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LETTER TO THE EDITORS

Brazil tightens the reins on Z-drugs: new regulations for zolpidem and eszopiclone

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The Brazilian Health Surveillance Agency (ANVISA) recently voted for increased control over zolpidem and eszopiclone sales.[1] The medication, previously classified as a controlled substance at dosages $\leqslant$ 10 mg, is now classified as a psychotropic medication (B1) at any dose, requiring a special prescription (benzodiazepines were already in the B1class). This new designation further restricts their prescription: now, prescribers must register with the local health surveillance authority, and each prescription must be numbered with an identification code directly controlled by ANVISA.

ANVISA's decision was based on concerns about the increasing prescription and sale of these medications, in addition to an increasing number of events indicative of problematic use and substance use disorder.[1] In the DSM-5-TR,[2] substance use disorders are classified as continuous and recurrent use of a substance with a low level of control despite significant problems related to its use, resulting in social impairment and organic complications. Symptoms of craving, tolerance, and withdrawal are typically involved in substance use disorders.

Although zolpidem has been approved by the U.S. Food and Drug Administration as an insomnia treatment, numerous side effects have been reported, including cognitive impairment, tolerance, rebound insomnia upon discontinuation, car accidents, falls, and substance use disorder.[3] Zolpidem is also linked to a high risk of short-term cognitive, memory, and psychomotor impairment.[4-6] Of note, the Food and Drug Administration only approved the use of zolpidem for a maximum of four weeks.

Using articles from 2018 to 2023, a narrative review on the consequences of prolonged zolpidem use found a high risk of substance use disorders after prolonged treatment, as well as a risk of inefficacy, especially if tolerance develops, with higher doses required to achieve the expected effect.[7] The ANVISA report also mentioned an increase in publications on zolpidem use disorder. A recent PubMed search using the terms (''zolpidem'' plus ''addiction'' or ''dependence'' or ''abuse'') found about 800 studies published between 1988 and 2024, with most published in recent years.[1]

The situation regarding zolpidem use is particularly important in Brazil. The International Narcotics Control Board, a United Nations agency, monitors global practices regarding the control and prevention of psychotropic substance misuse. According to their 2022 Annual Report, zolpidem was one of the most widely marketed psychotropic medications, with 117 countries reporting importation and consumption in all regions of the world.[8] Its production increased from 38.2 tons in 2021 to 39.1 tons in 2022, 4.2 of which were produced in Brazil.[8]

In recent years, zolpidem sales have significantly increased in Brazil, rising from 1,030,902 units in 2014 to 2,536,927 units in 2021, a 246% increase.[9] Although Brazil's population has also increased during this period, the rates are highly discrepant. Parallel to the significant rise in zolpidem sales, benzodiazepine sales increased by 7% between 2014 and 2019 and then decreased in 2020 and 2021 compared to 2014, reducing 2.5% and 26%, respectively. This suggests that zolpidem may be replacing benzodiazepines, probably due to the misconception that it is safer, a perception that today is clearly inaccurate.

The situation in Brazil appears to align with foreign data: a U.S. study found that Z-drugs are often prescribed to avoid benzodiazepines. However, these medications are not risk-free, and deaths involving Z-drugs in the United States have increased over the last two decades.[10]

Thus, ANVISA's effort to increase control over zolpidem and eszopiclone sales in Brazil is a necessary response to the current situation. The sale of these substances has increased considerably in recent years, despite their clear potential for misuse and dependence, in addition to their documented side effects. The box's new black-label warning should raise concern among doctors and make patients more cautious about using the medication. This welcome initiative will hopefully curb the overprescription of Z-drugs in Brazil, especially zolpidem, and mitigate the harmful effects of inappropriate use.

Marcelo G. **Lima**,[1] Vitor S. **Tardelli**,[2] Thiago M. **Fidalgo**[1]

[1] *Departamento de Psiquiatria, Escola Paulista de Medicina, Universidade Federal de São Paulo, São Paulo, SP, Brazil.* [2] *Instituto Bairral de Psiquiatria, Itapira, SP, Brazil.*

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Disclosure

The authors report no conflicts of interest.

Author contributions

ML: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration.
VT: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration.
TF: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration.
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