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Prescribing Trends of Benzodiazepine and other Sedatives in the Lisbon and Tagus Valley Regional Health Administration between 2013 and 2020: A Retrospective Study

Prescrição de Benzodiazepinas e outros Sedativos na Administração Regional de Saúde de Lisboa e Vale do Tejo de 2013 a 2020: Um Estudo Retrospetivo

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ABSTRACT

Introduction: Among the Organization for Economic Co-operation and Development members, Portugal has the highest reported consumption of anxiolytics, hypnotics, and sedatives, of which a large proportion are benzodiazepines or related drugs. These are known to cause tolerance and dependence. Other drugs with hypnotic effect, such as antidepressants, antihistamines, antipsychotics, or anticonvulsants have been identified by some reports as alternatives to benzodiazepines for the treatment of insomnia. In this regard, the aim of this study was to characterize the consumption of benzodiazepines, non-benzodiazepine anxiolytic, hypnotic or sedative effect drugs and other drugs with the potential to be used off-label to treat insomnia, and the results concerning benzodiazepine consumption related indicators in the primary health care setting in the Lisbon and Tagus Valley region.

Material and Methods: From 2013 to 2020, a census, descriptive and retrospective study was conducted. The evolution of the variables total defined daily doses, defined daily doses per 1000 inhabitants per day (DHD) and relevant indicators were characterized. Data were extracted from the SIARS platform used in the Lisbon and Tagus Valley regional Health Administration.

Results: There was a decrease in the consumption of benzodiazepines (from 57.44 to 63.11 DHD) and an increase of non-benzodiazepines and of drugs with potential off-label use (from 6.56 to 8.56 DHD and from 14.70 to 25.95 DHD, respectively). Among non-benzodiazepines, zolpidem was the most consumed drug, also showing an increasing trend (from 4.86 to 6.96 DHD). For the group of drugs with off-label use potential, there was an increased consumption of trazodone (from 3.81 to 7.92 DHD), mirtazapine (from 3.52 to 6.48 DHD), pregabalin (from 3.15 to 4.87 DHD), quetiapine (from 2.68 to 4.59 DHD) and gabapentin (from 1.32 to 1.90 DHD), which was only the case (or, at least, more significantly) for the lower dose formulations. The median of results of the Primary Health Care setting indicator "proportion of elderly patients without prescription of sedatives, anxiolytics, and hypnotics", was 81.0 in 2015 and increased to 84.9 in 2020. For the indicator "proportion of patients without prolonged prescription of sedatives, anxiolytics, and hypnotics", the median was 93.6 in 2019 and 94.3 in 2020.

Conclusion: There was, overall, a decreasing trend in the dispensing of benzodiazepines in the Lisbon and Tagus Valley Region. Even though this data suggests a change in the therapeutic pattern for insomnia, more robust studies are needed to confirm this observation.

Keywords: Benzodiazepines; Drug Utilization/trends; Hypnotics and Sedatives; Off-Label Use; Portugal; Practice Patterns, Physicians/trends

RESUMO

Introdução: Portugal é o país da Organização para a Cooperação e Desenvolvimento Económico com maior consumo de ansiolíticos, hipnóticos e sedativos, sendo uma proporção significativa constituída por benzodiazepinas ou análogos, associados a efeitos de tolerância e dependência. Por este motivo, em alternativa às benzodiazepinas para tratamento da insónia, algumas publicações identificam outros fármacos com efeito hipnótico, como antidepressivos, anti-histamínicos, antipsicóticos ou anticonvulsivantes. Assim, torna-se necessário compreender a evolução do consumo destes medicamentos, pelo que foi objetivo deste estudo avaliar a evolução da dispensa de benzodiazepinas, outros fármacos ansiolíticos, hipnóticos ou sedativos não benzodiazepínicos, fármacos com potencial uso *off-label* na insónia e os resultados de indicadores dos Cuidados de Saúde Primários neste âmbito na região de Lisboa e Vale do Tejo.

Material e Métodos: Realizou-se um estudo em base de dados, censitário e retrospetivo, no período de 2013 até 2020, avaliando-se a evolução das variáveis total de doses diárias definidas, doses diárias definidas por 1000 habitantes por dia (DHD) e dos indicadores relevantes. Os dados foram extraídos da plataforma SIARS da Administração Regional de Saúde de Lisboa e Vale do Tejo.

Resultados: Verificou-se uma diminuição da dispensa de benzodiazepinas (de 57,44 para 51,77 DHD) mas o aumento da dispensa de não benzodiazepinas e de fármacos com potencial uso *off-label* (de 6,56 para 8,56 DHD e de 14,70 para 25,92 DHD, respetivamente). O zolpidem foi o mais dispensado entre os fármacos não benzodiazepínicos, acompanhando a tendência crescente de dispensa (de 4,86 para 6,96 DHD). Do conjunto de fármacos com potencial para uso *off-label* verificaram-se aumentos da dispensa para a trazodona (de 3,81 para 7,92 DHD), mirtazapina (de 3,52 para 6,48 DHD), pregabalina (de 3,15 para 4,87 DHD), quetiapina (de 2,68 para 4,59 DHD) e gabapentina (de 1,32 para 1,90 DHD), mas mais significativo ou apenas

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verificado nas formulações com dosagem mais baixa. A mediana dos resultados do indicador "proporção de idosos sem prescrição de sedativos, ansiolíticos e hipnóticos" em 2015 foi de 81,0, tendo em 2020 aumentado para 84,9. A mediana do indicador "proporção de utentes sem prescrição prolongada de ansiolíticos, sedativos e hipnóticos" em 2019 foi de 93,6 e aumentou para 94,3 em 2020.
Conclusão: Globalmente, verificou-se uma redução da dispensa de benzodiazepinas prescritas na Região de Lisboa e Vale do Tejo. Parece existir uma alteração do padrão de prescrição no tratamento da insónia. São necessários estudos mais robustos para confirmar esta observação.
Palavras-chave: Benzodiazepinas; Hipnóticos e Sedativos; Padrões de Prática Médica/tendências; Portugal; Uso de Medicamentos/tendências; Uso Off-Label

INTRODUCTION

Benzodiazepines (BZD) are a group of central nervous system (CNS) depressant drugs with anxiolytic and hypnotic effects. Due to their efficacy and safety profile, they have been widely used for the treatment of anxiety or insomnia.[1,2]

However, BZDs are not devoid of risks. In the case of the elderly, due to pharmacokinetic changes associated with ageing (e.g., increased half-life) there is a greater propensity for adverse effects including drowsiness, ataxia, mental confusion, altered reasoning, anterograde amnesia, increased risk of falls and decreased cognitive function.[1,3] BZDs are also associated with tolerance and dependence phenomena, affecting all age groups.[1,2]

BZD treatment should be short term, not only due to the adverse effects, but also because dependence and tolerance can occur just a few weeks after starting treatment.[1,4] Withdrawal symptoms range from mild (nightmares, insomnia, anxiety) to severe (altered perception, psychosis, hyperpyrexia, life-threatening seizures).[1,2]

In line with the above, BZDs and analogues are recommended in the treatment of moderate to severe anxiety and insomnia for 4-12 weeks, including the weaning period, by the current national recommendations, updated in 2015. In the event of a therapeutic failure with this first approach in primary care, referral to a psychiatrist is usually recommended.[4]

In 2016, Portugal was the Organisation for Economic Co-operation and Development (OECD) country with the highest consumption of anxiolytics, hypnotics and sedatives (N05B-*Anxiolytics* and N05C-*Hypnotics and Sedatives*, according to the ATC 2017 - *Anatomical Therapeutical Chemical classification*), reaching a defined daily dose (DDD) of 114 per 1,000 inhabitants per day. AS regards benzodiazepines (BZD) and analogues (N05BA-*Benzodiazepine derivatives*, N05CD-*Benzodiazepine derivatives* and N05CF-*Benzodiazepine related drugs*, ATC 2017), a DDD of 80 has been found in Portugal in 2015, higher than 50, 22 and 12 found in Finland, Denmark, and the Netherlands, respectively. Contrary to what was found in these countries, more than 85 % of BZDs consumed in Portugal were anxiolytic, with consumption tending to increase with age and being higher among women.[5] However, from a pharmacological point of view, there is no clear distinction between hypnotic and anxiolytic BZDs, since most anxiolytic BZDs induce sleep if taken at night and most anxiolytic BZDs cause sedation if taken during daytime.[1] A DDD of 63 has been found in the 2016 assessment of BZD and analogues dispensed in community pharmacies within the *Administração Regional de Saúde de Lisboa e Vale do Tejo* (Regional Health Administration of Lisbon and the Tagus Valley) (ARSLVT), followed by Regional Health Administration (ARS) *Norte* (94), ARS *Centro* (97), ARS *Alentejo* (72), with the lowest value found in the ARS *Algarve* (49).[5]

The ARSLVT *Comissão de Farmácia e Terapêutica* (Pharmacy and Therapeutics Commission) (CFT) was aware of this issue and published the therapeutic bulletin "Benzodiazepine Use: A Serious Public Health Problem" in 2017. In addition to general recommendations for the rational use of BZDs, this bulletin provided guidelines to help doctors gradually discontinue these medications in the event of inappropriate use. In addition, a leaflet containing information for patients on BZDs was published in the ARSLVT website and subsequently disseminated at face-to-face meetings in primary care settings. This approach aimed to reinforce the recommendations of good practice in the use of this group of drugs and facilitate the adoption of strategies to promote their discontinuation.[6]

Considering that BZDs are one of the main strategies used for insomnia,[7-9] as an alternative and for this indication, the use of other drugs with a hypnotic effect has been advocated in Portugal in association with cognitive-behavioural therapy, namely antidepressants such as trazodone (25 to 150 mg/day), mirtazapine (7.5 to 30 mg/day) and trimipramine (10 to 150 mg/day), and antihistamines including doxylamine (25 to 50 mg/day) and hydroxyzine (37.5 to 75 mg/day).[10] Other pharmacological classes with hypnotic effect, such as antipsychotics (quetiapine) and anticonvulsants (gabapentin and pregabalin), have also been described internationally as being used off-label for insomnia, particularly when associated with comorbidities, especially psychiatric disorders.[11-13] Therefore, studying the evolution of the consumption of these drugs can be relevant in analysing the evolution of overall BZD consumption.

Considering the public issue of the use of BZD and the fact that most of the available information is aggregated by region, without distinction as to the place of prescription, generally not associated with the study of potential pharmacological alternatives to BZDs or the study of existing therapeutic monitoring indicators, it is important to assess

(i) the dispensing of BZDs, (ii) the dispensing of other non-benzodiazepine drugs with anxiolytic, hypnotic and/or sedative effects, (iii) the dispensing of other drugs with potential off-label use for insomnia and (iv) the primary care indicators related to BZD prescribing.

This study was aimed at a more comprehensive understanding of the issue, characterising the consumption of BZDs and a set of other drugs with similar indications and/or potential off-label use, as well as merging data with institutional contractualisation prescribing indicators, encouraging the discussion of potential opportunities for improvement and future medical and scientific research.

MATERIAL AND METHODS

This was an observational, census-based, and retrospective study carried out between 2013 and 2020.

The rationale for the definition of the evaluation period was related to understanding the trend prior to the measures implemented by the CFT with the therapeutic bulletin No. 1/2017: "Benzodiazepine Use: A Serious Public Health Problem". Data accessibility was also considered, particularly regarding primary care indicators.

Data on the use of BZDs and other non-benzodiazepine drugs with anxiolytic, sedative and/or hypnotic effects were obtained from the *Sistema de Informação da Administração Regional de Saúde de Lisboa e Vale do Tejo* (Lisbon and the Tagus Valley Regional Health Administration Information System) (SIARS), including data on the medicines prescribed throughout the ARSLVT if they were invoiced by community pharmacies in any region, according to the *Centro de Conferência de Faturas* (invoice assessment centre), considering the number of packs of each drug available on the market by international non-proprietary name (INN) according to dosage, form and presentation. This research was carried out for all BZDs included in the "2.9.1. Anxiolytics, sedatives, and hypnotics" *grupo farmacoterapêutico* (pharmacotherapeutic group - GFT), non-BZD drugs in the same GFT as well as for other drugs with hypnotic effect, as identified in the introduction, which the authors considered to be of potential off-label use for insomnia and which were not approved as a therapeutic indication. The list by INN is shown in the Appendix (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/18680/15097). Data were obtained and organised by year and by prescription sector, simultaneously for the whole evaluation period. Three independent extractions were made in this way, one for each group of drugs to be evaluated (BZD, non-BZD, and potential off-label use for insomnia).

An annual estimate was considered for each of the pharmacological groups:

- The total defined daily doses per year [DDD – a measuring unit defined by the World Health Organisation (WHO)], defined as the assumed average maintenance dose per day for a specific drug used for its main indication in adults].
- The number of DDDs per 1,000 inhabitants per day (DDD/TID), which can be interpreted as the percentage of the population on a daily treatment with a given medication, assuming a correct dose.
- Primary care indicators, according to the definitions of the *Bilhete de Identidade dos Indicadores dos Cuidados de Saúde Primários* (Identity Card of Primary Care Indicators - BI-CSP) of the *Administração Central do Sistema de Saúde* (Central Administration of the Healthcare System - ACSS)[14,15]:
  - Ratio of patients aged 65 and older with no long-term prescription for anxiolytics, sedatives or hypnotics within the evaluation period (SIARS code: 2013.297.01 FX)[15];
  - Ratio of patients with no long-term prescription for anxiolytics, sedatives or hypnotics, adjusted for a standard population (SIARS code: 2018.409.01 FX)[14].

As regards any medicines with no WHO-defined DDD, the average daily dose was estimated, according to the prescription medication label, for those that were dispensed during the evaluation period [Appendix 2 (Appendix 2: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/18680/15098)], to obtain the total DDD. The formulas for calculating the total number of DDDs and DDD/TIDs can be found in Appendix 3 (Appendix 3: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/18680/15099). In terms of prescriptions, considering the type of data that were available, the study population included all patients attending the ARSLVT, in the public or private sector. This population is therefore related to the data obtained from the database. In other words, as the data available regarded the medicines that were billed for a specific period, with no association to patients, the study population included all patients who potentially received a medical prescription within the ARSLVT during the same period. Whenever necessary, the estimate of the resident population within the ARSLVT catchment area (according to the National Statistics Institute) was used as an approximate value of the population for each year.

As regards primary care indicators, a different population was considered, including all patients registered with the ARSLVT health centre groupings (ACES) each year.

Data were exported and processed within the Microsoft Excel 365® software. Data cleaning was mainly based on extracting the numerical content in "dosage" (representing the dose of drug per tablet or the concentration in the case of solutions) and "presentation" parameters (corresponding

to the number of tablets or the quantity and capacity of containers in the case of solutions). For this purpose, IT system outputs were used, followed by a visual inspection of the data to ensure its fidelity. Data links between different databases were not used. The statistical evaluation was purely descriptive.

Ethical considerations

Given the census-based nature and the fact that linking data to any patient was made unavailable, the protection and confidentiality of personal data is considered to have been met. Likewise, the need for informed consent does not apply in this context. The protocol for this study was assessed and approved by the Health Ethics Committee of the ARSLVT, with the report 091/CES/INV/2020.

RESULTS

In 2013, a 76.2 million DDD of BZDs, 8.7 million DDD of non-BZDs and 19.5 million DDD of drugs with potential off-label use were prescribed within the ARSLVT and dispensed in community pharmacies; a 6.6 million lower DDD of BZDs, 2.8 million higher DDD of non-BZDs and 15.3 million higher DDD of drugs with potential off-label use were prescribed in 2020.

In 2013, these figures corresponded to 57.44 DDD per 1,000 inhabitants within the ARSLVT per day (DDD/TID) of

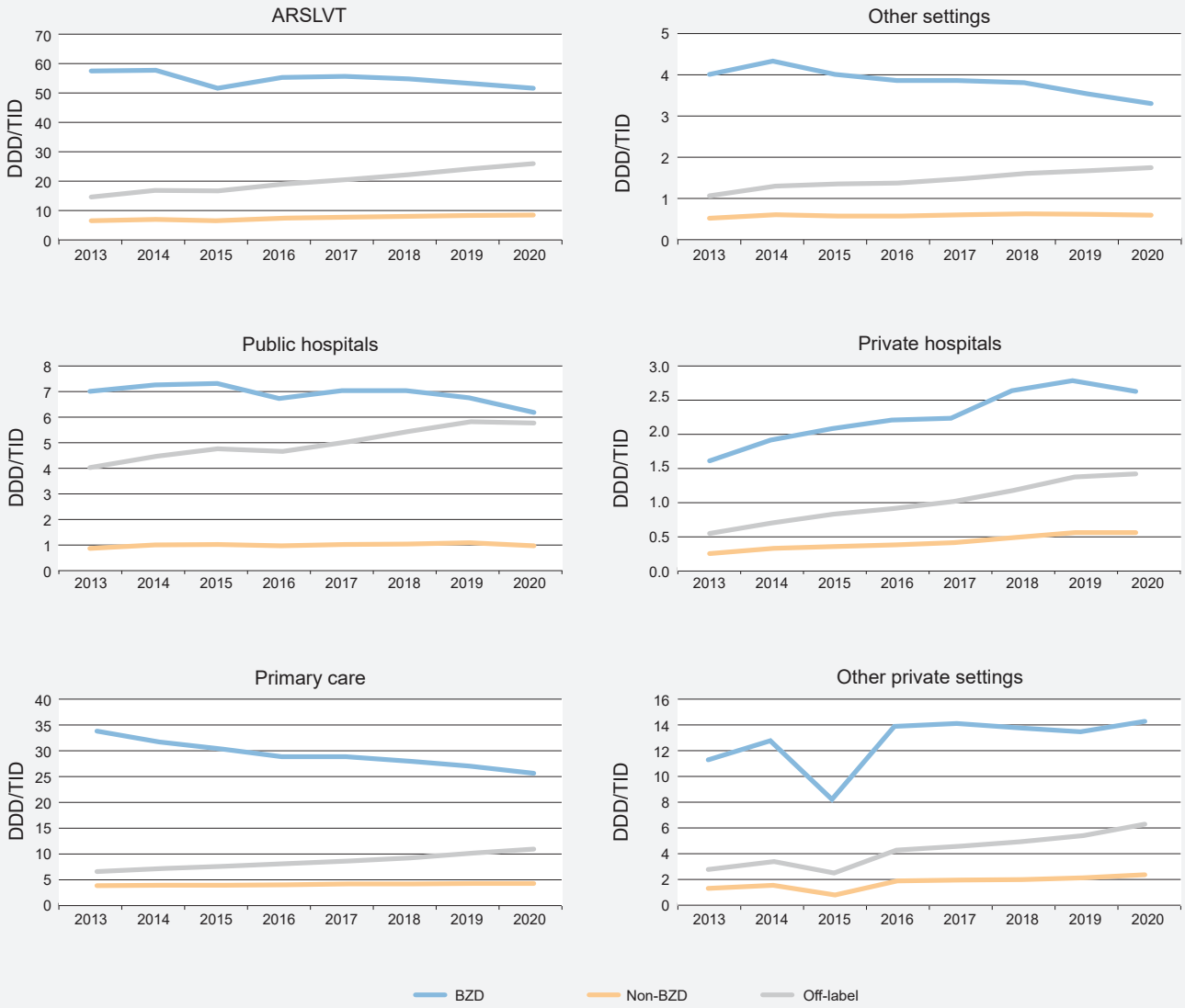

Figure 1 – Drug dispensation throughout the evaluation period per prescribing setting.
Other private settings, private clinics, and outpatient clinics; other settings, including associations (mutual healthcare associations, for instance), social sector, company doctors, integrated response centre, international vaccination centres, prison services, etc.; DDD/TID, defined daily doses per 1,000 inhabitants per day.

BZDs, 6.56 DDD/TID of non-BZDs and 14.70 of drugs with potential off-label use. In 2020, a 5.67 lower DDD/TID of BZD, 2.00 higher of non-BZD and 11.21 higher of drugs with potential off-label use were dispensed.

The trend towards a reduction in BZD dispensing and an increase in non-BZD dispensing and drugs with potential off-label use cuts across almost all prescribing sectors. This is not the case for private clinics (including charities), small private prescribers and the like, hereafter referred to as 'other private settings', as well as private hospitals, as BZDs also seem to be showing an upward trend (Fig. 1). However, a lower ratio of BZDs has been found in all three groups of drugs, regardless of the prescribing sector. On the other hand, an increase in drugs with potential off-label use has been found within the ARSLVT; despite the absolute decrease in DDD/TID of BZDs, an increase in the combined DDD/TID of the three groups of drugs (BZD, non-BZD and potential off-label use) has been found (Fig. 2).

Primary care was the main sector responsible for DDD/TID of the three groups of drugs, even though in a slightly lower ratio regarding the BZD and non-BZD group. Public hospitals have recorded the third highest ratio of DDD/TID of BZD and non-BZD, following the other private sectors. As regards drugs with potential off-label use, public hospitals accounted for the second largest share of DDD/TID, but their preponderance decreased over the years, up to 2020, in which the group of other private settings took second place. Private hospitals and other private sectors have

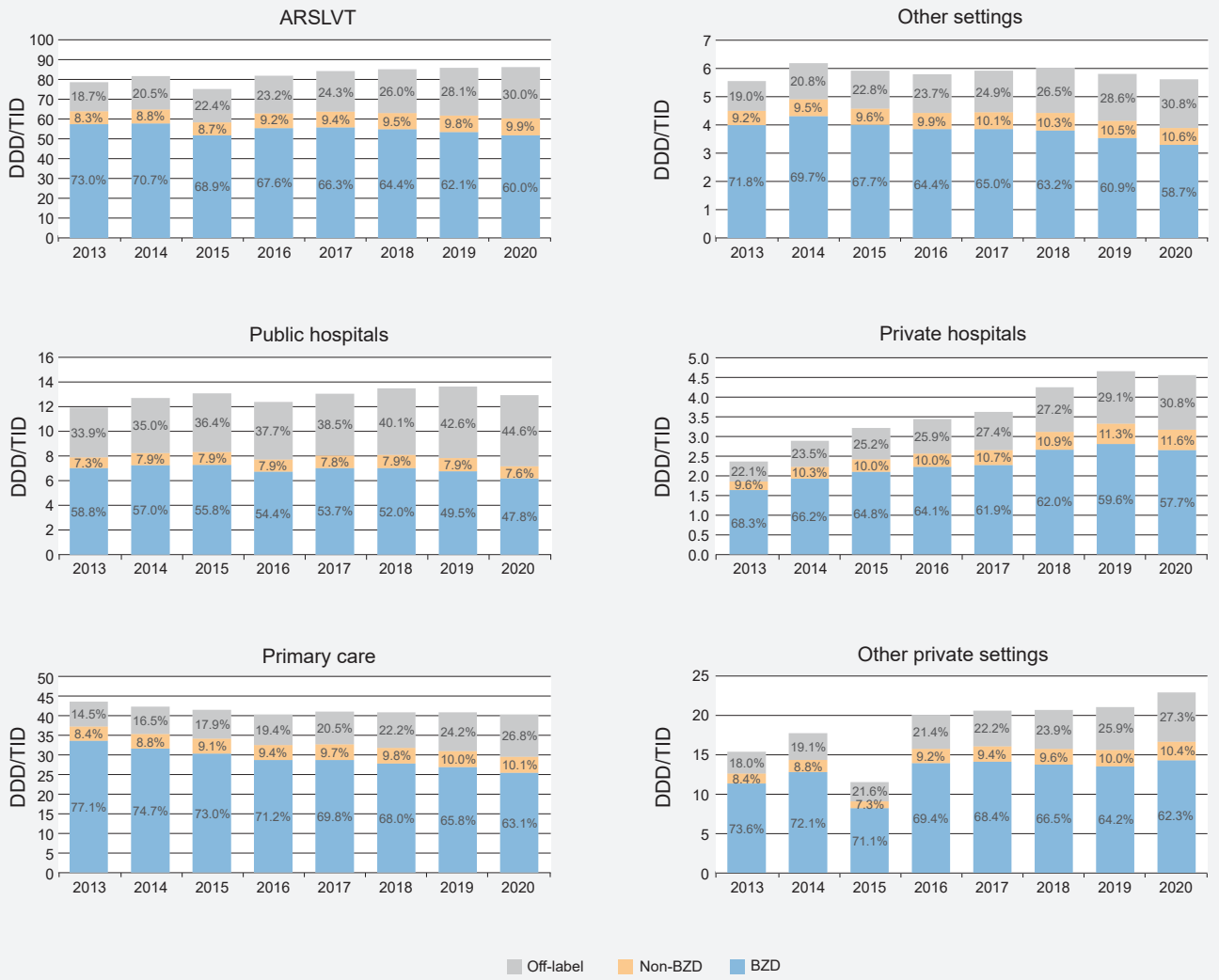

Figure 2 – Medication dispensing and ratios throughout the evaluation period, per prescribing setting. The legends correspond to the ratios of each drug group within that year.

Other private settings, private clinics and outpatient clinics; other settings, including associations (mutual healthcare associations, for instance), social sector, company doctors, integrated response centre, international vaccination centres, prison services, etc.; DDD/TID, defined daily doses per 1,000 inhabitants per day.

been gaining ground in the ratio of DDD/TID of drugs utilised within the three groups of drugs (Fig. 3).

As regards non-BZD drugs, zolpidem accounted for a DDD/TID of 4.86 in 2013, 5.18 in 2014 and 4.84 in 2015, steadily increasing up to 2020 and reaching a DDD/TID of 6.69, around 87% of the total DDD/TID for this group of drugs that year. This growth was uniform across the different prescription sectors. From 2013 to 2020, hydroxyzine (25 mg tablets) showed a maximum value of 1.56 DDD/TID in 2014 and a minimum of 1.06 in 2020, with a sustained decrease since 2016. A higher decrease has been found in primary care and in public hospitals. A progressive increase has also been found with buspirone, to a lesser extent and without a significant increase in DDD/TID. From 2013 to 2015, a DDD ranging between 572,570 (2014) and 502,617 (2015) has been found, with a progressive increase thereafter to 733,537 in 2020. This trend was similar within the different prescription sites.

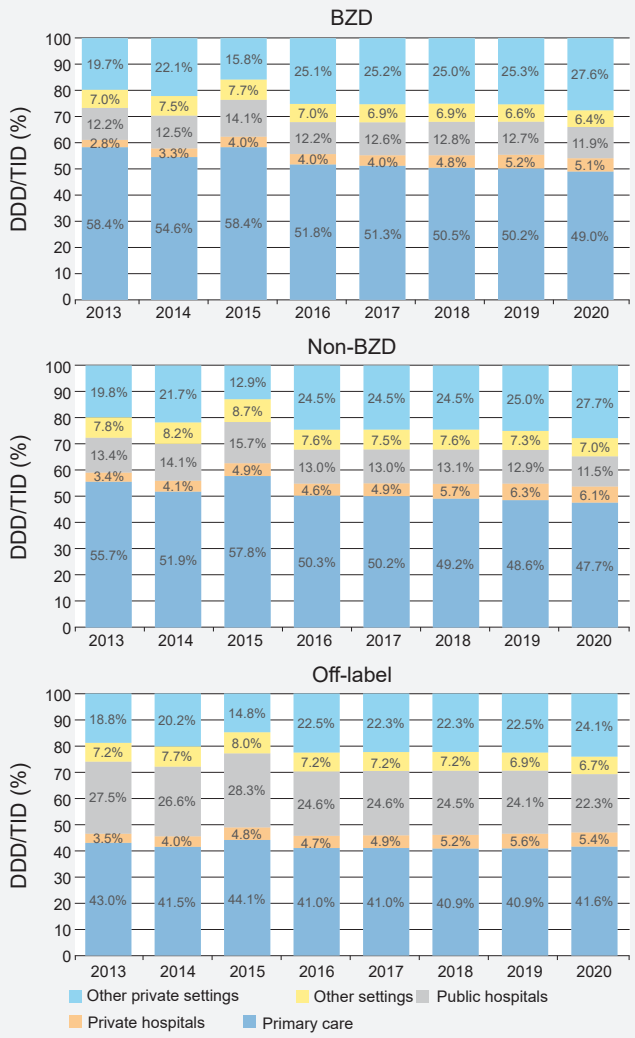

Figure 3 – Medication dispensing and ratios of the different prescription sources throughout the evaluation period.
Other private settings, private clinics, and outpatient clinics; other settings, associations (mutual healthcare associations, for instance), social sector, company doctors, integrated response centre, international vaccination centres, prison services, etc.; DDD/TID, defined daily doses per 1,000 inhabitants per day.

From all the drugs with potential off-label use, for the evaluation period, only trimipramine did not show a positive trend in DDD/TID (0.21 in 2013 and a minimum of 0.16 in 2020, a maximum of 0.21 in 2014). In 2020, the most prevalent drug was trazodone with a 7.92 DDD/TID (minimum of 3.81 in 2013, maximum in 2020), followed by mirtazapine with 6.48 (minimum of 3.52 in 2013, maximum in 2020), pregabalin with 4.87 (minimum of 3.15 in 2013, maximum in 2020), quetiapine with 4.59 (minimum of 2.68 in 2013, maximum in 2020) and finally gabapentin with 1.90 (minimum of 1.32 in 2013, maximum in 2020). As regards the last five drugs, the increasing behaviour was not the same for all doses (Fig. 4).

The analysis of primary care indicators was carried out from 2015 for the "Ratio of patients aged 65 or older with no long-term prescription for anxiolytics, sedatives or hypnotics" and from 2019 for the "Ratio of patients with no long-term prescription for anxiolytics, sedatives or hypnotics, adjusted for a standard population", as these are the only years with available results. There was a progressive improvement during the periods analysed (Fig. 5).

DISCUSSION

Overall, a decrease in dispensed BZD within the ARSLVT has been found from 2013 to 2020. However, this was not uniform among the different prescribing sectors from which the prescriptions dispensed in pharmacies originated. In fact, the trend in the private sector has generally been one of growth or stabilisation. The primary care sector was the main driver for the reduction within the healthcare region, due to the greater volume of patients, but probably also due to the magnitude of the decrease.

Overall, there was a mild increase across all prescription sectors as regards non-BZD drugs, mainly regarding zolpidem, despite the fact that in national recommendations it is classified as BZDs[4] and there is no clear evidence of a different safety and efficacy profile (probably safer than long-acting BZDs, but possibly less effective for the short-term treatment for insomnia than short- or intermediate-acting BZDs), as it is a less-studied substance.[16,17]

As for drugs with potential off-label use, a more significant increase has been found, across all prescription sectors. A significant combined increase in the dispensation of non-BZD drugs and drugs with potential off-label use has been found, showing a 3.25 decrease of DDD/TID over the evaluation period in primary care when the three groups of drugs were evaluated together. A 7.55 increase in DDD/TID

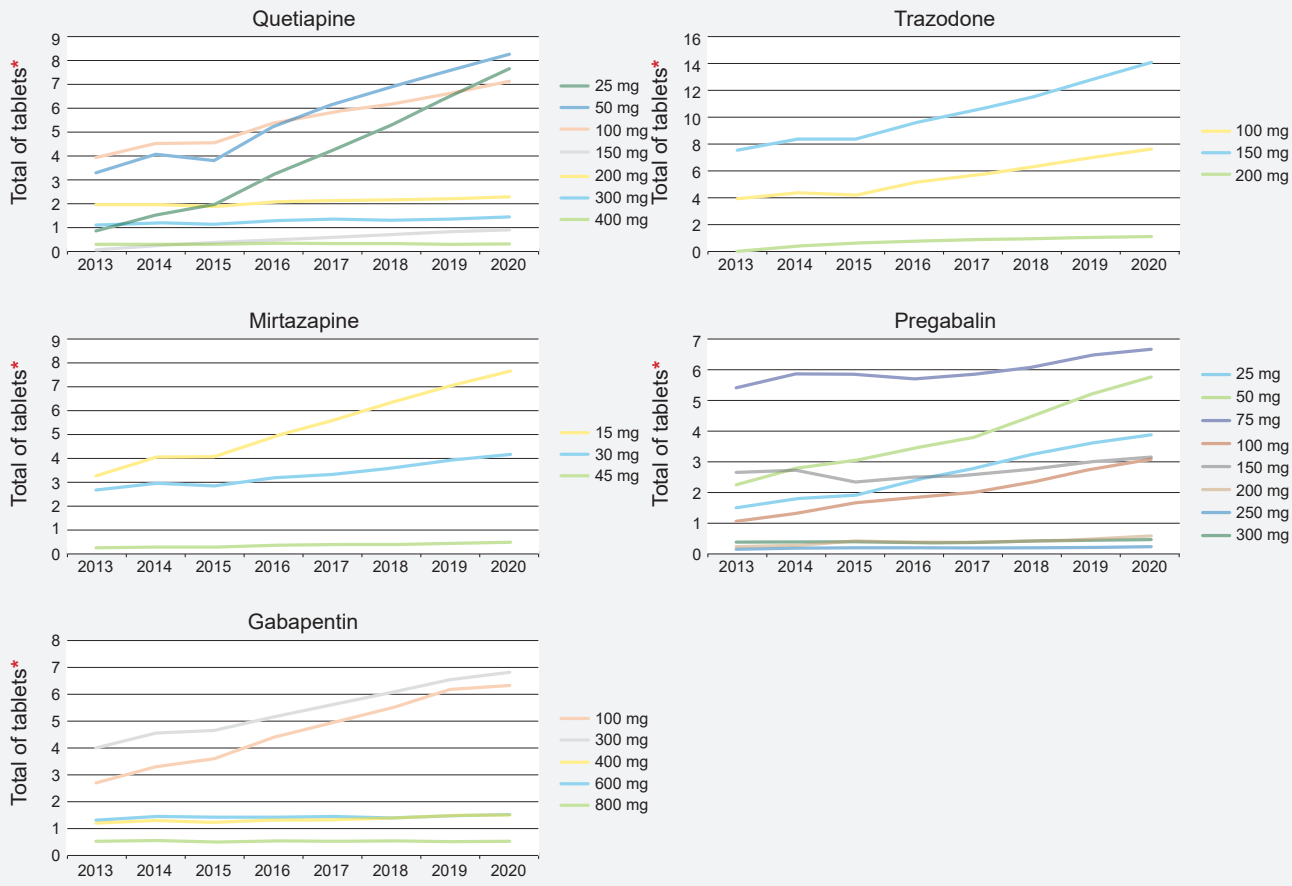

Figure 4 – Total number of dispensed tablets per dose, considering each drug with potential off-label use, with an increasing DDD/TID throughout the evaluation period, prescribed within the ARSLVT, regardless of the prescription setting.
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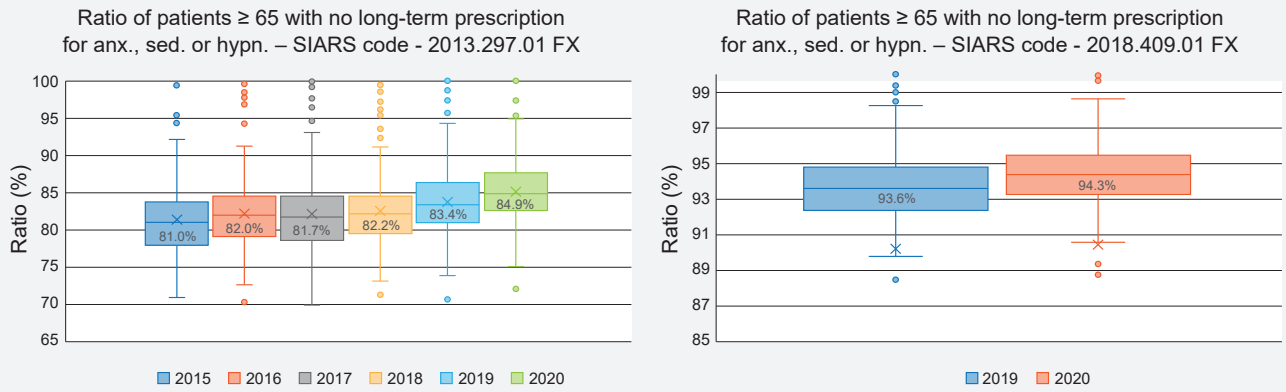

Figure 5 – Primary care indicators for each year with available data. Box and whisker plots representing the distribution of the results of all healthcare units for each year. The number within each box is the legend of the median value (represented by the box dividing line). The average value is represented by 'X' (no legend).

has been found within the ARSLVT, mostly driven by the private sector.

These data may suggest a shift in prescribing patterns, from the use of BZDs to the use of zolpidem, buspirone (although to a much lesser extent) and drugs with potential for off-label use for insomnia, including some antidepressants, gabapentinoids or antipsychotics.[10-13] However, it is worth mentioning that, as the clinical reason for their prescription is unknown, it is difficult to assume that they are used as a substitute or alternative to BZDs. Even if they have been used for insomnia, this may be secondary to pathologies for which these drugs may have an approved indication, such as anxiety or depression. Even so, this hypothesis is reinforced by the fact that, among the drugs with potential off-label use, the dosages corresponding to the most significant increases do not seem to be compatible with the DDD defined by the WHO, which is based on the daily dose that, on average, is required for therapeutic maintenance in the drug's main indication.[18] Using quetiapine as an example, with a DDD of 400 mg, there was a 911% increase in the number of 25 mg tablets dispensed in community pharmacies throughout the evaluation period (from 838,466 in 2013 to 7,638,686 in 2020), which seems disproportionate given the fact that this dosage, according to the drug's information label,[19] will mostly be used to titrate treatment up to the minimum effective dose in the approved indications. It would be expected that its use in terms of number of tablets would be marginal, which has not been the case. This apparently disproportionate increase in lower-dose formulations has also been found for other pharmacological groups with potential off-label use that have been evaluated. However, given the specific nature of the use of these drugs, this should be interpreted with care. To the best of our knowledge, there are no published international studies allowing for the comparison of these data with that of other countries.

OECD data shows that in Portugal the consumption of hypnotic and sedative drugs (ATC N05C, which includes BZDs with a hypnotic effect, BZD derivatives, melatonin derivatives, among others) has been decreasing (18.3 DDD/TID in 2013 to 16.3 in 2020), a trend that has been found since at least 2000.[20,21] In 2019, among the countries with available data, Portugal was the 12th country with the highest consumption (maximum of 65.9 DDD/TID and minimum of 0). As regards anxiolytic drugs (ATC N05B, including BZDs with anxiolytic effects, hydroxyzine, buspirone, among others), the trend for Portugal is also downwards (97.7 DDD/TID in 2013 and 84.8 in 2020).[21] This observation regarding the last seven years may correspond to a period of trend reversal, which is increasing in longer-term evaluations (from 2000 to 2018).[20] Even so, for this group of drugs, Portugal has been the leading consumer in the OECD since 2013, second only to Spain, which in turn has seen an upward trend in the consumption of these agents (52.3 DDD/TID in 2013 to 57.9 in 2020).

In 2019, the lowest consumption (2 DDD/TID) has been found in Turkey. Overall, among the different OECD members, the trend in consumption of these groups of drugs does not appear to be uniform, and there is also a very significant variation in the volume consumed. However, it is worth mentioning that the way the data is measured is not the same in the different countries, considering the fact that in some countries (such as in Portugal) hospital use is not taken into account.[21] Although not directly comparable given the use of different pharmacological classifications, the data obtained in this study on the evolution of the overall dispensation of anxiolytics, hypnotics and sedatives (GFT 2.9.1.) within ARSLVT, which was reduced from 64.0 DDD/TID in 2013 to 60.3 in 2020, are in line with those found in Portugal by the OECD (ATC N05C and N05B). However, the national average consumption is significantly higher than in this region. Whenever BZDs and analogues were evaluated, in the *ARS Norte*, between 2015 and 2018 and regarding primary care, an almost unchanged DDD/TID of approximately 58 has been found.[22] Considering all prescription sectors (except hospital use), this figure increased to 94 DDD/TID in 2016. Higher dispensation figures when compared to the ARSLVT have also been found that year within the *ARS Centro* (97 DDD/TID and *ARS Alentejo* (72 DDD/TID). The lowest figures (49 DDD/TID) were found in the *ARS Algarve*.[5] The difference in dispensed volume that seems to exist between the ARSLVT and the national average may therefore be due to the non-uniformity of the consumption of these substances between the different healthcare administrations.

The primary care indicators have shown a favourable trend, with a progressively higher ratio of patients with no long-term prescriptions for anxiolytics, sedatives, and hypnotics. This is in line with what has been found in primary care in this study. However, it is worth mentioning that the drugs with potential off-label use that were evaluated were not shown in these indicators.[14,15] This means that they are not sensitive in monitoring potentially inappropriate therapies if there is a transfer from prolonged BZD therapy to the use of off-label drugs, particularly for the treatment of insomnia.

Due to possible constraints in the access to healthcare[23] or the influence of confinement on mental health,[23,24] the presence of an impact of the COVID-19 pandemic from observing the data it is difficult to infer the existence of an impact of the COVID-19 pandemic, decreed in 2020 by the WHO, on the dispensations assessed during that year.

The observations made in the previous paragraphs are relevant as they support the need to include non-pharmacological measures in therapeutic plans, which are considered

first line in both anxiety and insomnia.[13,25-27] In addition, the need for a comprehensive monitoring of drug consumption is highlighted, particularly as a tool for the evaluation of the impact of clinical recommendations on therapeutic practice; they suggest that the impact of clinical recommendations is not uniform across the different prescription sectors, leaving the possibility of differentiated interventions by sector and, finally, they should motivate discussion and research in order to clarify the adequacy of the use of drugs with potential off-label use for insomnia, since systematically drawn up international recommendations do not, with some exceptions, support their use.[13,25,26] An evaluation similar to the one described in this study in other regions of the country could be of relevance to the scientific community and to public health.

From a methodological point of view, it was possible to obtain data on invoiced medicines that had been prescribed within the ARSLVT, but it was not possible to associate this prescription with the specific patient. Data were therefore processed on a census basis. Dispensed prescriptions were evaluated, overcoming the potential problems related to duplicate prescriptions not acquired by patients or with expired validity, which can lead to new prescriptions. We therefore believe that analysing the prescriptions dispensed within the ARSLVT and invoiced in any ARS in the country is quite reliable in gauging both prescribing and consumption practices in the Lisbon and Tagus Valley administrative region. However, it is worth considering that this approach may underestimate prescribing habits and overestimate consumption habits. On the other hand, dispensing without a prescription or illicitly acquired drugs are not considered, which in turn may lead to an underestimated consumption. To our knowledge, there are no Portuguese estimates regarding these sources of illicitly obtained prescription drugs.

However, there are limitations that should be discussed. First, the data obtained through the SIARS have not been validated by any study, to our knowledge. However, as it is an institutional platform and database, we believe that the information obtained is reliable.

Another direct limitation of the database is that the analysis does not include the consumption from hospital pharmacies, so the results for public and private hospitals may be underestimated. The unawareness regarding the indication for which drugs with potential off-label use were prescribed represents an additional issue that limits the interpretation of the results.

The fact that the population used to obtain the primary care indicators is different from the population used to measure the volume of prescriptions for anxiolytic and/or hypnotic drugs, although we speculate that this is not significant, preventing any direct comparison between both results. In addition, the population used to obtain DDD/TID reflects the INE (*Instituto Nacional de Estatística*) annual estimate of the population living within the ARSLVT's geographical area. However, the real population of the study included patients who received medical care within this same region. In other words, patients living out of the geographical area of interest even though getting their medical care there may have been included, while those living within the geographical area of interest but getting their medical care from outside the ARSLVT's coverage may have been excluded. Data sources did not allow this evaluation and therefore the closest source has been used.

As any association between medicines and the specific patients was unavailable, there is a possibility that the same patients were taking multiple drugs, which is not recognised by the measures used in this study. Similarly, the association between prescriptions and specific diagnosis was unavailable, reinforcing the purely exploratory nature of this study.

The doses used in the treatment of insomnia with off-label drugs are potentially lower than the DDD defined by the WHO.[10] This means that the DDD/TID value or total DDD of a given drug is not very sensitive for the evaluation of changes in the prescribing pattern of lower doses (generally only used in the titration period up to the higher maintenance doses). Therefore, the increase in DDD/TID for drugs with potential off-label use may not reflect the real magnitude of their use if these were being used for insomnia at lower dosages than recommended for the main indication.

Clonazepam, also a BZD, is included in the pharmacotherapeutic group "2.6 - Antiepileptics and anticonvulsants", which is why it was not selected for evaluation, according to the methodology applied in this study. However, the assessment of the dispensation of this drug in the group of potential off-label use for insomnia would have been interesting, as it is a BZD and, as such, drowsiness is one of its common side effects.[28] In addition to this, other drugs could have been studied in the group of potential off-label use for insomnia, such as the antidepressant amitriptyline or other antipsychotics.[13] Those that were eventually evaluated were selected either because they were referred to in a national recommendation[10] or because they seemed relevant in the national context, due to the authors' clinical experience.

Finally, the observational nature of this study does not allow reaching any definitive conclusions regarding a possible change in the therapeutic pattern for insomnia, but only to generate hypotheses. These should be evaluated and, when confirmed, their impact should be assessed in robust studies.

CONCLUSION

A reduction in BZD dispensing within the ARSLVT has been found, even though this trend was not uniform across

the different prescribing sectors. Overall, this reduction was accompanied by an increase in the prescription of non-BZDs and other drugs with potential off-label use. This may reflect a change in the therapeutic pattern rather than an improvement in the quality of prescribing, particularly regarding insomnia. More robust studies are required to confirm this hypothesis and assess the potential health impacts. Primary care indicators for long-term prescribing of sedatives, anxiolytics and hypnotics showed a favourable trend during the evaluation period.

AUTHOR CONTRIBUTION

SG: Data design, research, collection and treatment, critical reflection and writing of the manuscript.

PBG: Planning, research, critical reflection and revision of the manuscript.

MPG, DC, NR, CM: Planning, critical reflection and revision of the manuscript.

RA: Planning, research and data treatment, critical reflection and revision of the manuscript.

JC: Planning, critical reflection and revision of the manuscript.

HUMAN AND ANIMAL PROTECTION

The authors declare that this project complied with the regulations that were established by the Ethics and Clinical Research Committee, according to the 2013 update of the Helsinki Declaration of the World Medical Association.

DATA CONFIDENTIALITY

The authors declare that they have followed the protocols of their work centre on the publication of patient data.

CONFLICTS OF INTEREST

The authors declare that there were no conflicts of interest in writing this manuscript.

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