed with paradoxical insomnia were randomly assigned to receive olanzapine 10 mg or risperidone 4 mg.<sup>34</sup> Sleep quality was assessed at baseline and at the end of the 8 week study period using the PSQI and clinical assessments for metabolic side effects were performed periodically. There were no significant differences in the baseline characteristics of the 29 subjects (olanzapine  $n = 14$ ; risperidone  $n = 15$ ) who completed the study. Compared to baseline, sleep quality significantly improved in both treatment groups ( $p < 0.001$ ) at the end of the study period. In addition, sleep quality improvements in the olanzapine group were significantly higher compared to the risperidone group ( $p < 0.04$ ). No adverse effects were observed during the study period. The study authors note that paradoxical insomnia is likely a somatic delusion and the  $D_2$  blockade of olanzapine and risperidone in the treatment of schizophrenia and other delusional disorders may play a role.<sup>34</sup>

### CONCLUSIONS

At this time, the role of antipsychotics in the treatment of insomnia remains unknown and the evidence for efficacy of atypical antipsychotics is insufficient to recommend use in primary insomnia.<sup>5</sup> Available clinical evidence indicates that low-dose quetiapine, olanzapine, and risperidone may provide some benefit for insomnia with improvements noted in overall sleep quality, sleep efficiency, and TST. Most of the evidence, however, is based on patient-reported data from small observational, unblinded, and uncontrolled studies in adults (18 to 65 years). A 2011 AHRQ CER evaluating the off-label uses of

atypical antipsychotics concluded that atypical antipsychotics (including quetiapine) may not be effective in managing insomnia. In addition, the use of atypical antipsychotics, even at doses lower than those used for schizophrenia or bipolar disorder is not without risk. While many of the studies of atypical antipsychotics for the treatment of insomnia assessed sleep parameters, few monitored for and reported adverse effects. In low dose (<150 mg/day) quetiapine studies that monitored for adverse events patients reported xerostomia, morning sedation, weight gain, orthostatic hypotension, restless leg syndrome, and dizziness. Case reports describe fatal hepatotoxicity, restless leg syndrome and akathisia in patients using low-dose quetiapine for the treatment of insomnia. Reported adverse events in a 12 week study evaluating risperidone for insomnia included somnolence and sialorrhea. Patients treated with olanzapine over a 3 week period experienced sedation that impaired the ability to maintain a consistent morning rising time.

Comparative studies of atypical antipsychotics and other FDA-approved agents for insomnia, particularly those with anti-histaminic activity, would help to elucidate the mechanism of action of antipsychotics for insomnia. Furthermore, until long-term safety and efficacy can be demonstrated in larger, randomized, double-blind, controlled trials, the use of atypical antipsychotic agents for the off-label treatment of insomnia should not be recommended. Ultimately, the decision to use an atypical antipsychotic off-label needs to include an assessment of risks and benefits as well as patient education and appropriate monitoring for both efficacy and safety.

## REFERENCES

- Gold Standard, Inc. Atypical antipsychotics. Clinical Pharmacology [database online]. Available at: <http://www.clinicalpharmacology.com>. Accessed: September 3, 2013.
- Maher AR, Maglione M, Bagley S, Suttrop M, Hu JH, Ewing B, et al. Efficacy and comparative effectiveness of atypical antipsychotic medications for off-label uses in adults: a systematic review and meta-analysis. *JAMA*. 2011;306(12):1359-69. DOI: [10.1001/jama.2011.1360](https://doi.org/10.1001/jama.2011.1360). PubMed PMID: [21954480](https://pubmed.ncbi.nlm.nih.gov/21954480/).
- Maglione M, Ruelaz Maher A, Hu J, et al. Off label use of atypical antipsychotics: an update. Comparative Effectiveness Review No 43. Rockville, MD: Agency for Healthcare Research and Quality. September 2100. Available at: [www.effectivehealthcare.ahrq.gov/reports/final/cfm](http://www.effectivehealthcare.ahrq.gov/reports/final/cfm). Accessed: September 3, 2013.
- Alexander GC, Gallagher SA, Mascola A, Moloney RM, Stafford RS. Increasing off-label use of antipsychotic medications in the United States, 1995-2008. *Pharmacoepidemiol Drug Saf*. 2011;20(2):177-84. DOI: [10.1002/pds.2082](https://doi.org/10.1002/pds.2082). PubMed PMID: [21254289](https://pubmed.ncbi.nlm.nih.gov/21254289/); PubMed Central PMCID: [PMC3069498](https://pubmed.ncbi.nlm.nih.gov/PMC3069498/).
- Morin CM, Benca R. Chronic insomnia. *Lancet*. 2012;379(9821):1129-41. DOI: [10.1016/S0140-6736\(11\)60750-2](https://doi.org/10.1016/S0140-6736(11)60750-2).
- Miller DD. Atypical antipsychotics: sleep, sedation, and efficacy. *Prim Care Companion J Clin Psychiatry*. 2004;6(Suppl 2):3-7. PubMed PMID: [16001094](https://pubmed.ncbi.nlm.nih.gov/16001094/).
- Kane JM, Sharif ZA. Atypical antipsychotics: sedation versus efficacy. *J Clin Psychiatry*. 2008;69 Suppl 1:18-31. PubMed PMID: [18484805](https://pubmed.ncbi.nlm.nih.gov/18484805/).
- Monti JM, Monti D. Sleep in schizophrenia patients and the effects of antipsychotic drugs. *Sleep Med Rev*. 2004;8(2):133-48. DOI: [10.1016/S1087-0792\(02\)00158-2](https://doi.org/10.1016/S1087-0792(02)00158-2). PubMed PMID: [15033152](https://pubmed.ncbi.nlm.nih.gov/15033152/).
- Cohrs S. Sleep disturbances in patients with schizophrenia: impact and effect of antipsychotics. *CNS Drugs*. 2008;22(11):939-62. PubMed PMID: [18840034](https://pubmed.ncbi.nlm.nih.gov/18840034/).
- Monti JM, Jantos H. The roles of dopamine and serotonin, and of their receptors, in regulating sleep and waking. *Prog Brain Res*. 2008;172:625-46. DOI: [10.1016/S0079-6123\(08\)00929-1](https://doi.org/10.1016/S0079-6123(08)00929-1). PubMed PMID: [18772053](https://pubmed.ncbi.nlm.nih.gov/18772053/).
- Comparison of atypical antipsychotics. Pharmacist's Letter/Prescriber's Letter. October 2012; PL-Detail Document #281006.
- Wine JN, Sanda C, Caballero J. Effects of quetiapine on sleep in nonpsychiatric and psychiatric conditions. *Ann Pharmacother*. 2009;43(4):707-13. DOI: [10.1345/aph.1L320](https://doi.org/10.1345/aph.1L320). PubMed PMID: [19299326](https://pubmed.ncbi.nlm.nih.gov/19299326/).
- Seroquel (quetiapine fumarate) package insert. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2013 July.
- Sansone RA, Sansone LA. Is Seroquel developing an illicit reputation for misuse/abuse? *Psychiatry (Edgmont)*. 2010;7(1):13-6.
- Cohrs S, Rodenbeck A, Guan Z, Pohlmann K, Jordan W, Meier A, et al. Sleep-promoting properties of quetiapine in healthy subjects. *Psychopharmacology (Berl)*. 2004;174(3):421-9. DOI: [10.1007/s00213-003-1759-5](https://doi.org/10.1007/s00213-003-1759-5). PubMed PMID: [15029469](https://pubmed.ncbi.nlm.nih.gov/15029469/).
- Wiegand MH, Landry F, Brückner T, Pohl C, Veselý Z, Jahn T. Quetiapine in primary insomnia: a pilot study. *Psychopharmacology (Berl)*. 2008;196(2):337-8. DOI: [10.1007/s00213-007-0968-8](https://doi.org/10.1007/s00213-007-0968-8). PubMed PMID: [17922110](https://pubmed.ncbi.nlm.nih.gov/17922110/).
- Tassniyom K, Paholpak S, Tassniyom S, Kiewyoo J. Quetiapine for primary insomnia: a double blind, randomized controlled trial. *J Med Assoc Thai*. 2010;93(6):729-34.
- Juri C, Chaná P, Tapia J, Kunstmann C, Parrao T. Quetiapine for insomnia in Parkinson disease: results from an open-label trial. *Clin Neuropharmacol*. 2005;28(4):185-7. PubMed PMID: [16062098](https://pubmed.ncbi.nlm.nih.gov/16062098/).
- Terán A, Majadas S, Galan J. Quetiapine in the treatment of sleep disturbances associated with addictive conditions: a retrospective study. *Subst Use Misuse*. 2008;43(14):2169-71. DOI: [10.1080/10826080802290240](https://doi.org/10.1080/10826080802290240). PubMed PMID: [19085442](https://pubmed.ncbi.nlm.nih.gov/19085442/).
- Pasquini M, Specia A, Biondi M. Quetiapine for tamoxifen-induced insomnia in women with breast cancer. *Psychosomatics*. 2009;50(2):159-61. DOI: [10.1176/appi.psy.50.2.159](https://doi.org/10.1176/appi.psy.50.2.159). PubMed PMID: [19377025](https://pubmed.ncbi.nlm.nih.gov/19377025/).
- Robert S, Hamner MB, Kose S, Ulmer HG, Deitsch SE, Lorberbaum JP. Quetiapine improves sleep disturbances in combat veterans with PTSD: sleep data from a prospective, open-label study. *J Clin Psychopharmacol*. 2005;25(4):387-8. PubMed PMID: [16012285](https://pubmed.ncbi.nlm.nih.gov/16012285/).
- Cates ME, Jackson CW, Feldman JM, Stimmel AE, Woolley TW. Metabolic consequences of using low-dose quetiapine for insomnia in psychiatric patients. *Community Ment Health J*. 2009;45(4):251-4. DOI: [10.1007/s10597-009-9200-0](https://doi.org/10.1007/s10597-009-9200-0). PubMed PMID: [19472052](https://pubmed.ncbi.nlm.nih.gov/19472052/).
- Williams SG, Alinejad NA, Williams JA, Cruess DF. Statistically significant increase in weight caused by low-dose quetiapine. *Pharmacotherapy*. 2010;30(10):1011-5. DOI: [10.1592/phco.30.10.1011](https://doi.org/10.1592/phco.30.10.1011). PubMed PMID: [20874038](https://pubmed.ncbi.nlm.nih.gov/20874038/).
- Naharci MI, Karadurmus N, Demir O, Bozoglu E, Ak M, Doruk H. Fatal hepatotoxicity in an elderly patient receiving low-dose quetiapine. *Am J Psychiatry*. 2011;168(2):212-3. DOI: [10.1176/appi.ajp.2010.10091292](https://doi.org/10.1176/appi.ajp.2010.10091292). PubMed PMID: [21297052](https://pubmed.ncbi.nlm.nih.gov/21297052/).
- Pinninti NR, Mago R, Townsend J, Doghramji K. Periodic restless legs syndrome associated with quetiapine use: a case report. *J Clin Psychopharmacol*. 2005;25(6):617-8. PubMed PMID: [16282854](https://pubmed.ncbi.nlm.nih.gov/16282854/).
- Catalano G, Grace JW, Catalano MC, Morales MJ, Cruse LM. Acute akathisia associated with quetiapine use. *Psychosomatics*. 2005;46(4):291-301. DOI: [10.1176/appi.psy.46.4.291](https://doi.org/10.1176/appi.psy.46.4.291). PubMed PMID: [16000672](https://pubmed.ncbi.nlm.nih.gov/16000672/).
- Zyprexa (olanzapine, all formulations) package insert. Indianapolis, IN: Eli Lilly and Company; 2013 Jul.
- Giménez S, Clos S, Romero S, Grasa E, Morte A, Barbanoj MJ. Effects of olanzapine, risperidone and haloperidol on sleep after a single oral morning dose in healthy volunteers. *Psychopharmacology (Berl)*. 2007;190(4):507-16. DOI: [10.1007/s00213-006-0633-7](https://doi.org/10.1007/s00213-006-0633-7). PubMed PMID: [17205319](https://pubmed.ncbi.nlm.nih.gov/17205319/).

29. Sharpley AL, Vassallo CM, Cowen PJ. Olanzapine increases slow-wave sleep: evidence for blockade of central 5-HT<sub>2C</sub> receptors in vivo. *Biol Psychiatry*. 2000;47(5):468-70. PubMed PMID: [10704958](#).
30. Estivill E, de la Fuente V, Segarra F, Albares J. [The use of olanzapine in sleep disorders. An open trial with nine patients]. *Rev Neurol*. 2004;38(9):829-31. PubMed PMID: [15152350](#).
31. Sharpley AL, Attenburrow ME, Hafizi S, Cowen PJ. Olanzapine increases slow wave sleep and sleep continuity in SSRI-resistant depressed patients. *J Clin Psychiatry*. 2005;66(4):450-4. PubMed PMID: [15816787](#).
32. Risperdal (risperidone) package insert. Titusville, NJ: Janssen Pharmaceutica Products, L.P.; 2012 Aug.
33. Durán JC, Greenspan A, Diago JI, Gallego R, Martinez G. Evaluation of risperidone in the treatment of behavioral and psychological symptoms and sleep disturbances associated with dementia. *Int Psychogeriatr*. 2005;17(4):591-604. DOI: [10.1017/S104161020500219X](#). PubMed PMID: [16202185](#).
34. Khazaie H, Rezaie L, Darvishi F, Najafi F, Avis K. Treatment of paradoxical insomnia with atypical antipsychotic drugs. A comparison of olanzapine and risperidone. *Neurosciences (Riyadh)*. 2013;18(1): 64-9.
35. American Academy of Sleep Medicine. International classification of sleep disorders, revised: Diagnostic and coding manual. Chicago (IL): American Academy of Sleep Medicine;2001.

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