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DRUG ALTERNATIVES FOR THE *OFF-LABEL* USE OF QUETIAPINE HEMIFUMARATE IN DOSAGES OF 25 TO 100 MG AS A SLEEP INDUCER: A SYSTEMATIC REVIEW OF THE LITERATURE

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Abstract: Introduction: The second-generation antipsychotic drug quetiapine is increasingly being used outside the approved indication (*off-label*) to treat insomnia in the general population possibly to avoid standard medications with known addictive qualities and adverse side effects, however, evidence to support use in this way is scarce leading to weight gain and other metabolic effects. Objective: To investigate the efficacy of alternative medications for the *off-label* use of quetiapine hemifumarate at dosages of 25 to 100 mg in the treatment of insomnia. **Method**: Systematic literature review research with a search in the following databases: Pubmed, Medline and Scielo, a strategic research study with descriptive objectives, a qualitative approach and an exploratory research technique to acquire new knowledge about the population in relation to this theme using health descriptors. **Main results:** The drugs evaluated included: flurazepam, quazepam, temazepam, triazolam, eszopiclone, zaleplone, zolpidem, extended-release zolpidem, suvorexant, ramelteone and doxepin, revealing that eszopiclone had the greatest efficacy in terms of sleep latency, total sleep time and sleep quality, as well as being associated with lower dropout rates, and the effect of suvorexant on the parameter "time awake after sleep onset" was significantly greater than that of the other drugs analyzed. **Conclusion:** Each drug has its own characteristics in the treatment of insomnia and these results serve as a quantitative complement to clinical practice, reflecting the difference in efficacy of various drugs in the treatment of this pathology.

Keywords: Quetiapine fumarate. Insomnia. Metabolic disorders. Competitive agonists.

INTRODUCTION

Quetiapine hemifumarate is a second-generation antipsychotic drug indicated for the treatment of schizophrenia, bipolar affective disorder and as an adjunctive treatment in major depression. (Modesto-lowe; Harabasz; Walker, 2021). Despite being indicated for these illnesses, the use of this drug in dosages of 25 to 100mg in unconventional treatments is noteworthy in terms of its therapeutic indication (Shimizu *et al*., 2022).

According to Højlund et al. (2021)commonly used off-label for sedative-hypnotic purposes, are also associated with increased risk of type 2 diabetes. Objective: To investigate whether there is an association between prescription of low-dose quetiapine and the risk of type 2 diabetes. Design, Setting, and Participants: This cohort study examined nationwide Danish health registers for data regarding new users of quetiapine (n = 185938 it has been shown that quetiapine hemifumarate used for the therapy of sleep-related problems has gained considerable ground in the preference of prescribing professionals. However, despite the benefits of this medication, it is not yet possible to observe sufficient scientific proof of the safety of this drug for this purpose, in addition to the possibility of considerable side effects resulting from its use (Debernard; Frost; Roland, 2019).

Although it is widely prescribed in dosages of 25 to 100mg as "*off label*" use for the treatment of insomnia, there is a paradigm, if its clinical use is as positive as the side effects presented as: drowsiness, dizziness, dry mouth and after discontinuation of use causing withdrawal leading to increased triglyceride levels, elevated total cholesterol (more predominantly LDL and reduced HDL), weight gain, extrapyramidal symptoms and reduced glycated hemoglobin (Jahnsen; Widnes; Schjøtt, 2021)

Insomnia is a major health problem due to the impact it has on daily life, which can lead to stress, irritability, feelings of being depressed, problems concentrating on studies, lack of disposition at work and in physical activities, generating chronic health problems and proving to be a considerable risk factor for various diseases such as hypertension, diabetes mellitus, type 2 diabetes, asthma and gastroesophageal reflux. (Hu, y. *et al.*, 2021) insomnia, representing a substantial burden on the US healthcare system and vulnerable patient groups, where the combined direct and indirect costs of insomnia in the United States exceed $100 billion annually (Morin *et al*., 2020).

In Brazil, the situation is no different, burdening public coffers and causing losses to the Unified Health System (SUS) and patients' quality of life. (Barros; Silva, 2023). With the increase in cases of insomnia, the number of medical prescriptions for sleep therapy drugs has also risen exponentially. In this sense, taking into account the various drug alternatives available on the pharmaceutical market, attention is drawn to the increase in the number of prescriptions for the antipsychotic drug quetiapine hemifumarate in dosages of 25 to 100mg for primary insomnia therapy. (Monahan *et al*., 2021).

With this in mind, the aim of this study is to demonstrate safer and more effective drug alternatives for the use of quetiapine hemifumarate in dosages of 25 to 100mg for the treatment of this condition.

MATERIALS AND METHODS

To estimate the sample size, the *GPower: Statistical Power Analyses for Windows software* was used, taking into account the statistical treatment used (*Student's t-test)*, the number and type of variables analyzed, since the title of the study has an independent variable (quetiapine hemifumarate in dosages of 25

to 100mg) compared to a dependent variable (alternative drugs: flurazepam, quazepam, temazepam, triazolam, eszopiclone, zaleplone, zolpidem, extended-release zolpidem, suvorexant, ramelteone and doxepin). For an *effect size of* 0.3, type I error $\alpha < 0.05$ and type II error $\beta < 0.85$ and with 20% of the sample for discussion after passing the eligibility criteria.

This is a systematic review of the literature with studies published in the last five (5) years on drug alternatives for the *off-label* use of quetiapine hemifumarate in dosages of 25 to 100 mg as a sleep inducer, which consisted of the following steps: 1. Identification of the problem and selection of the hypothesis; 2. Database search with the delimitation of descriptors; 3. Definition of the information to be extracted from the selected studies; 4. Evaluation of the studies included in the review; 5. Analysis and understanding of the information obtained through the main results of the study and 6. Presentation of the results of the review.

The search for journals indexed in databases was carried out in the following databases: Latin American and Caribbean Health Science Literature (LILACS), *Medical Literature Analysis and Retrieval System Online* (MEDLINE), PubMed and *Scientific Electronic Library Online* (SCIELO) using the Health Sciences descriptors (DeCS) and their booleans "And" and "Or".

In the eligibility criteria, the inclusion criteria used to include articles in the sample calculation were: articles published in the last (05) five years in Portuguese and English, published in journals and in the scientific databases cited that included the following theme: drug alternatives for the "*off label*" use of quetiapine hemifumarate in dosages of 25 to 100 mg as a sleep inducer.

For the exclusion criteria, the following were excluded: studies or abstracts outside the research period, both repeated quantitative studies and qualitative reviews or opinions, exploratory studies not related to the topic, articles not published in databases or scientific journals, articles not in Portuguese and foreign languages whose topic was not relevant to the research and articles which, after searching and reading all the titles and abstracts, were selected as unsuitable for the study.

The data used in this systematic review to construct the research question came from the acronym PICOT, which stands for Patient, Intervention, Comparison, Outcomes, which was based on the answers to the following question from the hypothesis with the purpose of intervention: Is there any drug that is more effective and has fewer side effects than quetiapine hemifumarate in dosages of 25 to 100mg?

Considering the lack of diversity of works on the subject of drug alternatives for the "*off label*" use of quetiapine hemifumarate in dosages of 25 to 100 mg as a sleep inducer, in the first search, the criteria established for exclusion will initially be the titles of the works, sequentially to the central objectives of the literature, which, after successive readings of the texts available as full abstracts, parallel approaches and approaches different to the research interest were detected.

Based on this, three more filters were applied, repositioning the descriptors in the databases with the combination of the Boolean operators AND and OR, where it was found that the initial number of literatures found in the first search in both databases was reduced, excluding from the study: literature reviews, dissertations, doctoral theses, experience reports and case studies, as well as repeated studies, and studies outside the defined period.

Of the 76 studies identified, 15 were selected for review. The flowchart is organized according to the PRISMA criteria, illustrating how the studies were excluded (Figure 1). A summary of the main aspects relating to the objectives, methods, results and conclusions of the 15 selected studies can be found in Table 01.

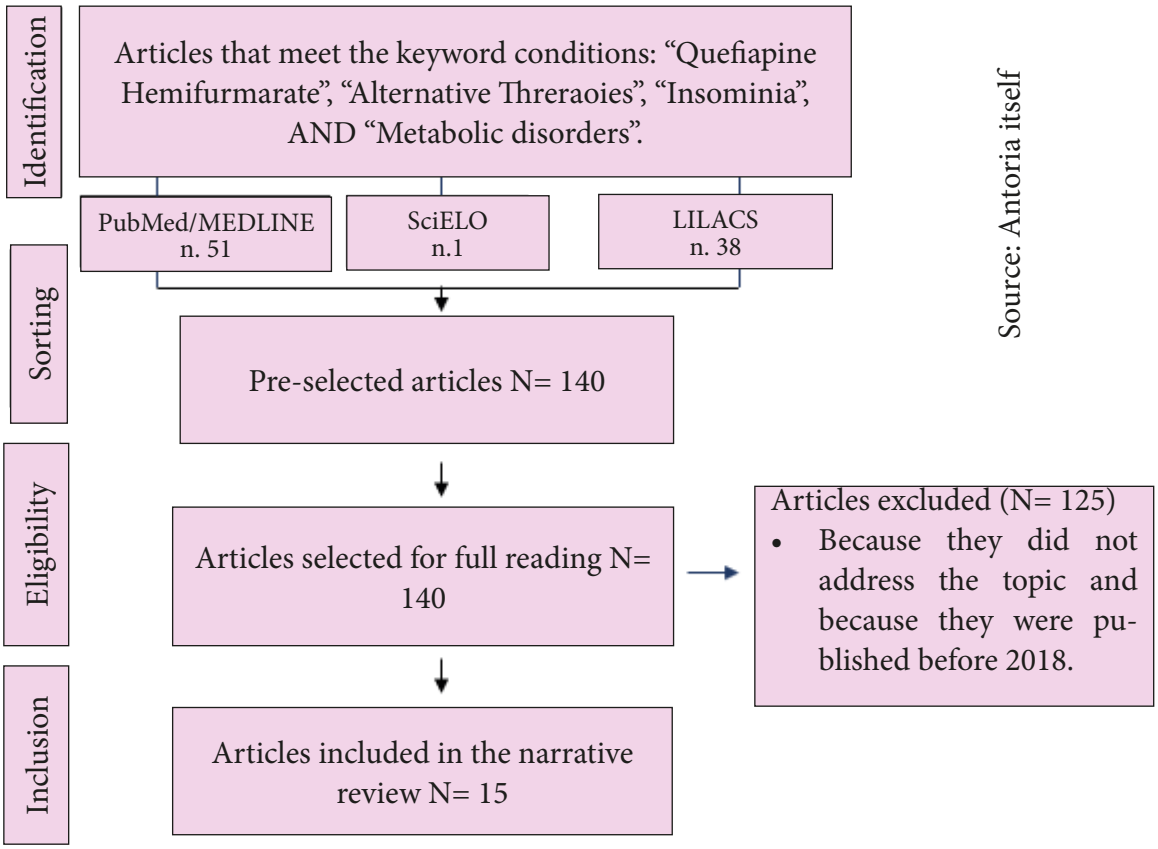

Figure 1- Flowchart of the selection of the sample of articles included in the review.

RESULTS

AUTHOR(S) YEAR	ARTICLE TITLE	TYPE OF STUDY	OBJECTIVE	MAIN RESULTS
X1, (DEBERNARD; FROST; ROLAND, 2019)	Quetiapine is not a sleeping pill	Systematic review of the literature.	Warn against prescribing quetiapine to sleep.	It is our opinion that an undesirable prescribing pattern has developed when the antipsychotic quetiapine is widely used to treat insomnia without the efficacy or safety of this treatment having been adequately documented.
X2, (MODESTO-LOWE; HARABASZ; WALKER, 2021)	Quetiapine for primary insomnia: Consider the risks	Cross-sectional study	Identify off-label for insomnia treatment in the general population, possibly to avoid standard drugs with known addictive qualities and adverse side effects.	Given the scant evidence in favor of using quetiapine in the general population to treat insomnia and the risk of metabolic side effects even at low doses, the drug should be used with caution and only after other options have been exhausted with another drug.
X3, (MONAHAN *et al.*, 2021)	**Quetiapine withdrawal: A systematic review**	Systematic literature review	Look for evidence of quetiapine withdrawal or symptoms associated with discontinuation.	Three studies reported the onset of a withdrawal dyskinesia characterized by abnormal choreiform movements, as well as confusion and speech disturbance in some cases, however, these findings were limited by the number and quality of case reports identified.

X4, (HØJLUND *et al.*, 2022)	Who prescribes quetiapine in Denmark?	Case studies	To evaluate the off-label use of quetiapine for its anxiolytic and hypnotic properties.	Future initiatives need to be taken to ensure the rational use of the drug quetiapine hemifumarate, especially among adults, and intensive pharmacovigilance should be carried out.
X5, (JAHNSEN; WIDNES; SCHJØTT, 2021)	Quetiapine, Misuse and Dependency: A Case-Series of Questions to a Norwegian Network of Drug Information Centers	Literature review study	Review questions to the Norwegian network of drug information centers regarding the potential safety problem of these drugs.	We concluded that our case series from the Norwegian drug information center reflects that quetiapine often involves clinical narratives of a history of addiction, polypharmacy or insomnia (off-label use), however, the case series did not reveal new information about the addictive potential of the drug.
X6, (MONAHAN *et al.*, 2021)	Quetiapine for insomnia: A review of the literature	Literature review study.	To evaluate the safety and efficacy of quetiapine in the treatment of insomnia in adults.	There are few robust studies evaluating the lack of safety and efficacy of quetiapine for the treatment of insomnia.
X7, (LIANG *et al.*, 2022)	Artificial Intelligence--Based Pharmacovigilance in the Setting of Limited Resources	Literature review study.	Analyze challenges and solutions for AI-based pharmacovigilance.	There are solutions and future prospects for AI-based pharmacovigilance in resource-limited environments.
X8, (PEREIRA, 2021)	Performance of the pharmacist in front of drugs, drug interactions and treatments in panic disorders - integrative review	Integrative review	Analyze the pharmacist's role in relation to drugs, drug interactions and treatment in Panic Disorder	Pharmacists should have adequate theoretical knowledge about the pharmacokinetics and pharmacodynamics of psychotropic drugs and should attend to patients in an empathetic way, always seeking their well-being and clarifying doubts about the use and effect of the drugs presented for treatment, and not just as a dispenser of drugs over the counter.
X9, (SILVA, G. G. S. Da *et al.*, 2020)	The importance of the clinical pharmacist in reducing drug interactions with cancer patients in the intensive care unit	Literature review	Describe the importance of the clinical pharmacist in reducing drug interactions with patients in intensive care units.	The clinical pharmacist plays a fundamental role with the healthcare team in the ICU, in making dosage adjustments in order to avoid MIs and contribute to improving the patient's quality of life.
X10, (ATKIN; COMAI; GOBBI, 2018)zopiclone, and zaleplon	Drugs for Insomnia beyond Benzodiazepines: Pharmacology, Clinical Applications, and Discovery	Integrative review	Describe drugs for insomnia.	In the last 20 years, pre-clinical and clinical sleep research has expanded tremendously. The study of knockout mice for specific receptors has generated new scientific knowledge of the unique role of each receptor in sleep regulation, the application of optogenetics to the study of sleep has elucidated new circuits, and the discovery of clock genes has generated insight into the cellular and molecular mechanisms that regulate sleep.
X11 (ZHENG, X. *et al.*, 2020)	Pharmacological interventions for the treatment of insomnia: quantitative comparison of drug efficacy	Meta-Analysis	Compare the efficacy of various pharmacotherapies for insomnia using modeling.	Each drug has its own characteristics in the treatment of insomnia, and this needs to be taken into account in order to meet individual clinical needs. These results serve as a quantitative complement to clinical practice, reflecting the difference in effectiveness of various drugs in the treatment of insomnia.

X12 (CEDERLÖF *et al.*, 2024)	Antipsychotic medications and sleep problems in patients with schizophrenia	Meta-Analysis	Clarify the use of antipsychotic drugs in relation to sleep.	The prevalence of sleep problems is strongly related to the antipsychotic medication the patient uses. These findings highlight the importance of considering and evaluating sleep problems when treating patients with schizophrenia with antipsychotics.
X13 (SHIMIZU *et al.*, 2022)	Risk assessment of accidental falls in patients taking trazodone, quetiapine, or risperidone for insomnia: A single-center, case-control study	Case studies	To assess the risk of falls with the use of trazodone, risperidone and quetiapine, which are recommended for use at Kanazawa University Hospital.	The association between risperidone and quetiapine with accidental falls was uncertain. However, interestingly, trazodone may help reduce the risk, making it a potential pharmacological treatment option for insomnia in patients at high risk of accidental falls.
X14 (SUN, C. *et al.*, 2023)	Cryo-EM structures reveal native GABAa receptor assemblies and pharmacology	Randomized Study	Studying sets of GABAARs that contain α1, linked to endogenous neurosteroids.	The data reveal the main α1-containing GABAAR clusters linked to endogenous neurosteroids, thus defining a structural landscape from which subtype-specific drugs can be developed.
X15 (ISJANOVSKI, V.; ISJANOVSKI, I., 2019)	Comparison of the Use of Hypnotic in Psychiatric Patients with Insomnia at the Mental Health Center Prolet in Skopje	Randomized clinical trial	To compare the hypnotic effects of flurazepam and zolpidem applied to psychiatric cases at the "Prolet" mental health center in Skopje, Republic of Macedonia.	The results show that there were no significant differences between the two drugs in terms of inducing sleep, its duration and quality, and the number of awakenings, but there was a significant difference between the hypnotic drugs and the placebo.

DISCUSSION

In X1, the authors report that quetiapine is a second-generation antipsychotic approved for the treatment of schizophrenia and bipolar disorder and as a complementary treatment for depression, where the recommended dose for these indications is 300-800 mg per day, they state that in recent years the prescription of quetiapine in doses of 25-100 mg to treat insomnia has increased and that this practice has also become widespread in Norway, including children, adolescents and the elderly and that it has become evident, for example, from questions asked to the Regional Center for Drug Information and Pharmacovigilance (RELIS), where in a new Norwegian study for the period 2004-2017 showed that the average prescribed daily dose of quetiapine in Norway is less than 100 mg and that only about 4% of users received doses and reimbursements consistent with the use of quetiapine for an approved indication.

In X2, the authors warn of the common adverse effects of the second generation of antipsychotics, which include weight gain and motor disorders. Clozapine and olanzapine are best known for causing weight gain, but prolonged use of quetiapine is also associated with moderate weight gain (10 kg on average), as well as the development of metabolic syndrome.

In X3 the authors ratify that one third of the patients (n = 5) reported nausea and vomiting, while 46% (n = 7) of the cases presented symptoms related to the cardiovascular system, including palpitations, tachycardia, dizziness, fainting, hypertension and/or orthostatic hypertension, three patients, also developed acute onset movement abnormalities characterized by irregular and involuntary spasmodic head movements, facial grimaces, ataxic and involuntary gait, arrhythmic and choreiform movements of the neck and limbs, facial grimaces, mild dysarthria, general hypotonia and gait disturbance and in one case there was hand tremor.

In X4, the authors report a reduction in the use of benzodiazepines due to their potential for dependence and adverse events which may have offset a corresponding increase in the "*off-label*" use of quetiapine (and other antipsychotics), however, the use of quetiapine is problematic as it has been associated with adverse events including prolongation of the QT interval, drowsiness, weight gain and metabolic dysregulation as stated in X1, X2 and X3.

In X5, the authors point out that historically, the pharmacological treatment of insomnia has been a source of prescription drug misuse and that from barbiturates to benzodiazepines, Z-line drugs and each new class of drug, the idea of the promise of effective treatment with reduced risks has been disseminated, leading clinical practice to the idea of effective pharmacological treatment for insomnia, with extensive use of "*off-label*" pharmacological treatment of quetiapine. In Norway, quetiapine is approved for the treatment of schizophrenia and bipolar disorder and as a complementary treatment for depression, while the dispensing pattern of quetiapine probably reflects abuse and inappropriate "*off-label*" use against insomnia. In this context, the lack of systematic studies on the safety profile of quetiapine when used for insomnia is worrying.

In X6, the authors bring up polypharmacy as a potential factor in adversely affecting patient safety by increasing side effects and drug interactions while reducing adherence. The researchers expressed concern about off-label and widespread polypharmacy prescribing among young patients who are substance abuse disorder patients and since there is a lack of many studies and clinical information needed to make such assessments, the definition of polypharmacy most often used is the use of five or more drugs by the patient with an increased possibility of drug interactions.

In X7, the authors show that on the American continent, only two studies evaluating the impact of educational interventions to promote pharmacovigilance were identified, one in Brazil and one in the United States, which reflects the fact that the studies conducted in these places, especially in Brazil, are aimed at measuring and identifying the causes and results associated with unsafe drug use, with the aim of estimating the prevalence of hospitalizations due to Adverse Drug Reactions (ADRs), their undesirable effects based on their clinical manifestations, therapeutic ineffectiveness, deviations in drug quality and medication errors.

In X8 and X9, the authors point out that pharmacists are trained to identify, in addition to ADRs, the occurrence of other problems related to medicines, such as therapeutic ineffectiveness, deviations in the quality of medicines and medication errors, which may be associated with the signs and symptoms presented by patients, and which may be mistakenly reported as suspected ADRs.

In X10, the authors conclude that quetiapine has been widely marketed "*off-label*", including for insomnia, and the manufacturer, AstraZeneca, has been fined for this in the U.S. Prescribing quetiapine for sleep-related problems may also be a factor that causes an overestimation of the existing evidence base. Doctors should be aware that by using quetiapine for insomnia, they are prescribing "*off-label*", therefore taking on a greater responsibility especially with respect to patient safety, as it is an undesirable prescribing pattern, with no efficacy or assurance that this treatment is suitable, where quetiapine is not a sleeping pill and should not be used as such.

In X11, X12 and X13, the authors demonstrate the predicted absolute efficacy (relative efficacy of the drug plus the response to placebo) for each treatment group that was estimated for SL (sleep latency), WASO

(time awake after sleep onset) and TST (total sleep time) at median baseline values. Using four weeks as an example (median treatment duration), we found that, in addition to ramelteon being comparable to placebo in reducing WASO and improving TST, the effect of other drugs on all three sleep parameters was significantly better than that of placebo.

Eszopiclone showed a better level of efficacy in reducing FS and increasing TST, being 16 and 34 minutes longer, respectively, compared to the placebo group. Suvorexant had the highest level of efficacy in reducing WASO, being 27 minutes longer than in the placebo group, in addition, doxepin was less effective in reducing SL, which was significantly lower than the effect produced by eszopiclone, and only 5 minutes longer than the placebo effect.

In X14 and X15, the authors report a noteworthy finding that although eszopiclone had a significant effect on SL and TST, it had a weaker effect on WASO, which was only 17 minutes greater than that of placebo and also significantly less than the effect of suvorexant. Similarly, although suvorexant did well in the WASO, it had a slightly weaker effect in the TST, being only 20 minutes longer than in the placebo group, which is significantly less than the effect of eszopiclone. In these articles, the authors analyzed sleep quality only over 4 ± 2 weeks and due to the limited availability of data, the results suggest that with the exception of zaleplon, the 'Z' line drugs are significantly better than placebo at improving sleep quality, among them, eszopiclone had the best level of efficacy and other types of drugs' sleep quality was similar to that of placebo."

FINAL CONSIDERATIONS

In view of the results obtained through the research, it is suggested that more complete studies be carried out into the safety and efficacy of the use of the drug quetiapine hemifumarate in doses of 25 to 100mg/day for the treatment of primary insomnia, because in addition to not having a therapeutic indication registered with the regulatory body for the treatment of primary insomnia, the advantages observed in its *off-label* use are very small compared to its undesirable effects, which include weight gain, metabolic syndromes, daytime sleepiness, increased risk of developing cardiovascular diseases and diabetes, among others, encouraging the use of eszopiclone, as it had the best level of efficacy in the studies analyzed.

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