

Texas Vendor Drug Program

Drug Use Criteria: Quetiapine (low-dose)

Publication History

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Notes

- Information on indications for use or diagnosis is assumed to be unavailable. All criteria may be applied retrospectively; prospective application is indicated with an asterisk [*]. The information contained is for the convenience of the public. The Texas Health and Human Services Commission (HHSC) is not responsible for any errors in transmission or any errors or omissions in the document.
- Medications listed in the tables and non-FDA approved indications included in these retrospective criteria are not indicative of Vendor Drug Program formulary coverage.

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1 Dosage

HHSC does not support low-dose quetiapine use as non-FDA-approved sleep aid monotherapy. Data included in these criteria address available studies evaluating low-dose quetiapine in insomnia, the limits of these studies, as well as risks associated with quetiapine use for this indication. Additionally, evidence-based use of lower quetiapine doses for FDA-approved and pediatric purposes is also discussed.

1.1 Adults

Quetiapine, a dibenzothiazepine antipsychotic agent, is FDA-approved for acute manic and mixed episodes of bipolar disorder, acute depressive episodes associated with bipolar disorder, maintenance therapy of bipolar disorder when used adjunctively with lithium or divalproex, major depressive disorder when used as adjunctive therapy to antidepressants (extended-release formulation only), and schizophrenia.¹⁻⁶ Recommended quetiapine dosages are summarized in Table 1.

Table 1. Quetiapine Approved Adult Dosage Recommendations¹⁻⁶

Treatment Indication	Dosage Form	Usual Dosage Range	Maximum Recommended Dosage
BD treatment: depression	IR, ER	300 mg/day	300 mg/day
BD treatment: mania	IR, ER	400-800 mg/day	800 mg/day
BD: maintenance	IR, ER	400-800 mg/day	800 mg/day
Major depressive disorder, adjunctive therapy	ER	150-300 mg/day	300 mg/day
Schizophrenia: acute	IR	150-750 mg/day	750 mg/day
Schizophrenia: maintenance	IR, ER	400-800 mg/day	800 mg/day

While not FDA-approved, quetiapine has been evaluated in adults with insomnia utilizing doses less than 150 mg/day in the literature. Measurements commonly used to assess insomnia treatment effectiveness include sleep period time (SPT; the duration of time from sleep onset to final awakening), total sleep time (TST; the difference of time between SPT and the time spent awake), and sleep efficiency

(SE; the ratio of TST compared to the amount of time spent in bed).⁷ Patient-reported outcomes are also often assessed. The Spiegel Sleep Questionnaire (SSQ) is comprised of 7 items that are each scored from 1 to 5, with higher scores indicating positive outcomes.⁸ The Insomnia Severity Index scale (ISI) is a tool used to measure a patient’s perception of his or her insomnia. This instrument also consists of 7 items, but each item is scored from 0 to 4. Higher scores correlate with more severe insomnia.⁹ Clinical evidence of low-dose quetiapine use for insomnia is exhibited in Table 2.

Table 2. Quetiapine Studies/Case Reports for the Treatment of Insomnia

Study	Population	Design	Intervention	Outcomes
Cohrs et al ⁷ (2004)	14 patients: •healthy males •age: 18-65 years	DB, PC, R, crossover, single-center study Duration: 3 consecutive nights, 4 days apart	Quetiapine: •25 mg one hour before bedtime •100 mg one hour before bedtime Control: placebo	Under standard sleep laboratory conditions: •25 mg: significant differences for SPT, TST, and SE compared to placebo •100 mg: significant difference for SPT compared to placebo Under Acoustic Stress: [*] •25 mg: significant differences for SPT, TST, and SE compared to placebo 100 mg: significant differences at SPT, TST and SE compared to placebo

Study	Population	Design	Intervention	Outcomes
Juri et al ¹⁰ (2005)	14 patients: •male and female •Parkinson's disease	Open-label study Duration: 12 weeks	Quetiapine: •initial dose: 12.5 mg at bedtime •dose adjusted according to response and tolerance mean dose: 31.9 mg at bedtime at week 12	Sleep Latency: •decrease of 82 ± 65.4 vs 28.6 ± 22.7 minutes from baseline (p less than 0.05) •no correlation between response and dose of levodopa or dopamine agonist Safety: •two patients withdrew due to restless leg symptoms that subsided after quetiapine discontinuation •two patients reported increased diurnal sleepiness •no reports of orthostatic symptoms or significant changes in blood pressure
Fernando et al ¹¹ (2005)	1 patient: •34 year-old male •insomnia due to chronic back pain	Case report	Quetiapine: titrated up to 200 mg at bedtime	Observations: •improved quality of sleep •improved sleep latency
Sokolski et al ¹² (2006)	1 patient: •42 year-old white male •25 year history of major depression •insomnia exacerbated by phenelzine use	Case report	Quetiapine: •initial dose: 6.25 mg at bedtime •dose increased by 6.25 mg every 3 - 4 days until reached 25 mg at bedtime •later increased to 37.5 mg at bedtime •max dose: 50 mg at bedtime	Observations: •insomnia dramatically improved •patient slept 6 - 7 hours per night without interruption Safety: •only reported adverse event was morning sedation; patient gradually habituated •patient continued on phenelzine and quetiapine for more than 1 year with no report of adverse events

Study	Population	Design	Intervention	Outcomes
Wiegand et al ¹³ (2008)	18 patients: •primary insomnia	Open-label pilot study Duration: 6 weeks	Quetiapine: •initial dose: 25 mg at bedtime •increased to 50 mg at bedtime (n = 7) •increased to 75 mg at bedtime (n = 1)	Objective Sleep Parameters: •significant improvements in TST and SE •initial improvements observed at 2 weeks and continued throughout study period •sleep onset latency not significantly ↓'d no test variable showed a decline from baseline over the study period Safety: •reports of xerostomia and morning sedation (frequency not defined) •no reports of severe adverse events
Terán et al ¹⁴ (2008)	52 patients: •drug abusers in detoxification process •insomnia as primary withdrawal symptom •included both outpatients and inpatients	Retrospective study Follow-up period of at least 60 days	Quetiapine: •median dose: 50 mg at bedtime •mean dose: 62.35 mg at bedtime •range: 22 mg - 225 mg at bedtime	Change in SSQ: •75% improvement from baseline (p less than 0.001) •greatest improvement in mean score occurred in first week (p less than 0.001) •benzodiazepine use decreased from baseline (83% vs 22.6% of patients) Safety: •well tolerated •no patients dropped out due to adverse events •xerostomia most common adverse event (n=18; 34.5%)

Study	Population	Design	Intervention	Outcomes
Pasquini et al ¹⁵ (2009)	6 patients: •females •localized breast cancer receiving tamoxifen	Case series Duration: 6 weeks	Quetiapine: •initial dose: 25 mg one hour before bedtime •max dose: 100 mg one hour before bedtime	Efficacy: •swift improvement in insomnia in 5/6 patients →→patients moved from the moderate ISI category (score of 15 to 21) to absence of insomnia •effect maintained after 6 weeks Safety: •weight gain (n=2) •dizziness (n=1)

Study	Population	Design	Intervention	Outcomes
Cates et al ¹⁶ (2009)	43 patients: •male and female psychiatric patients •19 – 65 years old •receiving at least one other psychotropic medication •mean BMI = 31	Retrospective study	Quetiapine: •mean initial dose: 109.3 mg ± 47.3 per day •mean final dose: 120.3 mg ± 58.6 per day •most common regimen: 100 mg at bedtime •mean duration: 11.1 months ± 8.2	Efficacy: <u>Primary Outcome:</u> •changes in weight, BMI, and waist circumference compared to baseline →→mean weight gain of 4.9 lb over approximately 11 months →→statistically significant increase in weight (p = 0.037) →→statistically significant increase in BMI (p = 0.048) →→increase in waist circumference not statistically significant →→male mean increase in weight: 10.5 lb ± 15.6 (p = 0.009) →→male mean increase in BMI: 1.3 points ± 2.1 (p = 0.016) <u>Secondary Outcome:</u> (compared to baseline) •correlation of metabolic changes with patient and treatment variables; no significant differences were found

Study	Population	Design	Intervention	Outcomes
Tassniyom et al. ¹⁷ (2010)	13 patients: •primary insomnia •mean age: 45.95 years	R, DB, PC Duration: 3 weeks Sleep diary kept for 1 week prior to treatment	Quetiapine (Q): •25 mg every night X 2 weeks Placebo (P): •every night x 2 weeks	Efficacy: <u>Primary Outcome:</u> •TST, sleep latency, daytime alertness/functioning, sleep satisfaction →→TST: increased 124.92 min (Q) vs 72.24 min (P) – NS →→SL: decreased 96.16 min (Q) vs 23.72 min (P) – NS Safety: dry lips, dry tongue, morning drowsiness in two Q patients

- BMI = body mass index
- DB = double-blind
- ISI = Insomnia Severity Index scale
- PC = placebo-controlled
- R = randomized
- SE = sleep efficiency
- SL = sleep latency
- SPT = sleep period time
- SSQ = Spiegel Sleep Questionnaire
- TST = total sleep time
- * = Acoustic Stress = staccato piano tones ranging in pitch and tone intensity played in short spurts during the 8 hour bedtime period (duration: 4-5 seconds; interval: 30 – 90 seconds)

Based on available clinical evidence, low-dose quetiapine has shown some benefit for adult patients suffering from insomnia.⁷⁻¹⁹ Quetiapine not only improved the quantity of sleep, by increasing TST and SE, but also the quality of sleep, by increasing patient-reported outcomes. However, available results are based on data from case reports and uncontrolled trials, and include few patients over 65 years of age or those in nursing homes. Too, the mechanism of action for low-dose quetiapine targets histamine H1 and alpha-1 adrenergic receptors rather than serotonergic and dopaminergic receptors, which may aid in promoting sleep but does not significantly impact mood or psychotic disorders. Additionally, quetiapine has been assigned black box warnings: increased mortality in elderly patients with dementia-related psychosis; and, increased risk of suicidality in children, adolescents, and young adults taking antidepressants for major depressive and other psychiatric disorders. Other warnings include leukopenia, neutropenia,

neuroleptic malignant syndrome, metabolic changes, and agranulocytosis.^{2, 3, 19-21} Commonly reported adverse events include xerostomia, morning sedation, and weight gain. Reports of weight gain despite the use of low quetiapine doses may predispose some patients to metabolic disturbances (e.g., diabetes, dyslipidemia) associated with second generation antipsychotic (SGA) use.^{16, 19}

Long-term efficacy of low-dose quetiapine treatment for insomnia has yet to be demonstrated in larger, randomized, controlled trials. Additional safety data are also needed before quetiapine can be prescribed with confidence for insomnia patients. Until strong evidence is established, low-dose quetiapine should be used with caution for the off-label treatment of insomnia, especially when other FDA-approved agents for insomnia are available and more economically feasible.²²

Patients with co-morbid conditions and insomnia, however, may find some benefit from low-dose quetiapine, with close monitoring for potential long-term adverse events.^{14, 23}

A comparative effectiveness review published by the Agency for Healthcare Research and Quality (AHRQ) evaluated physician prescribing patterns for off-label uses of atypical antipsychotics. Researchers found one small trial (n = 13) in which physicians prescribed quetiapine to patients for insomnia and concluded that quetiapine may not be effective in managing insomnia; the strength of evidence used to determine the efficacy of quetiapine in insomnia was very low.²³

Quetiapine doses less than 150 mg/day are not routinely recommended. However, elderly patients (defined as 65 years of age and older) and debilitated patients may not tolerate higher initial quetiapine doses due to decreased oral quetiapine clearance. Slower titration schedules using doses of 25-50 mg/day until clinical response is achieved are necessary to avoid adverse events.¹⁻⁶ Some patients have been managed with doses as low as 25 mg to 50 mg/day for psychosis and bipolar disorder.²⁴⁻²⁶ Quetiapine is not FDA-approved for use in doses lower than 150 mg/day, except in elderly and debilitated patients, and will be reviewed.

1.2 Pediatrics

Quetiapine is FDA-approved for acute mania in bipolar disorder in pediatric patients 10-17 years of age, and acute management of schizophrenia in adolescents 13-17 years of age. Pediatric quetiapine dosages are summarized in Table 3.

Table 3. Quetiapine Approved Pediatric Dosage Recommendations¹⁻⁶

Treatment Indication	Dosage Form	Usual Dosage Range Per Age Group	Maximum Recommended Dosage
BD treatment: acute mania	IR, ER	10-17 years of age: 400-600 mg/day	600 mg/day
Schizophrenia: acute	IR, ER	13-17 years of age: 400-800 mg/day	800 mg/day

Currently there is no FDA-approved indication for low-dose quetiapine use (150 mg/day or less) in the pediatric population. Data have been published that address quetiapine safety and efficacy for the treatment of various conditions in the pediatric population, and some of the patients included were taking quetiapine doses of 150 mg/day or less. Summary details of these publications can be found in Table 4.

Evidence suggests that quetiapine use in children for a variety of indications including conduct disorder, attention-deficit/hyperactivity disorder, bipolar disorder, and other psychoses may be beneficial as monotherapy in some situations and as combination therapy in others. Although most trials used a mean dose greater than 300 mg/day, all studies presented in Table 4 utilized quetiapine doses of 150 mg/day or less. Based on the trials collectively, using quetiapine in patients younger than 18 years of age resulted in significantly improved scores on many of the psychiatric evaluations. Although average doses in the trials exceeded 150 mg/day, efficacy did not seem to be limited to higher quetiapine doses.²⁷⁻³⁷ However, many of these trials had several limitations that are important to consider. All trials were open-label trials, included very small numbers of participants, and were relatively short in duration. Only one trial was randomized, and most did not have a comparator or control group.³³⁻³⁶

While efficacy results seem promising from these trials, there are important adverse effects associated with quetiapine use in children. Weight gain, other metabolic changes, and sedation/somnolence, well known adverse effects associated with quetiapine use, were frequently reported by trial participants.³³⁻³⁶ Moreno et al.³⁸ published a trial examining the metabolic effects of quetiapine and other SGA medications on children being treated for bipolar disorder as well as other psychotic and nonpsychotic disorders. This study found that after three months of treatment with an SGA, over 70% of patients experienced abnormal weight gain. Due to the frequency of weight gain and sedation occurring with SGA use, Penzner et al.³⁹ studied the effect of co-prescribing a stimulant, which can cause weight loss and insomnia, to neutralize the adverse effects of the

antipsychotic. Investigators found no significant differences in body composition and metabolic profiles between SGA-treated patients managed concurrently with or without stimulants.

Low-dose quetiapine treatment for children with various psychotic or behavioral disorders has been beneficial in some cases. However, possible adverse events that may negatively impact health and quality of life need to be considered before treatment initiation.

Table 4. Quetiapine Dosages in Pediatric Patients

Study	Age	Quetiapine Dosage	Disease State
Stathis et al. ²⁷	15 to 17 years of age (mean age 16.7 yrs)	dose range 50 mg - 200 mg/day (mean dose: 133 mg)	Posttraumatic stress disorder
Findling et al. ²⁸ (2006)	6-12 years of age (mean age 8.9 yrs)	range 75mg -300 mg/day (median dose: 150 mg/day; mean dose: 4.4 mg/kg/day)	Conduct disorder
Marchand et al. ²⁹	4-17 years of age (mean age 10.8 yrs)	dose range 100 mg - 1000 mg/day (mean dose: 407 ± 230 mg/day)	Bipolar disorder
Findling et al. ³⁰ (2004)	12-17 years of age (mean age 14.6 ± 2.3 yrs)	mean maximum total daily dose range 100 mg - 450 mg/day (overall mean dose: 291.7 mg/day)	Autistic disorder
Mukaddes et al. ³¹	8-16 years of age (mean age 11.4 ± 2.4 yrs)	dose range 50 mg - 100 mg/day (mean dose: 72.9 mg ± 22.5 mg/day)	Tourette's disorder
Tufan ³²	17-year-old-female	100 mg/day in divided doses (plus sertraline 50 mg/day)	Autism; pervasive developmental disorder with mental retardation and self-injurious behavior
Arango et al. ³³	12-18 years of age	dose range 73.2 mg – 992.4 mg/day (mean dose: 532.8 mg/day)	Schizophrenia; bipolar disorder

Study	Age	Quetiapine Dosage	Disease State
Findling et al. ³⁴ (2007)	6-12 years of age	dose range 75 mg-350 mg/day (mean dose at study end: 158.3 mg/day) (methylphenidate administered adjunctively in majority of patients)	Conduct disorder
Duffy et al. ³⁵	13-20 years of age	<i>throughout study:</i> dose range 64.4 mg – 617.4 mg/day (mean dose: 340.9 mg/day) <i>at study end:</i> dose range 27.3 mg – 561.9 mg/day (mean dose: 294.6 mg/day)	Bipolar disorder
Kronenberger et al. ³⁶	12-16 years of age	dose range 120.2 mg – 538.2 mg/day (mean dose: 329.2 mg/day) (given in conjunction with methylphenidate)	ADHD* - combined type and disruptive behavior disorder with conduct disorder
Golubchik et al. ³⁷	13-17 years of age	dose range 50 mg-150 mg/day (mean dose: 122.7 ± 39.5 mg/day)	Autistic spectrum disorder

2 Duration of Therapy

Low-dose quetiapine (less than 150 mg/day) is only FDA-approved as part of a drug titration schedule to aid patients in getting to the target quetiapine dosage goal (see Table 1). Therefore, quetiapine dosages less than 150 mg/day should not be prescribed for more than 30 days, except in elderly and debilitated patients. Quetiapine dosages less than 150 mg/day prescribed for greater than 30 days, except in elderly and debilitated patients, are not recommended and will be reviewed.

3 Drug-Drug Interactions

Patient profiles will be assessed to identify those drug regimens which may result in clinically significant drug-drug interactions. Drug-drug interactions considered clinically relevant for quetiapine are summarized in Table 5. Only those drug-drug interactions classified as clinical significance level 1 or those considered life-threatening which have not yet been classified will be reviewed:

Table 5. Select Drug-Drug Interactions for Quetiapine

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level [#]
Atypical antipsychotics (AAs)	Antihypertensive agents	Potential for enhanced antihypertensive effects due to AA-associated alpha1-adrenergic receptor antagonism	Use cautiously together; monitor for amplified hypotensive effects	3-moderate (CP)
AAs	CNS depressants	Potential for additive CNS effects	Use cautiously together; observe patients for enhanced CNS adverse effects	Major (DrugReax) 3-moderate (CP)
AAs (except pimavanserin)	Drugs affecting seizure threshold (e.g., tramadol)	Increased seizure risk as AAs have been associated with seizures (incidence varies)	Avoid drug combination if possible; if combination necessary, closely monitor patients for seizure activity and discontinue therapy as indicated	Major (DrugReax) 2-major (CP)

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level [#]
AAs	Metoclopramide	Adjunctive therapy enhances potential for increased extrapyramidal symptoms (EPS) and neuroleptic malignant syndrome (NMS) as both agents block dopamine receptors	Combination contraindicated by metoclopramide manufacturer; if combination necessary, monitor for signs/symptoms of EPS or NMS-discontinue metoclopramide if symptoms develop	Contraindicated (DrugReax) 1-severe (CP)
Select AAs (aripiprazole, brexpiprazole, cariprazine, clozapine, iloperidone, pimavanserin, quetiapine, ziprasidone)	CYP3A4 inhibitors (e.g., ketoconazole, ritonavir*)	Potential for decreased AA clearance, increased AA serum concentrations, and enhanced pharmacologic/adverse effects as select AAs metabolized by CYP3A4	Monitor for enhanced AA pharmacologic/adverse effects and adjust doses as necessary (50% dose reduction recommended for aripiprazole, brexpiprazole, iloperidone)	Moderate (DrugReax) 2-major, 3-moderate (CP)
Select AAs (aripiprazole, brexpiprazole, clozapine, olanzapine, pimavanserin, quetiapine, risperidone, ziprasidone)	CYP3A4 inducers (e.g., carbamazepine**, phenytoin)	Potential for significant reductions in AA plasma concentrations (by as much as 50%) due to enhanced AA hepatic microsomal metabolism	Monitor AA efficacy in patients; adjust doses as necessary when CYP3A4 inducer added, deleted, or changed to therapeutic regimen (brexpiprazole dose should be doubled over 1-2 weeks when prescribed with CYP3A4 inducer)	Moderate (DrugReax) 2-major, 3-moderate (CP)

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level [#]
Select AAs (aripiprazole, asenapine, clozapine, iloperidone, olanzapine, paliperidone, pimavanserin, quetiapine, risperidone, ziprasidone)	QTc interval-prolonging medications	Potential for increased cardiotoxicity (e.g., torsades de pointes, cardiac arrest) due to additive QT interval prolongation	Avoid concurrent use; if combination necessary, closely monitor cardiac function; discontinue therapy in patients with QTc measurements greater than 500 msec	Major (DrugReax) 1-severe, 2-major (CP)

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