Deprescribing benzodiazepines: Do Brazilian package inserts address this issue?

Desprescrição de benzodiazepínicos: As bulas brasileiras abordam essa temática?

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ABSTRACT

OBJECTIVE: To analyze the presence and quality of content on drug deprescribing in Brazilian package inserts for benzodiazepine drugs.

METHODS: Documentary study where we analyzed data on deprescribing extracted from electronic package inserts of drugs containing benzodiazepines; these documents were available at the Brazilian Health Surveillance Agency website. Our search was performed independently by 2 researchers who used the following keywords: “deprescription,” “withdrawal,” and “tapering.” The deprescribing plan, when presented by the package insert, was compared to deprescribing protocols for benzodiazepines found in the literature. Moreover, we assessed the presence of guidance on the maximum length of treatment and risks of long-term use.

RESULTS: We found 12 package inserts for benzodiazepines and 100% of them suggested gradual withdrawal; only 1 (8.33%) suggested a systematized deprescribing plan. One document (8.33%) did not offer guidance on maximum treatment duration. Eleven (91.67%) had the information on long-term use possibly causing dependence or tolerance, and 1 (8.33%) did not describe the risks of continuous use.

CONCLUSIONS: It is known that benzodiazepines should be withdrawn in a gradual and schematized manner, but package inserts do not currently bring this information in detail. It is of utmost importance that health professionals be educated on their conduct, hence the necessity for updating medication package inserts.

KEYWORDS: benzodiazepine receptors; deprescription; package inserts.

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INTRODUCTION

The Brazilian demographic profile has been changing since the 1970s, with smaller nuclear families (a reduction in birth rate) and increasing life expectancy, initiating a process of population aging. Population studies demonstrated that the chronic use of medications and polypharmacy (the use of 5 or more medications) are a reality in the life of older Brazilian people, with a higher prevalence among those aged over 70 years with polymorbidity. Continuous medication use and polypharmacy are associated with a higher risk of adverse reactions such as rebound effect, delirium, drug withdrawal, and intoxication, in addition to the occurrence of falls, which are determinant in health complications in the older population. This higher risk is attributed to this age group owing to physiological (pharmacokinetic and pharmacodynamic) changes and the presence of polymorbidity, which leads to the use of multiple medications.

In this context, the rational consumption of potentially inappropriate medications (PIM) by older adults becomes a challenge for health care managers and physicians in geriatrics. Baldoni et al. showed that 59.2% of the older adults interviewed in their study used at least one PIM according to the 2019 Beers criteria. A reason for this high prevalence would be the use of psychotropic medications. Isidoro et al. reported a high PIM prescription rate among older patients at primary health care, with a predominance of medications for treating central nervous system conditions (among which were benzodiazepines [BZD]: clonazepam, alprazolam, diazepam, lorazepam, and chlordiazepoxide). PIM are those with active principles that present more risks than benefits to the older person, have an increased risk of adverse reactions and are directly related to an increase in mortality. Moreover, the mean health expenditure with patients who use PIM (including BZD) exceeded that for patients who used medications that are not potentially inappropriate, as recorded in the Medical Expenditure Panel Survey (MEPS).

The use of BZD is effective in the short-term (up to 3 months) treatment of mental disorders such as anxiety and insomnia. Long-term use of BZD by older adults causes prolonged sedation (potentializing risks of falls and fractures), in addition to the risks of tolerance, dependence, cognitive decline, and motor vehicle accidents, which justifies the classification of these medications as PIM for older adults.

BZD are among the most frequently prescribed medications in Brazil and their use has a high lifetime prevalence: 9.8%, with higher rates among older patients and women. This highlights the need for elaborating and searching for intervention strategies for a gradual and guided withdrawal of these medications. When the potential benefits of medicalization do not outweigh damages to the therapy prognosis, the health professional may consider deprescribing (process of tapering or interrupting the medication) with the patient.

The scarcity of validated studies that aid in deprescribing BZD is currently noticeable. Scott et al. reported the importance of systematic deprescribing protocols. In addition to scientific evidence, another source of information related to medications consists in the package inserts. These are documents that contain technical and scientific information on the medication, its ingredients, characteristics, and usage, whose content is standardized by Collegiate Directory Resolution (RDC) No. 47 of September 8, 2009, published by the Brazilian Health Surveillance Agency (ANVISA). Package inserts are a source of easily obtainable and free information for health professionals and patients, being available for the thousands of medications commercialized in Brazilian pharmacies and drugstores.

Considering the importance of deprescribing BZD in older patients and the need for protocols that are easily accessible by health professionals, the aim of this study is to analyze the presence and quality of content on deprescribing in Brazilian BZD package inserts.

METHODS

This is a documentary study where we analyzed data from electronic package inserts available at the ANVISA website (https://consultas.anvisa.gov.br/#/medicamentos/). We identified BZD cited by the 2019 Beers criteria and the Brazilian Consensus of Potentially Inappropriate Medications for the Elderly and researched package inserts for health professionals regarding brand name BZD drugs with valid ANVISA registrations on June 24, 2020. For cloxazolam and nitrazepam, data were collected from generic and similar medication package inserts, respectively, due to the absence of valid registrations for brand name drugs.

We analyzed package inserts of brand name drugs because we believe the information contained in these documents is comparable to that found in generic and similar medication package inserts, since ANVISA requires the standardization of this information according to RDC No. 47 of 2009.

For data collection, we elaborated an instrument prior to the research, with information to be collected from BZD package inserts.

When searching for content on deprescription, two researchers read the package inserts in full. In order to help identify this content, we used the keywords “tapering,” “withdrawal,” and “deprescription.” Moreover, we verified relevant information...
on the theme (related directly to the deprescribing process), such as maximum treatment duration, risks of long-term use, and adverse reactions. After gathering information of interest, a third researcher reviewed the collected information.

For comparison, we considered explicit and systematized guidance on deprescribing and adverse reaction alerts found on the literature when the package insert presented a logical plan for gradual withdrawal, describing the dose and/or percentage to be reduced throughout the process and the presence of safety information. The retrieved information was compared with the BZD deprescribing guideline proposed by Pottie et al.,22 in addition to the Beers criteria.9

RESULTS

We found 12 package inserts for BZD with valid registrations at the ANVISA website: alprazolam, bromazepam, clobazam, clonazepam, cloxazolam, diazepam, estazolam, flunitrazepam, flurazepam, lorazepam, midazolam, and nitrazepam (Chart 1).

All package inserts (100%) approach the theme by suggesting drug tapering. Only one document (8.33%) presented explicit and systematic guidance on dose reduction.

As for the maximum treatment duration, the information varied for each drug, and 1 package insert (8.33%) did not present this information. Regarding the risks of long-term use, 11 (91.67%) package inserts reported a risk of dependence and/or tolerance, and 1 (8.33%) stated that data available in the literature do not offer a real estimate of the risk.

When analyzing other problems related to the long-term use of BZD, 4 (33.33%) package inserts did not approach the risk of falls, and 5 (41.67%) did not address the risk of fractures in older adults. The risk of cognitive impairment is not reported by 6 (33.33%) package inserts, whereas the risk of motor vehicle accidents is mentioned by all 12 (100%) analyzed package inserts.

Information on deprescribing, maximum treatment duration, and risks of tolerance and dependence in long-term use are described on Chart 1.

DISCUSSION

After critically reading the package inserts, we noticed that the information contained in these documents in not specific and does not offer adequate support to the prescribing professional for performing gradual deprescribing, as recommended by the literature19.

Moreover, the package insert for alprazolam was the only one that brought information on how the deprescribing process should be performed, although not as established in the literature. Pottie et al.22 recommended that deprescribing for BZD be performed gradually, with dose reductions of 25% every 14 days and, if possible, of 12.5% near the end of the process. They also suggested days without medication as an alternative to the proposed tapering.

Regarding the absence of systematized guidance on deprescribing clonazepam, it is important to highlight that a Brazilian study validated a protocol for deprescribing this drug that suggests 25% reductions every 14 days. In addition to guiding the patient during the deprescribing process, it describes non-pharmacological measures to be adopted, such as sleep hygiene.23 Therefore, evidence already indicates how deprescribing should be performed considering the context of Brazilian older adults, to which package inserts refer only as “tapering.”

When it comes to the maximum treatment period, the available information varies, recommending from 2 weeks to 8 months depending on the drug and indication, with no specific guidance for the older population. The package insert for clonazepam, whose consumption in Brazil is the second largest worldwide,23 does not provide any information on the maximum treatment period. For treating insomnia, guidelines recommend its limited use in adults (for around 4 weeks)24,25 and that it be avoided as first-line treatment in older adults.9

As for long-term use, all package inserts provided information related to the risk of dependence and/or tolerance, except for estazolam, which informed that scientific data do not offer an estimate of the real risk of long-term use. However, this BZD is also considered a PIM, and the literature indicates a risk of dependence and various other symptoms caused by its chronic use.8,26

Considering the other signs and symptoms of long-term BZD use, such as risk of dementia, cognitive decline, psycho-motor disturbances, daytime sleepiness, and motor vehicle accidents,27,28 the package inserts for alprazolam, estazolam, flurazepam, and lorazepam do not carry information on the increased risk of falls and fractures in the older population. Fracture risk is also not mentioned by the package insert for clobazam. Continuous use of this drug class is associated with a decrease in attention and motor coordination as well as mental confusion, which contributes to an increased risk of falls and fractures in older adults,29 thus the lack of information on this matter impairs the use of package inserts as source of information when considering the safety and rational use of medications by the older population.

As for limitations of our study, it is important to highlight that it is limited to the analysis of only one package
### Chart 1. Analysis of the presence and quality of content on deprescribing, maximum treatment duration, and risks of long-term use in Brazilian package inserts for benzodiazepines.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Deprescribing*</th>
<th>Guidance on deprescribing?</th>
<th>Maximum treatment duration</th>
<th>Risk of tolerance and dependence</th>
<th>Risk of falls (Yes/No)</th>
<th>Risk of fractures (Yes/No)</th>
<th>Risk of cognitive impairment (Yes/No)</th>
<th>Risk of motor vehicle accidents (Yes/No)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alprazolam (Frontal®)</td>
<td>Yes</td>
<td>Reduction of up to 0.5 mg every 3 days, slower if necessary</td>
<td>Up to 6 months for anxiety disorders and up to 8 months for panic disorders</td>
<td>Risk of dependence</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Bromazepam (Lexotan®)</td>
<td>No</td>
<td>Tapering</td>
<td>8 to 12 weeks, including gradual discontinuation</td>
<td>Risk of tolerance and dependence</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Clozapam (Frisium®)</td>
<td>No</td>
<td>Tapering</td>
<td>8 to 12 weeks, including the stabilization process</td>
<td>Risk of dependence</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Clorazepam (Olcadil®)**</td>
<td>No</td>
<td>Tapering</td>
<td>4 to 6 weeks, including gradual dose reduction</td>
<td>Risk of tolerance and dependence</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Diazepam (Valium®)</td>
<td>No</td>
<td>Tapering</td>
<td>Treatment should not exceed 2 to 3 months, including the gradual withdrawal period</td>
<td>Risk of tolerance and dependence</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Estazolam (Noctal®)</td>
<td>No</td>
<td>Tapering</td>
<td>Up to 12 weeks</td>
<td>The available data do not allow a real estimate of the risk</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Flunitrazeepam (Rohypnol®)</td>
<td>No</td>
<td>Tapering</td>
<td>From a few days to 2 weeks, maximum 4 weeks including tapering</td>
<td>Risk of tolerance and dependence</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Flurazepam (Dalmadorm®)</td>
<td>No</td>
<td>Tapering</td>
<td>From a few days to 2 weeks, maximum 4 weeks including tapering</td>
<td>Risk of dependence</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Lorazepam (Lorax®)</td>
<td>No</td>
<td>Tapering</td>
<td>Should be prescribed only for short periods of time (eg, 2–4 weeks). Continuous long-term use is not recommended</td>
<td>Risk of tolerance and dependence</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Midazolam (Dormonid®)</td>
<td>No</td>
<td>Tapering</td>
<td>From a few days to 2 weeks maximum</td>
<td>Risk of tolerance and dependence</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Nitrazepam (Sonebon®)**</td>
<td>No</td>
<td>Tapering</td>
<td>Should be used for short periods only (eg, 2–4 weeks)</td>
<td>Risk of tolerance and dependence</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>


*Explicit and systematized; **Generic package insert; ***Similar package insert.
insert for each drug. Nevertheless, this limitation may have less impact due to RDC No. 47 No. 47 of September 8, 2009, published by ANVISA, which standardizes the content of package inserts and establishes the minimum requisites for the elaboration, harmonization, updating, publication, and availability of this document in patient and health professional versions. 20 Jokanovic et al. 20 demonstrated that the comprehension of the deprescribing process for drugs such as BZD can be achieved with simple information contained in a patient information leaflet.

On the other hand, to the best of our knowledge, this is the first study to assess the technical quality of package inserts regarding the matter of deprescribing BZD. Furthermore, the results of this investigation may subsidize technical and legal change, within pharmaceutical industries and ANVISA, relative to the technical content provided by drug manufacturers and approved by the Brazilian drug regulatory agency.

CONCLUSION

BZD are potentially inappropriate drugs for older adults, and yet widely used. Risks involved in their use should be considered, as well as the possibility of deprescribing. It is known that BZD should be withdrawn in a gradual and schematized manner, but current package inserts do not bring this type of information in detail. It is of utmost importance that health professionals be guided in their conduct and, therefore, package inserts should be updated.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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AUTHORS’ CONTRIBUTIONS

MST: conceptualization, data curation, formal analysis, writing – original draft, writing – review & editing. MOB: conceptualization, data curation, formal analysis, writing – original draft, writing – review & editing. EOS: data curation, formal analysis, writing – original draft, writing – review & editing. AMP: writing – original draft, writing – review & editing. PRDC: writing – original draft, writing – review & editing. MLP: writing – original draft, writing – review & editing. FMDC: conceptualization, data curation, formal analysis, writing – original draft, writing – review & editing. AOB: conceptualization, data curation, formal analysis, writing – original draft, writing – review & editing.

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