



THERAPEUTICS INITIATIVE

Evidence Based Drug Therapy



Is use of quetiapine for sleep evidence-based?

Quetiapine (Seroquel® and generics) has been available in Canada since 1998. It is approved for schizophrenia, bipolar disorder and, as of 2010, for major depressive disorder (MDD) refractory to treatment with antidepressants.¹ It is widely prescribed in low doses for management of sleep disorders, despite lacking approval for this use.²

In 2010 almost \$20 million was spent on quetiapine in British Columbia, placing it 21st in cost, ahead of pantoprazole and amlodipine. At almost 1 million prescriptions, quetiapine was the 9th most frequently prescribed drug in B.C., leading rabeprazole and citalopram and close behind zopiclone and metformin. Given the wide range of drugs available for psychosis and mood disorders, these indications likely account for a minority of quetiapine's use in 2010. This is supported by the fact that 58% of B.C. quetiapine prescriptions were for the 25 mg tablet, whereas the recommended dose range for the approved disorders is 150 to 800 mg/day. Similarly in the United States, up to 70% of newer antipsychotic prescribing is for conditions other than psychosis.³ This letter examines efficacy and safety evidence about use of low dose quetiapine for sleep disorders.

What is quetiapine?

Quetiapine is a dibenzothiazapine derivative which antagonizes multiple receptors, including serotonin (5HT_{1A} and 5HT₂), dopamine (D₁ and D₂), histamine H₁ and adrenergic alpha₁ and alpha₂ receptors, but the mechanism of action for any use is unknown. At least one metabolite, norquetiapine, may also be pharmacologically active, including antagonism of muscarinic M₁ receptors (anti-cholinergic).¹

Pharmacokinetics and cost

Quetiapine is eliminated by metabolism in the liver with average half-life of 6-7 hours. This is prolonged in people > 65 years. Norquetiapine is present at lower concentrations, but has a longer half-life.¹ Quetiapine 25 to 50 mg daily costs \$0.32-\$0.64 per day in B.C.

Evidence for use in primary insomnia

Two published randomized controlled trials evaluated quetiapine's effect on sleep in patients not suffering from other medical conditions or psychiatric illness.^{4,5} Only one studied patients suffering from primary insomnia⁵; the other was in healthy subjects without insomnia⁴.



The healthy subject study evaluated 14 males using a randomized, double-blind, crossover, placebo-controlled, single-center design. Placebo or quetiapine at 25 and 100 mg doses were given on 3 consecutive nights with a 4-day washout period before crossover. Polysomnographic recordings were made nightly and subjective sleep-rating questionnaires completed each morning. Both doses of quetiapine produced statistically significant improvements in objective and subjective ratings of sleep, including total sleep time, sleep efficiency, sleep latency and duration of stage 2 sleep. The 100 mg dose increased periodic leg movements and decreased REM sleep. Two out of 14 subjects taking quetiapine withdrew from the study because of symptomatic orthostatic hypotension.⁴

In the primary insomnia study, 25 patients were randomized to quetiapine 25 mg or placebo. Patients were asked to record a sleep diary for one week before and two weeks after initiation of treatment. No statistically significant improvements were found in the primary outcomes of total sleep time, sleep latency, daytime alertness and sleep satisfaction.⁵

Potential adverse effects

Very few data are available concerning adverse effects of low dose quetiapine. Two out of 14 healthy males using 25 or 100 mg withdrew due to orthostatic hypotension during short-term use. Extrapyramidal symptoms, including dystonia, akathisia, and tardive dyskinesia have been associated with quetiapine with both high and low dose regimens.¹ A recent case report describes two patients on low dose quetiapine for insomnia



who discontinued the drug due to akathisia.⁶ Two out of 13 patients discontinued quetiapine due to exacerbation of restless leg symptoms in an open-label trial of low dose quetiapine for insomnia in Parkinson's disease.⁷

Most adverse effects observed with quetiapine have been reported during high dose treatment (150 to 800 mg daily) of bipolar mania or schizophrenia. Common side effects at high doses include weight gain, somnolence, increased cholesterol and triglyceride levels, insulin resistance, dry mouth, dizziness, and orthostatic hypotension. Life-threatening adverse events are rare with high dose quetiapine, but include neuroleptic malignant syndrome and neutropenia.¹ One small double-blind RCT found that quetiapine worsened cognitive decline in dementia.⁸ Quetiapine increases mortality in elderly demented patients (ARI=2.3%) and as a result has a "black box" warning in the US similar to other antipsychotic drugs.¹ Quetiapine is also known to have abuse potential.⁹⁻¹³

Does the evidence warrant use of quetiapine for insomnia?

The two small trials described above do not provide sufficient evidence to justify prescribing quetiapine for insomnia. A recent review reached similar conclusions.¹⁴ Two general reviews of primary insomnia also conclude that antipsychotics are not a recommended treatment.^{15,16} Widespread use of quetiapine as a sleep aid is occurring in the absence of evidence for effectiveness or safety.²

Why is this happening? Benzodiazepine and non-benzodiazepine hypnotics such as the "z-drugs" (e.g. zopiclone) are the short-term drug treatment of

choice for insomnia. However, their use has been constrained by their adverse effects, the rapid development of tolerance, withdrawal effects, and the potential for dependence and abuse.^{17,18,19} The adverse effects of low dose quetiapine are largely unknown. Case reports suggest that akathisia and other extrapyramidal symptoms, periodic leg movements, restless leg syndrome and orthostatic hypotension may be of concern. It is unknown whether weight gain and metabolic changes may complicate chronic low dose use.

A large double-blind RCT comparing quetiapine with benzodiazepines or "z-drugs" is needed to evaluate the short-term efficacy of quetiapine for primary insomnia with a primary outcome of improved sleep measures documented in a sleep laboratory. In addition long-term effectiveness needs to be studied in RCTs in patients taking such drugs over at least one year, either daily or intermittently. This is necessary to establish whether the benefits outweigh the harms for long-term use and properly elucidate the incidence of adverse effects, withdrawal symptoms and potential for abuse.

Conclusions

- **Quetiapine is not approved nor recommended for primary insomnia.**
- Quetiapine is commonly prescribed off-label as a sleep aid, but only one RCT examined its use in patients with insomnia. It found no benefit.
- No published RCT evidence exists comparing quetiapine with other drugs for insomnia.
- Management of primary insomnia should focus on education and encouragement of appropriate sleep habits. Drugs should be limited to short duration, intermittent use, or daily use only in exceptional cases.

The draft of this Therapeutics Letter was submitted for review to 65 experts and primary care physicians in order to correct any inaccuracies and to ensure that the information is concise and relevant to clinicians.

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