Revista ARACÊ
ISSN: 2358-2472

INDICATION FOR THE USE OF QUETIAPINE FOR THE TREATMENT OF INSOMNIA: AN INTEGRATIVE REVIEW

https://doi.org/10.56238/arev6n4-091

Submitted on: 11/06/2024 **Publication date:** 12/06/2024

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ABSTRACT

This research is an integrative review on the off-label use of quetiapine for the treatment of insomnia. Insomnia, a common and multifactorial disorder, affects a large part of the population and can be associated with several conditions, such as psychiatric disorders. Although quetiapine is approved for the treatment of disorders such as schizophrenia and bipolar disorder, its use for insomnia is not officially indicated. However, clinical practice has shown that it can be effective in managing insomnia, especially in patients with psychiatric comorbidities, such as treatment-resistant depression and anxiety disorders. The research included five recent papers that pointed to benefits in treating insomnia with quetiapine, although it also raised concerns about the risks of side effects such as weight gain, excessive sedation, and potential dependence, especially in vulnerable populations. The results suggest that, despite the efficacy, off-label use of quetiapine for insomnia should be done with caution, taking into account the risks and benefits, and being more appropriate for patients with coexisting psychiatric disorders. The study concludes that more studies on the safety and efficacy of quetiapine for this purpose are needed.

Keywords: Insomnia. Use of Medications. Quetiapine.

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ISSN: 2358-2472

INTRODUCTION

Sleep disorders are common and multifactorial conditions. About a third of the general population has some sleep disorder. The risk of these disorders increases with age. Among sleep disorders, insomnia is the most prevalent (Sá; Motta; Oliveira, 2019).

Insomnia is considered a difficulty in initiating sleep or maintaining it, when there may be a total or partial decrease in the quantity or quality of sleep. Insomnia can be classified as initial, intermediate or final, and, as to duration, transient, short-term or chronic. Regarding the etiology, insomnia can be primary or secondary to some known factor (Sá; Motta; Oliveira, 2019).

As for sleep disorders, health promotion is directly related to sleep quality. It is found that a large part of the population with sleep disorders resorts to psychotropic medications, which sometimes cause more harm than good, because of the side effects (Brasil, 2023).

In recent years, it has been possible to observe more and more the recommendation of quetiapine as a treatment for sleep disorders, especially when associated with psychiatric disorders (schizophrenia, anxiety, and depression), although there is no formal clinical recommendation for this, that is, off-label use (Gomes et al., 2023).

Regarding this type of drug use, *off-label* use is an increasingly present topic in the context of public health, especially when it refers to the discussion about the rational use of drugs. The definition for off-label drug use is the use of drugs by indication, group of people or management system, for which there has not yet been approval by a competent authority. This type of use is based on the freedom of the prescriber to weigh the benefits for patients (Silva; Abreu, 2021).

In view of this scenario, the present study sought to identify the efficacy of recommending the use of quetiapine as an *off-label* medication for sleep disorders.

THEORETICAL FRAMEWORK

CHARACTERISTICS OF QUETIAPINE

Quetiapine fumarate was discovered in 1984, it was first marketed through AstraZeneca under the trade name Seroquel®. Later, it was approved in more than 70 countries, in 1997 it received approval from the FDA (*Food and Drug Administration*) as a psychotropic drug. In 2006, it received an indication for the treatment of various disorders, including depressive disorders associated with bipolar I and II, alcoholism, post-traumatic

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stress, Parkinson's, Tourette's Syndrome and as a sedative for insomnia and anxiety therapy (Gonçalves; Silva, 2016).

Quetiapine is considered one of the main second-generation antipsychotics, therefore, it stands out as one of the most widespread molecules of this group. Quetiapine is a dibenzothiazepine derivative that has moderate affinity for 5-HT2A, alpha 1, M1, and H1 receptors, and lower affinity for D2 and 5-HT1a receptors, and an even lower affinity for 5-HT2c, alpha 2, and D receptors (Caixeta *et al.*, 2023).

Due to the weak blocking of dopaminergic receptors D1 and D2, quetiapine has little or no extrapyramidal effect, even because it has a lower affinity for the receptors of the nigrostriatal dopaminergic system and also does not promote an increase in prolactin (Unifesp, 2014).

It is estimated that quetiapine causes an increase in dopamine levels in the prefrontal region by antagonizing 5-HT2a receptors, while acting as a partial agonist of 5-HT1a receptors, so that it increases the action of the neurotransmitter serotonin. It is accepted that norquetiapine, the active metabolite of quetiapine, also has anxiolytic and antidepressant effects by inhibiting the norepinephrine transporter and by activating the serotonin receptor (Caixeta *et al.*, 2023).

Quetiapine is a drug with oral absorption and hepatic metabolism, it does not change with the presence of food, its plasma peak is reached in up to 2 hours, its half-life is short, lasting 7 hours, Its dosage can be administered 2 to 3 times a day, it is advisable to use higher doses at night due to its sedative effects (Gonçalves; Silva, 2016).

In addition, quetiapine was considered effective and well tolerated by patients sensitive to side effects and has an effectiveness equivalent to typical antipsychotics, as well as having efficacy similar to that of risperidone and olanzapine (Unifesp, 2014).

The sedative effects of quetiapine sometimes occur at a lower intensity when higher doses of the drug are used, possibly caused by the high affinity of its metabolite, norquetiapine, for norepinephrine transport, and the resulting high levels of synaptic norepinephrine (Caixeta *et al.*, 2023).

INDICATED USES OF QUETIAPINE

Quetiapine is a second-generation psychotropic drug used in the treatment of schizophrenia that has efficacy similar to first-generation drugs, its action causes a reduction in positive and negative symptoms, with a lower frequency of side effects and,

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consequently, decreases the length of hospital stay of affected patients (Da Silva Filho; Fields; Ramos, 2021).

Extended-release quetiapine is a therapeutic option for cases of generalized anxiety disorder (GAD) that are non-responsive, intolerant, or have contraindications to the use of antidepressants. In these cases, quetiapine can be used when the use of benzodiazepines is avoided due to clinical contraindication or risk of dependence (Mochcovitch, 2015).

Regarding mood stabilizers, quetiapine is the only atypical antipsychotic that is indicated as the first line of treatment in the various existing treatment guidelines, both in the acute phases of mania and hypomania as well as depression and in the prevention of all these conditions (Miranda-Scippa, 2020).

Quetiapine was the first atypical antidepressant drug approved for monotherapy in the treatment of bipolar disorder, for the phases of mania and depression, as well as for the maintenance phase (Villalobos, 2013).

Quetiapine may have primary antidepressant actions intrinsically or through additional benefit for treatment-resistant depression. In addition, quetiapine also has antidepressant efficacy in experiments on unipolar major depression, because its metabolite norquetiapine probably acts to inhibit norepinephrine reuptake, so it could be used as a monotherapy for depression. It has off-label use for insomnia. (Goodman; Gilman, 2012).

Quetiapine is one of the atypical sedative antipsychotic drugs, its sedative effect is explained by its high affinity for the H1 receptor, so it has *off-label* use for insomnia. (Goodman; Gilman, 2012).

In general, for the treatment of insomnia, antipsychotics are not recommended for people without psychosis, regarding quetiapine, the benefits in the treatment of insomnia do not outweigh the potential risks of using the drug, even in patients with comorbidities that justify its use (Ribeiro, 2016).

However, because of the disadvantages of long-term use of benzodiazepines, there is a need for other options for the treatment of insomnia. In clinical practice, quetiapine is often prescribed *off-label* for the treatment of insomnia (Campos *et al.*, 2023).

For the management of acute bipolar depression in the elderly, quetiapine and quetiapine ER are accepted as the agent of choice in all guidelines, while in maintenance therapy, quetiapine is also recommended as adjunctive therapy with lithium or divalproex (Alves *et al.*, 2017).

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Quetiapine is one of the most effective options of atypical antipsychotics for the treatment of agitation and psychosis of Alzheimer's disease. While in Huntington's disease with a predominance of rigidity, quetiapine may be more effective for the treatment of paranoia and psychosis (Goodman; Gilman, 2012).

In Parkinson's disease, quetiapine has been shown to be particularly useful, because this drug does not appear to cause worsening of the motor manifestations of the disease. Although epidemiological studies have shown that this use is associated with an increased risk of stroke and cerebrovascular disease, which makes it necessary to better assess the risks and benefits of treatment in these situations (Golan, 2014).

MAIN SIDE EFFECTS

The main effects reported with the use of quetiapine are: headache, drowsiness, weight gain, tachycardia, dizziness, abdominal pain, dry mouth, anorexia, weakness, cough, increased cholesterol, hypothyroidism, and increased appetite (Gonçalves; Silva, 2016).

Other effects adverse factors of quetiapine are: orthostatic hypotension, dyspepsia, and constipation (Unifesp, 2014). Another limitation to the use of quetiapine is the increased risk of weight gain and development of metabolic syndrome (Goldman; Gilman, 2012; Mochcovitch, 2015).

Regarding the occurrence of hyperglycemia and diabetes mellitus (DM), the atypical antipsychotics, clozapine and olanzapine are the most associated with these adverse effects, although there are fewer reports of these effects also associated with the use of quetiapine and risperidone (Teixeira; Rocha, 2006).

Most studies on the association between dyslipidemia and psychotropic drugs have been carried out with antipsychotic drugs. Of these, clozapine and olanzapine were the most related to the greatest increases in total cholesterol, LDL cholesterol and triglycerides and to the greatest decrease in HDL cholesterol. Studies on quetiapine, on the other hand, are discordant, especially in the elevation of triglyceridemia (Teixeira; Rocha, 2006).

Also included in the package insert of quetiapine are the adverse reactions in the respiratory system: respiratory difficulty in neonates; dyspnea (common); rhinitis (uncommon), sinusitis, nasal congestion, epistaxis (possible events). In addition to recommending its use with caution in patients with a history or at risk for sleep apnea and who are using central nervous system depressants (De Freitas, 2017).

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METHODOLOGY

This integrative review uses as a method the proposal described by Souza *et al.* (2010), which respects the principles of Evidence-Based Practice (EBP) and consists of six distinct phases: elaboration of the guiding question; search or sampling in the literature; data collection; critical analysis of the included studies; discussion of the results and presentation of the integrative review (SOUZA *et al.*, 2010).

The guiding question was defined as: "Is quetiapine indicated for the treatment of insomnia?". Data collection took place electronically, from July to September 2024; via the Virtual Health Library (VHL), Scientific Electronic Library Online (Scielo), Latin American and Caribbean Literature in Health Sciences (Lilacs) and *Medical Literature Analysis and Retrieval System On-line* (MEDLINE).

In order to find relevant studies that answered the guiding question, descriptors indexed in Portuguese and English were used. The choice of words was based on the Health Sciences Descriptors (DeCS) with the aid of the Boolean operator (AND) resulting in the following combinations of keywords: "Quetiapine", "Insomnia" and "use" and their correspondences in the English language: "*Quetiapine*", "*Insomnia*" and "*Use*".

The inclusion criteria are: original studies published in full in national and international journals in Portuguese and English; free of charge and with a period of publication of articles from the last 05 years (2019-2024). Duplicate articles or those that did not answer the guiding question after reading the abstracts or evaluating them in full, as well as letters to editorials and conclusion papers, were excluded.

The survey was carried out from August to November 2024. In order to synthesize the findings, the chosen screened articles were categorized and the following data were extracted organized in a spreadsheet using the Excel program: authors, year, methodology (type of study) and conclusions.

RESULTS AND DISCUSSION

According to the methodology applied, 05 articles were selected that met all the selection criteria, a process detailed in figure 1.

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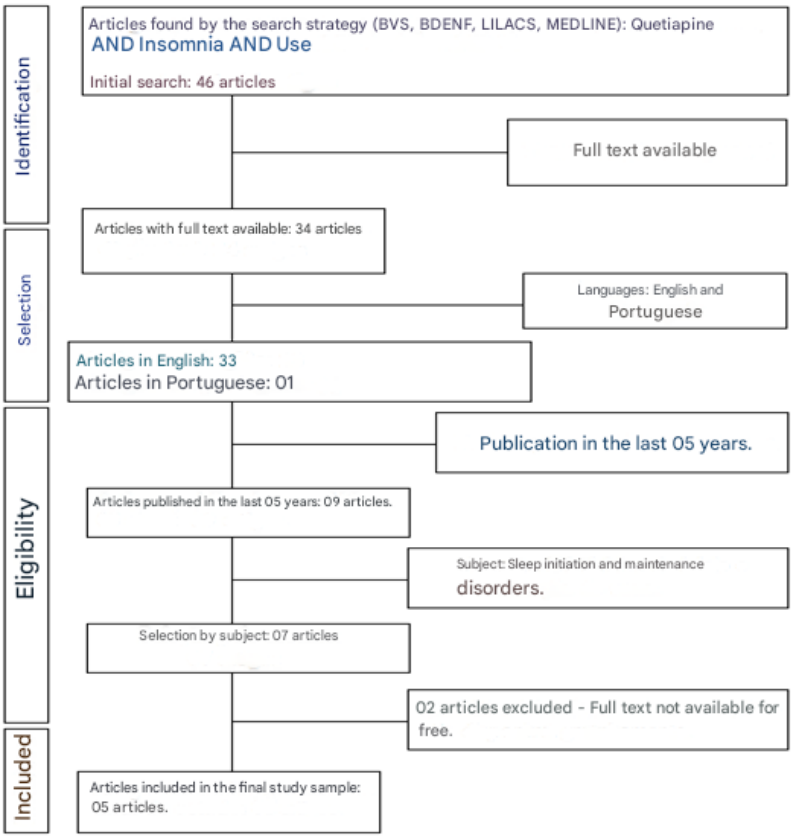
Figure 1. Flowchart: Selection of articles.



Source: authors, 2024.

Subsequently, a precise interpretation of the selected articles was carried out, with content analysis, and discussions with the literature found, in order to reach a consensus on the proposed theme.

Of the 05 selected articles, 04 were published in English and one published in Portuguese. As for the date of publication, one article was published in the year 2019, while the other 04 were published in 2023. Chart 1 shows the description of the authorship, year of publication, conclusion and type of these studies.

Table 1. Articles selected for review.

Authors	Year of publication	Type of study	Conclusion
MODERIE, Christophe et al.	2023	Retrospective cohort study from health record review of 38 patients with treatment-resistant depression (TRD)	Quetiapine induced greater improvements in sleep-maintaining insomnia among TRD/PD+ patients than TRD/PD−. These findings suggest that quetiapine may have a therapeutic role for insomnia in PD, underscoring a distinct underlying neurobiological mechanism of sleep disturbance in people living with PD.

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GOMES, Samuel et al.	2023	This was a retrospective cross-sectional study in a database.	Overall, there was a reduction in the dispensation of prescribed benzodiazepines in the Lisbon and Tagus Valley Region. There seems to be a change in the pattern of prescription in the treatment of insomnia. More robust studies are needed to confirm this observation. Keywords: Benzodiazepines; Hypnotics and Sedatives; Medical Practice Patterns/trends; Portugal; Medication Use/trends; Off-Label Use.
KROUSE, R. A. et al.	2023	Secondary analysis of baseline cross-sectional and longitudinal assessments of individuals with alcohol use disorder (AUD) recruited in a randomized, placebo-controlled, double-blind trial of quetiapine treatment for heavy drinkers.	Although craving is associated with insomnia, quetiapine treatment may improve insomnia but not craving in patients with concomitant TUA and insomnia.
HUANG, Cho-Yin et al.	2023	Prospective observational study	Diagnoses included schizophrenia (*n* = 25), bipolar disorder (*n* = 51), major depression (*n* = 15), dysthymic disorder (*n* = 9), and others (*n* = 7). The daily dose (DD) of quetiapine ranged from 25 to 800 (175.9 ± 184.4) mg, with the mean Cp being 105.6 ± 215.3 ng/ml, with a mean Cps/DD ratio of 0.58 ± 0.55 ng/ml/mg. There was a moderate positive linear correlation between the dose and the Cps of quetiapine (*r* = 0.60), and the interpatient variation in the Cps/DD ratio was up to 26-fold.
HE, Sean et al.	2019	Secondary analysis of data from a clinical trial of patients with AD (Alcohol Dependence) seeking treatment who drank heavily	Insomnia was associated with a higher craving for alcohol and quetiapine differentially reduced the desire to drink in people with insomnia.

Source: authors, 2024.

In the study by Moderie *et al.* (2023) found that patients with treatment-resistant depression showed significant improvement in sleep items T0 and T3 of the Hamilton depression rating scale. In patients with personality disorder associated with depression, the improvement in sleep was even greater. Thus, in this study, quetiapine produced considerable improvements in sleep-maintaining insomnia among patients with treatment-resistant depression associated with personality disorder.

Gomes *et al.* (2023) demonstrated in the study carried out in Portugal a reduction in the dispensation of benzodiazepines prescribed in the Lisbon and Tagus River Valley Region, due to the increase in the dispensation of other non-benzodiazepine drugs prescribed for insomnia and with an off-label indication, among these, quetiapine.

The work of Krouse *et al.* (2023) was conducted in patients with insomnia and alcohol use disorder, this study showed that the use of quetiapine can improve insomnia in these patients although it did not reduce the desire for alcohol consumption.

Huang *et al.* (2023) proved that quetiapine is used in various doses to treat many psychiatric disorders in addition to psychosis, and that it is also generally prescribed as a

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secondary antipsychotic for symptoms such as insomnia or agitation. Among the diagnoses verified in the sample of this study were: schizophrenia, bipolar disorder, major depression, and dysthymic disorder.

The study by He et al. (2019), was another study conducted with patients with alcohol use disorder, in which it was found that insomnia was associated with a higher desire for alcohol and quetiapine differentially reduced the desire to drink in people with insomnia.

In publications that did not meet the selection criteria of the present review, the article by Soeiro-de-Souza et al. (2015) demonstrated that, although quetiapine monotherapy has shown greater efficacy compared to placebo in the treatment of uncomplicated generalized anxiety disorders (GAD), the issue of adverse effects and tolerability may limit its use.

Also, the study by Jahnsen, Widnes, and Schjøtt (2021) brings a worrying perspective on the use of quetiapine. These authors emphasize the need for effective pharmacological treatments for insomnia that do not present a risk of abuse, which has led to the expansion of the *off-label* use of quetiapine. The lack of systematic studies on the safety profile of quetiapine when used for insomnia is alarming. The research focused on spontaneous issues related to the misuse or dependence of quetiapine, raising concerns about its addictive potential when prescribed as an antipsychotic.

FINAL CONSIDERATIONS

Based on the studies evaluated in this research, it was found that the efficacy of quetiapine in the treatment of insomnia, especially when used *off-label*, is a complex issue, involving both significant benefits and concerns regarding safety and risk of abuse.

Regarding the analysis of the studies presented, it was found that quetiapine can be a valuable option for the treatment of insomnia, as long as it is used in specific contexts, especially by patients with coexisting psychiatric disorders, such as treatment-resistant depression, personality disorder, alcohol use disorder, and anxiety disorders.

The articles analyzed showed, in addition to the clinical efficacy of quetiapine for the treatment of insomnia, the concern with its *off-label* use for this therapeutic purpose, since its safety profile has not yet been properly evaluated by systematic studies. The risks related to misuse are more pronounced in vulnerable populations, such as patients with substance use disorders or a history of dependence.

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Although quetiapine shows efficacy in the treatment of insomnia, especially in patients with coexisting psychiatric disorders, *off-label* use for this condition should be carefully considered. It is crucial that healthcare professionals consider the potential clinical benefits in relation to the risks of adverse effects and dependence, and that pharmacological alternatives with a more established safety profile are explored. Continuing rigorous clinical studies on the safety and efficacy of quetiapine in the treatment of insomnia is critical to clarify its therapeutic place in a safer and more informed manner.

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