boletim de FARMACOVIGILÂNCIA

VOLUME 27
NÚMERO 1
JANEIRO/FEVEREIRO
2023

Do Editor

Neste Número, em que se consolida a nova periodicidade bimestral do Boletim, continuamos a divulgar uma seleção dos pósteres apresentados no Dia da Farmacovigilância do INFARMED, I.P. Em foco: a importante temática da segurança dos psicotrópicos.

O primeiro trabalho procura responder à pergunta se a segurança das benzodiazepinas, tão usadas no nosso país, variará com a semivida das mesmas. Serão mais seguras as benzodizepinas de curta, média ou longa duração de ação?

Segue-se um conjunto de quatro trabalhos, no âmbito do MisuMedPT, um projeto que tem como objetivo caracterizar a epidemiologia do abuso de medicamentos psicoativos em Portugal. Os autores analisam a dispensa deste tipo de medicamentos sujeitos a receita médica em farmácias comunitárias na região de Lisboa e Vale do Tejo, os internamentos hospitalares associados a abuso, as chamadas recebidas pelo Centro de Informação Antivenenos (CIAV) com reporte de intoxicação intencional envolvendo pelo menos um fármaco psicoativo. Finalmente, é também estudado o papel destes medicamentos nas mortes de causa violenta ou desconhecida em Portugal Continental.

A temática encerra com uma revisão, a nível nacional, das notificações de reações adversas a medicamentos psicotrópicos em crianças.

FICHA TÉCNICA

Diretora: Márcia Silva
Editor (Coordenador): Rui Pombal
Corpo Redatorial: Adriana Gamboa, Ana Severiano, Ana Sofia Martins, Cristina Mousinho, Fátima Bragança, Fátima Hergy, Magda Pedro, Márcia Silva, Patrícia Catalão, João Paulo Fernandes, Luís Vítor Silva
Colaboração na Edição: Inocência Pinto
Conselho Consultivo: Conselho Diretivo do INFARMED, I.P.
INFARMED – Autoridade Nacional do Medicamento e Produtos de Saúde, I.P.
Parque de Saúde de Lisboa, Av. do Brasil, N.º 53, 1749-004 Lisboa
Telefone: +351 217 987 100
Correio eletrónico: farmacovigilancia@infarmed.pt
Paginação: Letras & Sinais, Comunicação e Imagem, Lda.
ISSN: 0873-7118

Short, intermediate and long-acting benzodiazepines Different in safety?

Fernandes, P [1,2]; Pereira, M [1,2]; Esteves, C [1,2]; Fernandes, J [2]; Silva, M [2];

[1] Faculdade de Farmácia da Universidade de Lisboa
[2] INFARMED - National Authority of Medicines and Health Products – I.P., Directorate for Risk Management for Medicines, Lisboa, Portugal

Introduction

Benzodiazepine´s (BZD) use in Portugal has been widely studied over the years. Portugal has almost the **double of the average use** when compared with other European countries, being the **second** one with more usage among the elderly.

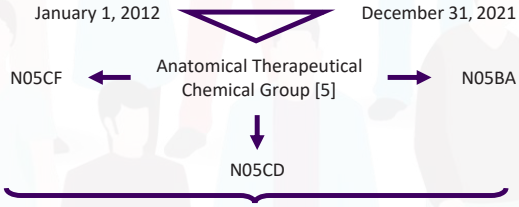
In 2016, BZD or analogues were dispensed at least once to about 1.9 million users. The users are mainly individuals between **55 and 79 years old** and **mostly female** (70%) [1-3]. BZD can be classified as **short acting** (SA), **intermediate acting** (IA) or **long acting** (LA), however, we couldn't find studies aiming to differentiate the safety profiles between these groups [2][4].

Objective

We propose to assess **Individual Case Safety Reports** (ICSR) received by the **Portuguese National Pharmacovigilance System** (SNF) related to SA, IA or LA BZD, aiming to **compare the safety profile of BZD groups**.

Methods

We performed a **retrospective search** on **Portal RAM** accordingly to the following diagram:



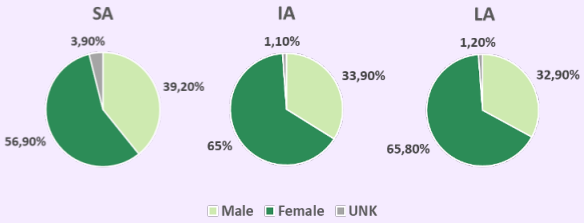
SA: less than 8 hours
IA: Between 8 and 24 hours
LA: longer than 24 hours

Were excluded:

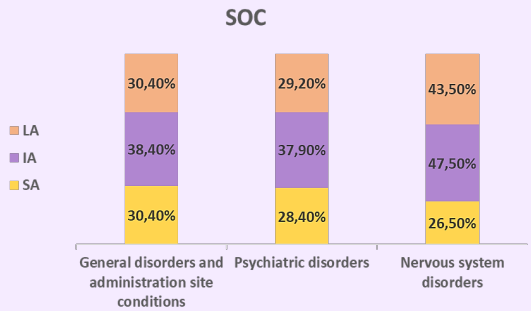
- ICSR with more than one BZD belonging to **different half-life groups**;
- ICSR referring to usage **outside** the terms of the marketing authorization, **without clinical purpose**;
- MedDRA preferred terms (PTs) related to **medication access**.

Results

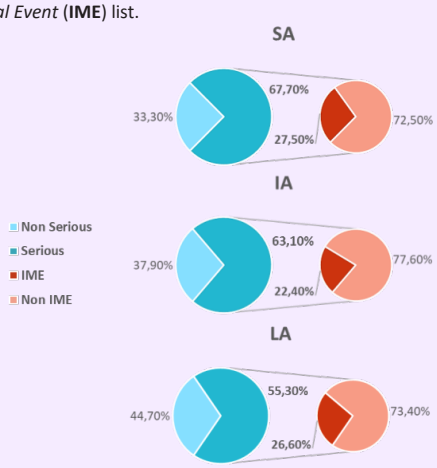
The search retrieved, for the studied period, **440 ICSR** distributed over the **3 groups** under analysis: SA (n=102), IA (n=177) and LA (n=161). There was a **predominance of female patients** in all 3 groups (SA: n=58; 56.9%|IA: n=115; 65.0%|LA: n=106; 65.8%). The average age was 55 ± 21.4; 56 ± 19.9 and 51 ± 19.1 years, for SA, IA and LA BZD, respectively.



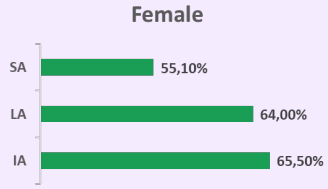
For the total of ICSR of each group, the number of reports containing at least one adverse reaction belonging to one of the MedDRA System Organ Class was higher for **General disorders and administration site conditions** (SA: n=31; 30.4%|IA: n=68; 38.4%|LA: n=49; 30.4%), **Psychiatric disorders** (SA: n=29; 28.4%|IA: n=67; 37.9%|LA: n=47; 29.2%) and **Nervous system disorders** (SA: n=27; 26.5%|IA: n=84; 47.5%|LA: n=70; 43.5%).



Most of the ICSR were classified as **serious** (SA: n=68; 66.7%|IA: n=110; 62.1%|LA: n=89; 55.3%). From these reports, 27.5% (n=55), 22.4% (n=139) and 26.6% (n=94) of the PT reported in the serious cases of SA, IA and LA groups belonged to the European Medicines Agency *Designated Medical Event* list (**DME**) and/or to the *Important Medical Event* (**IME**) list.



In the serious ICSR there was a **predominance of females** (SA: n=35; 55.1%|IA: n=72; 65.5%|LA: n=57; 64.0%) and the average age was 53 ± 21.7; 55 ± 20.6 and 48.5 ± 19.5 years, for SA, IA and LA BZD, respectively.



Literature

Conclusions

This study provides an overview of the ICSR received by the Portuguese SNF related to different BZD groups in a ten-year period. Our findings seem to indicate that there are **no relevant differences in the safety profiles of BZD when compared by their half-life**. The results of our demographic analysis are also **consistent with the characteristics of the Portuguese population user of these medicines.**

The use of prescription benzodiazepine's and its **impact in the Public Health** is a topic of great importance, so there is a need of a **close and attentive monitoring** in order to guarantee it's **safe and rational use.**

USE AND MISUSE OF PRESCRIPTION OPIOIDS AND OTHER PSYCHOACTIVE MEDICINES IN THE LISBON REGION OF PORTUGAL - THE MisuMedPT PROJECT

A. Araújo [1, 2], C. Bulhosa [3], J.P. Guerreiro [3], J. Goulão [4], A.P. Martins [1, 2]

[1]iMed - Research Institute for Medicines, Faculty of Pharmacy, University of Lisbon, Lisbon, Portugal
[2]ISBE - Institute for Evidence Based Health, Faculty of Medicine, University of Lisbon, Lisbon, Portugal
[3]Centre for Health Evaluation & Research, National Association of Pharmacies, Lisbon, Portugal
[4]SICAD - General Directorate for Intervention on Addictive Behaviours and Dependencies, Lisbon, Portugal

BACKGROUND AND AIMS

Prescription drug misuse is a known problem in some countries worldwide. Analgesic opioids are often misused, as other psychoactive medicines. We aimed at characterising prescription, dispensing and misuse of prescription opioids, benzodiazepines, antidepressants and antiepileptics in the Lisbon and Tagus Valley region of Portugal (ARSLVT), considering misuse to cover all situations where a medicinal product is intentionally and inappropriately used not in accordance with the terms of the marketing authorisation, including non-medical use, doctor shopping and abuse.

METHODS

The goal of the MisuMedPT project is to characterise the epidemiological pattern of misuse of psychoative medicines in Portugal, focusing mainly on 19 medicines, sold in community pharmacies, of the therapeutic groups opioids (strong opioids: buprenorphine for pain and for opioid dependence treatment, fentanyl, morphine, oxycodone and tapentadol; weak opioids: tramadol, tramadol + paracetamol and paracetamol + codeine), benzodiazepines (BZD - alprazolam, bromazepam, diazepam, ethyl loflazepate and lorazepam), Z-drugs (zolpidem), antiepileptics (clonazepam and pregabalin) and antidepressants (sertraline and trazodone). Among the several sources of evidence on medicines' misuse of the MisuMedPT project, namely morbimortality, poisoning and pharmacovigilance data, is dispensing information on medicines with psychoactive effects. The present retrospective cross-sectional study analyses dispensing of prescription-only psychoactive medicines in ARSLVT community pharmacies in 2017, covering all patients dispensed at least one package of any of 19 selected medicines against a valid medical prescription. Consumption was measured in defined daily doses (DDD) according to the DDD-ATC methodology of the WHO Collaborating Centre for Drug Statistics Methodology. Prescribers' medical specialty was studied, and use was analysed by looking at prevalence of medicines' consumption, dispensed medicines ranking and patients' diagnoses. Misuse was studied by estimating non-medical use, defined as use of a prescription medicine without the corresponding medical prescription, as well as doctor shopping, a practice where patients obtain overlapping prescriptions from different prescribers, ultimately resulting in the access to a daily dose of medication that is higher than that intended by each prescriber, indicating the risk of abuse of a given medicine[1]. Non-medical use was estimated using Health Market Research (HMR Portugal) global sales data for the studied psychoactive medicines in the ARSLVT region, with and without a valid medical prescription. Indicators of doctor shopping were calculated based on the number of overlaps of prescriptions of a given medicine, or therapeutic class, from different prescribers for a given patient[2].

RESULTS

About a quarter of psychoactive medicines are prescribed by general practitioners (GPs), except for buprenorphine for opioid addiction, where GPs account for 44% of prescription. Surgical specialties prescribe more opioids for pain, of these mainly weak opioids (72%), than any of the other therapeutic groups (Figure 1). Only 4% of opioids are prescribed by psychiatrists and neurologists, but the proportion of strong opioid prescription is higher than for surgical specialists (38% vs. 28%).

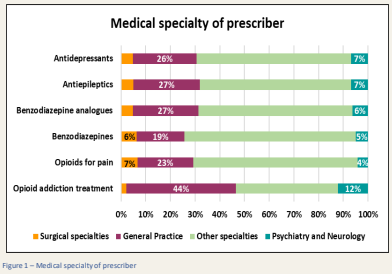


Figure 1 – Medical specialty of prescriber

Use of psychoactive medicines is twice as prevalent among ARSLVT females than in males (26% vs 13%). This female predominance is valid for all psychoactive medicines included in the study, except for buprenorphine for drug addiction, in which consumption is led by men (80% of users). Prevalence of strong opioid use is 0.8% and of weak opioid use 5.6%. Strong opioid users are older than weak opioid users (mean 67.9 vs. 62.5 years), and there are 3 times more women using strong opioids than men (21,298 vs. 7,086 users). Prevalence of BZD use is 11.6%, and antidepressants are used by 4.9% of the ARSLVT population, with females responsible for 70% and 73%, respectively, of total consumption of these therapeutic groups in ARSLVT.

Total number of opioid users was 218,562, 71% of the association tramadol + paracetamol, with 13% of all ARSLVT older females (65+ years) having been dispensed at least one package of this combination. About 11% and 8% of older females are alprazolam and sertraline users, respectively. Buprenorphine (pain) and fentanyl users are older (mean 71.8 and 70.2 years), and buprenorphine (opioid addiction) and ethyl loflazepate users are younger (mean 47.5 and 55.3 years).

Therapeutic class	Active substance	Number of users	Age (mean ± SD)
Opioid adiction treatment	Buprenorphine for addiction	2 220	47.5 ± 10.0
Opioids for pain	Tramadol + Paracetamol	154 674	63.5 ± 16.8
	Tramadol	34 914	61.4 ± 17.4
	Paracetamol + Codeine	27 498	59.9 ± 18.6
	Tapentadol	21 153	67.0 ± 14.4
	Fentanyl	4 391	70.2 ± 15.0
	Buprenorphine for pain	3 365	71.8 ± 14.9
	Morphine	2 161	65.7 ± 15.5
	Oxicodone	158	64.6 ± 13.4
Benzodiazepines	Alprazolam	148 633	62.4 ± 16.3
	Diazepam	111 122	57.6 ± 18.3
	Ethyl loflazepate	73 467	55.3 ± 16.9
	Bromazepam	73 110	67.3 ± 15.0
	Lorazepam	63 891	69.3 ± 15.4
Z-drug	Zolpidem	71 004	62.4 ± 15.8
Antiepileptics	Pregabalin	59 481	62.8 ± 15.6
	Clonazepam	36 137	60.5 ± 17.2
Antidepressants	Sertraline	100 718	61.8 ± 18.5
	Trazodone	91 915	62.0 ± 15.8

Table 1 – Number of users and mean age by active substance

Regarding consumption data, expressed in daily defined doses (DDD = assumed average maintenance dose per day for a drug used for its main indication in adults), strong opioids account for 24% of total opioid consumption (mean 0.4 DDD/user/day). Top consumed medicines per day were sertraline, buprenorphine (pain and opioid addiction) and lorazepam, all with a mean consumption of > 360 DDD/user/year. Considering chronic use to be consumption of at least 180 DDD in a year[3], 21.2% of strong opioid users are chronic users, contrasting with only 10.9% of weak opioid users. Further characterising this chronic use of ≥ 180, ≥ 360, or ≥ 720 DDD of a psychoactive medicine within a year, as long-term, daily, and excessive use[4], 10 of the 19 psychoactive substances studied fall into these categories, with lorazepam and the two buprenorphines being used daily, and sertraline showing excessive use.

Active substance	DDD/user/year	DDD/user/day	Long-term / Daily / Excessive use
Sertraline	801	2.2	Excessive use
Buprenorphine addiction	439	1.2	Daily use
Buprenorphine pain	425	1.2	Daily use
Lorazepam	408	1.1	Daily use
Alprazolam	303	0.8	Long-term use
Pregabaline	261	0.7	Long-term use
Trazodone	226	0.6	Long-term use
Ethyl loflazepate	193	0.5	Long-term use
Zolpidem	191	0.5	Long-term use
Diazepam	180	0.5	Long-term use
Fentanyl	164	0.4	-
Bromazepam	124	0.3	-
Morphine	112	0.3	-
Tapentadol	108	0.3	-
Tramadol	104	0.3	-
Clonazepam	99	0.3	-
Oxicodone	77	0.2	-
Tramadol + Paracetamol	64	0.2	-
Paracetamol + Codeine	60	0.2	-

Table 2 – Classification of psychoactive medicine use in ARSLVT by active substance

The probability of an opioid user to have a cancer diagnosis reaches 20% for strong opioid users and 15% for weak opioid users, with such a diagnosis being present for 35% of morphine, 30% of fentanyl and 15% of tapentadol users. Assuming diagnoses as a proxy for therapeutic indications, off-label use (use outside the approved therapeutic indication) of BZD, Z-drugs and antidepressants is frequent: only 18% of patients treated with BZD were diagnosed with anxiety (the main indication of BZD) and only 13% of patients treated with zolpidem had a diagnosis of sleeping disorder (the only therapeutic indication of zolpidem approved in Portugal). Depression was diagnosed to 41% of patients treated with antidepressants and to 33% of patients treated with antiepileptics.

Regarding non-medical use, 31% of all packages, especially of paracetamol + codeine (52%), zolpidem (45%) and lorazepam (44%), were initially dispensed without the corresponding medical prescription. However, further detailed analysis of these data is needed, as the presentation of a valid medical prescription in the days following dispensing, a common practice in Portugal that turns an initial non-medical use into a legitimate medical use, overestimates our non-medical use analysis. In fact, a limitation of our data is that all sales for which the medical prescription is not presented at the pharmacy in the same day of dispensing, are considered non-medical use.

Doctor shopping indicators were calculated using the method developed by Pradel et al[1]. For each prescriber/patient couple, the time interval between the first and the last observed dispensing defines a prescription period. This prescription period is not necessarily continuous and can be interrupted up to a threshold, defined as 37 days in our study (30 days, the mean validity of duration of prescriptions in Portugal in 2017, plus a delay of 7 days). The Doctor Shopping Quantity (DSQ) is computed for each dispensing period using the formula: $DSQ_i = [(n_i-1)/n_i]*Q_i$, in which n_i is the number of prescription periods overlapping at the date of dispensing i, and Q_i the quantity dispensed. Five parameters were calculated for each therapeutic class and each active substance: 1) Dispensed quantity (Qtot): the sum of total quantities dispensed to all patients; 2) Total DSQ (DSQt): the sum of doctor shopping quantities for all medication users; 3) Doctor Shopping Indicator (DSI): total DSQ divided by the dispensed quantity Qtot, indicating a signal of possible abuse; 4) Corrected DSI (DSIc): DSI minus 1%, in order to eliminate the background noise of medically legitimate prescription overlaps, considered to be of 1%, common to all abused and non-abused medications; 5) Corrected DSQ (DSQc): the product of dispensed quantity (Qtot) by corrected DSI. DSIc and DSQc are calculated only for medicines or therapeutic classes with DSI superior to 1% (below it is considered that there is no signal of abuse).

Therapeutic class	DSI (%)	DSIc (%)	DSQc (DDD/100,000 inhab/day)	Active substance	DSI (%)	DSIc (%)	DSQc (DDD/100,000 inhab/day)
Strong opioids for pain	6.64%	5.64%	20.2	Fentanyl	10.91%	9.91 %	5.4
				Morphine	9.20 %	8.20 %	1.5
				Tapentadol	5.44 %	4.44 %	7.7
				Oxicodone	3.91 %	2.91 %	0.0
				Buprenorphine for pain	3.30 %	2.30 %	2.5
Weak opioids for pain	4.77%	3.77%	43.9	Tramadol	5.15 %	4.15 %	11.5
				Tramadol + Paracetamol	4.26 %	3.26 %	24.8
				Paracetamol + Codeine	3.89 %	2.89 %	3.6
Opioid adiction treatment	4.85%	3.85%	2.9	Buprenorphine for addiction	4.85 %	3.85 %	2.9
Benzodiazepines	3.01%	2.01%	174.8	Lorazepam	3.40 %	2.40 %	47.7
				Alprazolam	2.93 %	1.93 %	66.3
				Bromazepam	2.88 %	1.88 %	13.0
				Diazepam	2.46 %	1.46 %	22.2
				Ethyl loflazepate	1.29 %	0.29 %	3.2
Z-drug	3.68%	2.68%	27.7	Zolpidem	3.68 %	2.68 %	27.7
Antiepileptics	4.26%	3.26%	47.5	Clonazepam	4.17 %	3.17 %	8.6
				Pregabalin	3.99 %	2.99 %	35.4
Antidepressants	1.90%	0.90%	69.2	Sertraline	1.73 %	0.73 %	45.1
				Trazodone	1.56 %	0.56 %	8.9

Table 3 – Doctor shopping indicators by therapeutic class and active substance

Results show that strong opioids for pain have the highest DSIc (5.64%), especially fentanyl (9.91%), morphine (8.20%) and tapentadol (4.44%); buprenorphine for opioid addiction also has a considerable DSIc (3.85%). For weak opioids, widely used in ARSLVT, tramadol and its association with paracetamol have the highest risk of abuse: 4.15% and 3.26%, respectively. Opioids as a whole have a DSIc of 4.21%. Antidepressants seem to pose no risk of significant abuse, with a DSIc of less than 1% (0.90%). Although the DSQc (that provides an estimate of the degree of medicines' abuse) for BZD is almost 3-fold higher than for opioids (174.8 vs. 64.1 DDD/100,000 inhabitants/day), their DSIc is half the DSIc of opioids (2.01% vs 4.21%). This apparent contradiction highlights the fact that the extent of psychoactive medicine abuse is a combination of the abuse potential and the availability of the medicine: in Portugal BZD are widely prescribed, whereas physicians refrain from prescribing opioids, which are almost all controlled substances in our country, in line with the United Nations Single Convention on Narcotic Drugs of 1961.

CONCLUSIONS

Use of psychoactive medicines is twice as prevalent among ARSLVT females as in males. Although prevalence of strong opioid consumption in ARSLVT is low (0.8%), females account for 75% of their use. Mean number of DDD/user/day reaches 2.2 for sertraline, showing excessive use, and 1.2 for lorazepam and buprenorphine (for addiction treatment and for pain), showing daily use, with most BZD used long-term. Cancer diagnosis is present only in one-fifth of opioid users, suggesting their main use in non-cancer pain.

In the doctor shopping method used, the extent of psychoactive medicines' abuse results from the combined effect of their abuse potential and their availability, this being the reason why abuse of opioids, having higher doctor shopping indicators but relatively lower doctor shopping quantities than BZD, does not seem to be an emerging problem in Portugal.

Considering that concomitant use of opioids and BZD can have significant health risks, co-prescription of these two classes and main risk factors for their possible adverse consequences would be interesting to investigate.

REFERENCES

1. Pradel V, Thirion X, Ronfle E, Masut A, Micallef J, Bégaud B. Assessment of doctor-shopping for high dosage buprenorphine maintenance treatment in a French region: development of a new method for prescription database. Pharmacoepidemiol Drug Saf. 2004 Jul;13(7):473-81. doi: 10.1002/pds.892. PMID: 15269931.
2. Ponté C, Lepelley M, Boucherie Q, Mallaret M, Lapeyre Mestre M, Pradel V, Micallef J. Doctor shopping of opioid analgesics relative to benzodiazepines: A pharmacoepidemiological study among 11.7 million inhabitants in the French countries. Drug Alcohol Depend. 2018 Jun 1;187:88-94. doi: 10.1016/j.drugalcdep.2018.01.036. Epub 2018 Apr 4. PMID: 29649695.
3. Luijendijk HJ, Tiemeier H, Hofman A, Heeringa J, Stricker BH. Determinants of chronic benzodiazepine use in the elderly: a longitudinal study. Br J Clin Pharmacol. 2008. Apr;65(4):593-9. doi: 10.1111/j.1365-2125.2007.03060.x. Epub 2007 Dec 17. PMID: 18093258; PMCID: PMC2291382.
4. Schonmann Y, Goren O, Bareket R, Comaneshter D, Cohen AD, Vinker S. Chronic hypnotic use at 10 years-does the brand matter? Eur J Clin Pharmacol. 2018 Dec;74(12):1623-1631. doi: 10.1007/s00228-018-2531-4. Epub 2018 Aug 8. PMID: 30090968.

Acknowledgements

The authors would like to thank António Faria Vaz and Isa Nunes (ARSLVT), as well as João Norte and João Barateiro (HMR Portugal), for making ARSLVT and HMR data available for the MisuMedPT Project.

Contact Information

Corresponding author: Ana Araújo
Email: ana.araujo@ff.ulisboa.pt

MORBIDITY CONSEQUENCES OF MISUSE OF PSYCHOACTIVE PRESCRIPTION DRUGS IN PORTUGAL
THE MisuMedPT PROJECT

Ana Araújo[1], Rita Casal[1], João Goulão[2], Ana P. Martins[1]

[1]iMed.ULisboa – Research Institute for Medicines, Faculty of Pharmacy, University of Lisbon, Portugal
[2]SICAD - General-Directorate for Intervention on Addictive Behaviours and Dependencies, Lisbon, Portugal

BACKGROUND

Hospital emergency admissions of patients suffering from psychoactive medicines' adverse effects provide important evidence on the risks associated to medicines acting on the central nervous system (CNS). This information can help to identify situations of misuse, making morbidity data useful as part of an active surveillance system for monitoring psychoactive medicines' misuse.

OBJECTIVES

To characterise admissions to emergency departments of Portuguese hospitals of patients with misuse to psychoactive medicines, defined as having a diagnosis of abuse, poisoning or dependence of psychoactive medicines.

METHODS

Retrospective observational study of visits to emergency departments (ED) of Portuguese hospitals of patients presenting at least one diagnosis of abuse, poisoning or dependence to psychoactive medicines (2014-2018), either as causing the admission (primary diagnosis) or as secondary diagnosis. The variables studied were demographic characteristics of individuals, geographical distribution of admissions, therapeutic classes of medicines involved, hospitalisation length, episode severity, type of diagnoses and mortality risk.
Descriptive statistics and hypothesis testing were performed in IBM SPSS Statistics® version 28.0.1.1.

RESULTS

A total number of 13,813 admissions took place in Portuguese hospitals, increasing during the 5-year period (1,781 in 2014 to 3,933 in 2018) (Fig 1), 7,591 females (55%) and 6,222 males (Fig 2), with a mean age of 47.4 years (±19.8).

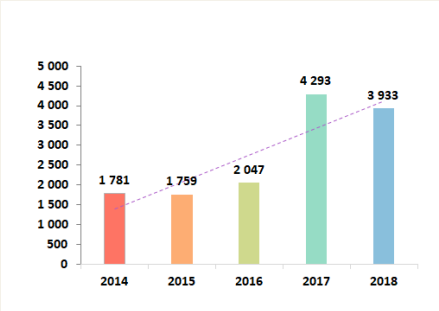


Figure 1. Annual admissions in Portuguese public hospital with a diagnosis of misuse

Clear female predominance was found between 2014 and 2016 (≈70% of total ED visits). However, in 2017 and 2018, more than half of admissions concern males (55%).

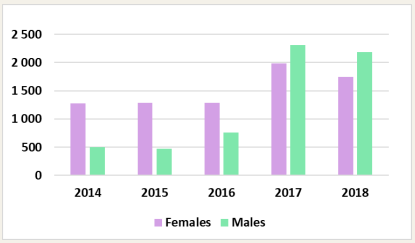


Figure 2. Number of admissions with misuse per gender

Geographical analysis (patient's district of residence), taking into account census data, shows that an average of 25.5 admissions per 100,000 habitants took place in Portuguese hospitals during the 5-year period. Vila Real was the district with the highest number of admissions of patients presenting at least one diagnosis of misuse during the study period (39.6 admissions per 100,000 habitants), followed by Setúbal (34.3) and Lisboa (32.1).

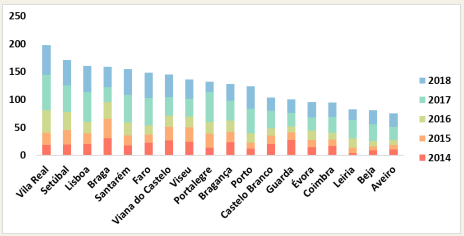


Figure 3. Geographical distribution per 100,000 habitants

Although more than half of the studied admissions were for other reasons, the diagnoses of interest not causing the ED visit (secondary diagnoses), about 48% of cases were due to psychoactive medicines' misuse (primary diagnosis). About 68% of the 13,813 total admissions had a diagnosis of poisoning, 28% of dependence and 7% of abuse.

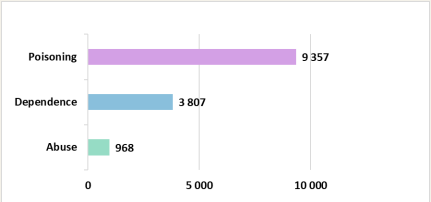


Figure 4. Type of diagnosis in total admissions

In 88% of ED visits there was effective hospitalisation (mean length of stay: 11.3 ± 18.8 days). There were statistical differences regarding the median duration of hospitalisation in admissions caused by misuse compared to admissions for other causes , with hospitalisations for misuse being shorter than hospitalisations where misuse was only a secondary diagnosis (median 4 vs. 8 days). Considering severity to be the degree of physiological decompensation of the patient, taking into account comorbidities and seriousness of primary diagnosis, about a quarter of cases were considered to be of extreme and major severity (33% minor).

About 18% of admissions presented extreme and major mortality risk. A statistically significant relationship was found between admission cause (misuse vs. other causes) and episode severity (p<0.001), as well as mortality risk (p<0.001).

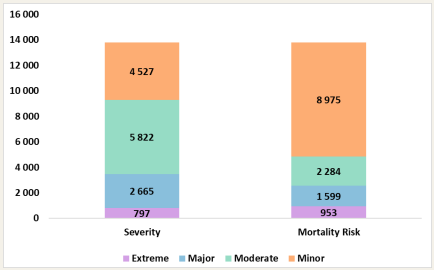


Figure 5. Episode severity and mortality risk

The top therapeutic classes responsible for hospital admissions were anxiolytics (65%), followed by antidepressants (16%), both with a clear female predominance (73 and 75%, respectively), as opposed to prescription and illegal opioids that caused only 3.4% of ED visits, (65% of which men). However, these admissions due to prescription and illegal opioids had a median duration of hospitalisation (6 days) significantly higher than the remaining users admitted due to misuse of other psychoactive therapeutic classes (p<0.001). This is expected taking into consideration that the use of illegal drugs is potentially more harmful than the use of medicines.

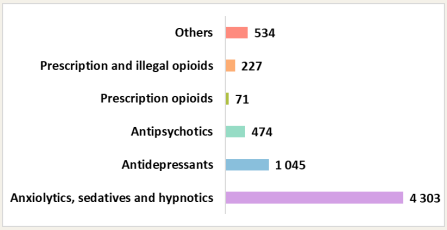


Figure 6. Top therapeutic classes involved in admissions

CONCLUSIONS

Our preliminary results show that anxiolytics, especially benzodiazepines, as well as antidepressants, are the main types of therapeutic groups responsible for hospital admissions involving psychoactive medicines, which show significant severity and mortality risk. Considering these classes are on the top of CNS-acting medicines' consumption in Portugal, our results call for further investigation. Work is currently undergoing to triangulate all use and misuse-related morbi-mortality data collected from the different sources that compose the MisuMedPT Project, in order to have a holistic but detailed picture of psychoactive medicines' misuse and its consequences in Portugal.

Contact Information

Corresponding author: Ana Araújo
Email: ana.araujo@infarmed.pt

MORBI-MORTALITY CONSEQUENCES OF MISUSE OF PSYCHOACTIVE PRESCRIPTION DRUGS IN PORTUGAL: A RETROSPECTIVE OBSERVATIONAL STUDY

Ana Araújo[1], Ana Godinho, João Goulão[2], Ana P. Martins[1]

[1]iMed.ULisboa – Research Institute for Medicines, Faculty of Pharmacy, University of Lisbon, Lisbon, Portugal
[2]SICAD - General-Directorate for Intervention on Addictive Behaviours and Dependencies, Lisbon, Portugal

ispe ICPE 2022

DISCLOSURE STATEMENT

Ana P. Martins is an employee of Gilead Sciences, Inc. The remaining authors have no relationships to disclose.

BACKGROUND

Drug exposure is difficult to measure due to the specificity of the exposure and its socio-demographic-economic and clinical determinants.
Estimating the potential for prescription drug misuse and dependence is further complicated by the fact that it is a behavior often concealed, which usually concerns a small number of individuals compared to the total number of patients exposed.
Monitoring systems of medicines' misuse can be based on several sources of information: drug-related deaths, drug-related emergency visits, data from poison control centers (PCCs), prescription/reimbursement databases, pharmacovigilance data (spontaneous reports and risk management plans) and electronic prescription monitoring programmes. PCCs can act as near-real-time sentinel indicators of prescription drug misuse and be part of an active surveillance system with data collected from different sources.
In Portugal, there are no published data on the health-related consequences of prescription drug misuse, which is therefore a public health issue of unknown dimension in our country.

OBJECTIVE

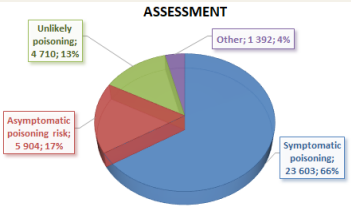
To characterize calls received by the Portuguese Poison Information Centre (CIAV) reporting intentional poisonings involving at least one psychoactive medicine.

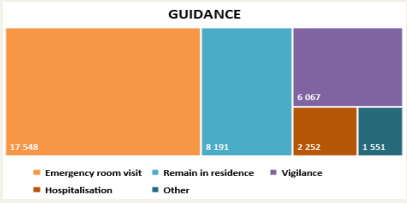
METHODS

Retrospective observational study of intentional exposures to 69 active substances, sold in community pharmacies, of the therapeutic groups opioid analgesics, antiepileptics, anxiolytics, hypnotics and sedatives, antidepressants and psychostimulants, as well as illegal drugs and alcohol, reported to the Portuguese Poison Information Centre (CIAV) between 2014 and 2018. For calls involving more than one substance, each substance was considered as a unique exposure (or case mention).
The variables studied were demographic characteristics of individuals, geographic distribution of calls, co-exposure to alcohol or illicit drugs, call origin and circumstance, case evaluation and case guidance. Annual rates of intentional exposure based on census and medicines' use data (sales information from Health Market Research Portugal), were estimated.

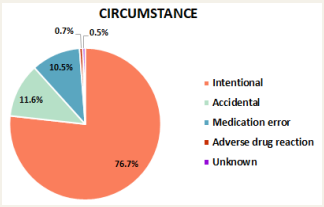
RESULTS

Between 2014 and 2018, 27,308 calls were received at CIAV reporting 39,421 intentional exposures to any medicinal product (34,203), alcohol (3,512) or illicit drug (1,706). Of the total number of intentional exposures reported to any medicine, 31,169 (91,1%) involved one of the psychoactive medicines included in the study. Of the total number of calls received at CIAV (35,609), 66% (23,603 calls) concerned symptomatic poisonings, 17% (5,904) reported asymptomatic poisoning risk and 13% (4,710) unlikely poisonings. Regarding case guidance, in 17,548 calls the advice was to visit an emergency room service and in 2,252 to be hospitalized, 8,191 to remain in residence and in 6,067 calls, only vigilance was suggested.





Regarding call circumstances and origin, analysis shows that almost 77% of calls reported intentional exposures, with only 11.6% reporting accidental exposures. In what concerns call origin, 68% of calls came from the medical emergency central (112) and health information hotline (Saúde 24).



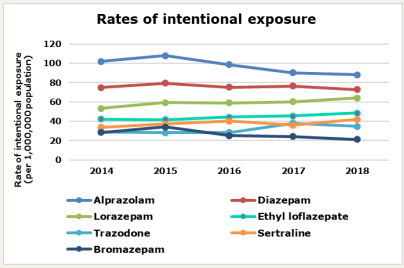
Demographic characterisation of calls shows that 63% referred to females and 37% to the 35-54 age group. In this age group, a higher mean number of substances mentioned per call and higher SD were observed.

Age group (years)	Number of calls		Mean number substances involved (SD)		Range of the number of substances	
	F	M	F	M	F	M
15-24	4 173	2 052	1.31 (0.61)	1.30 (0.60)	1 - 5	1 - 5
25-34	3 246	1 804	1.45 (0.76)	1.41 (0.67)	1 - 5	1 - 5
35-44	4 870	1 983	1.48 (0.77)	1.47 (0.72)	1 - 5	1 - 5
45-54	4 918	1 540	1.49 (0.76)	1.46 (0.71)	1 - 5	1 - 5
55-64	2 617	788	1.44 (0.73)	1.47 (0.71)	1 - 5	1 - 5
65-74	1 408	475	1.36 (0.64)	1.31 (0.60)	1 - 5	1 - 4
75-84	921	384	1.25 (0.55)	1.28 (0.58)	1 - 5	1 - 4
> 85	414	170	1.30 (0.59)	1.24 (0.50)	1 - 5	1 - 3
	63%	26%				

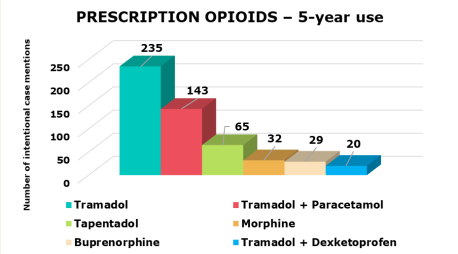
Analysing exposures reported to prescription drugs and alcohol, female and 35-54 age group predominance is noted, contrasting with exposures to illicit drugs, which occurred mainly in younger males. This is in accordance with the patterns of use of these substances in Portugal (female and middle age predominance in prescription drug use, rising prevalence of alcohol consumption in women and higher prevalence of illicit drug use by young males).

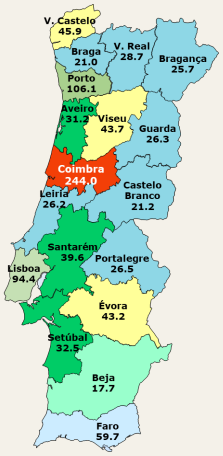
Age group (years)	Prescription drugs		69 Prescription drugs		Alcohol		Illicit drugs	
	F	M	F	M	F	M	F	M
< 15	787	189	658	174	25	10	21	46
15 - 24	4 581	1 544	4 001	1 334	244	273	231	468
25 - 34	3 856	1 570	3 506	1 413	262	312	113	375
35 - 44	6 015	1 913	5 508	1 761	495	433	61	217
45 - 54	6 038	1 456	5 617	1 348	498	407	19	100
55 - 64	2 914	720	2 737	662	222	168	1	22
65 - 74	1 175	316	1 107	298	56	48	0	2
75 - 84	484	171	456	158	9	12	0	0
> 85	151	61	138	58	0	2	0	0
Total	26 001	7 940	23 728	7 206	1 811	1 665	446	1 230

Benzodiazepines (62.0%) and antidepressants were the prescription medicines most frequently involved in intentional exposures, with alprazolam on the top, declining since 2015. Rates of intentional exposure using census data show that the second active substance more frequently reported was diazepam (72.7 intentional exposures per million inhabitants in 2018), followed by lorazepam (64.0). Sertraline, occupying the 5th position in the ranking, has seen an increase in the reporting rate of intentional exposures from 2017 to 2018, contrasting with another antidepressant, trazodone, whose reporting rate has declined in that period.



Of note is the fact that prescription opioids are quite underrepresented among the top therapeutic classes, with the first opioid - tramadol - being the 25th most frequently reported prescription medicine in intentional exposures. Among analgesic opioids, tramadol and its associations represent 73% of the total case mentions reported involving prescription opioids during the study period (methadone was excluded from the analysis since it is not available in community pharmacies).





In what concerns geographic distribution of calls, the highest rates of intentional exposures to the medicines of interest were observed in the districts of Coimbra, Porto and Lisbon.
We speculate that one of the reasons for the high rate of intentional exposures reported in the district of Coimbra, compared with Lisbon and Porto, might be the fact that Coimbra is an academic city with a very significant student population, as such probably more prone to experiment substance use and therefore suffer from their possible negative consequences.

CONCLUSIONS

Contrasting with evidence coming from the USA and other countries affected by the prescription opioid crisis, in Portugal prescription opioids are responsible for a very small number of intentional poisonings for which advice was sought from CIAV.
According to the Global Burden of Disease Study 2018, depression and anxiety disorders are two of the six main causes of disability in Portugal, with Portugal ranking second among OECD countries in the consumption of benzodiazepines and z-hypnotics. It is therefore not surprising that benzodiazepines and antidepressants are in the top of the most frequently reported psychoactive medicines in intentional poisonings.

Contact Information

Corresponding author: Ana Araújo
Email: ana.araujo@ff.ulisboa.pt

MORTALITY CONSEQUENCES OF MISUSE OF PSYCHOACTIVE PRESCRIPTION DRUGS IN PORTUGAL
THE MisuMedPT PROJECT

ispe ICPE 2022

Ana Araújo[1], Carolina Bulhosa[2], José P. Guerreiro[2], João Goulão[3], Ana P. Martins[1]

[1]iMed.ULisboa – Research Institute for Medicines, Faculty of Pharmacy, University of Lisbon, Lisbon, Portugal
[2]Centre for Health Evaluation & Research, National Association of Pharmacies, Lisbon, Portugal
[3]SICAD - General-Directorate for Intervention on Addictive Behaviours and Dependencies, Lisbon, Portugal

DISCLOSURE STATEMENT

Ana P. Martins is currently an employee of Gilead Sciences, Inc. The remaining authors have no relationships to disclose.

BACKGROUND

Forensic data, together with poison center and hospital information on medicine-related events, are useful to evaluate the possible health-related consequences of medicines' misuse.

Triangulating data from these sources contributes to enhance knowledge on the possible risks associated to psychoactive medicines' use and can be useful as part of an active surveillance system for monitoring their misuse.

OBJECTIVE

To investigate demographic characteristics, polydrug use and medicines' role in violent or unknown cause deaths occurring in Portugal mainland, taking into account exposure data on psychoactive medicines.

METHODS

Observational study of all medico-legally investigated deaths from 2014 to 2018 involving psychoactive medicines (benzodiazepines, antidepressants, antiepileptics and prescription opioids), included in the database of the National Institute of Legal Medicine and Forensic Sciences (INMLCF). Polydrug use with alcohol or illegal drugs was also analyzed.

Using sales data from Health Market Research Portugal, medicine utilization-based death rates were estimated. In addition, Pearson correlation coefficient was calculated to study the relationship between the number of deaths and psychoactive medicines' exposure.

RESULTS

A total of 7 653 deaths involving at least one psychoactive medicine occurred in Portugal mainland during the study period, increasing year after year (Figure 1). The rate of deaths involving at least one psychoactive medicine, among all violent or ignored cause deaths, has decreased from 2014 to 2016, but increased in 2017 and 2018, reaching 26.7% in 2018 (17.4 deaths/100 000 inhabitants), 71.1% of which unintentional.

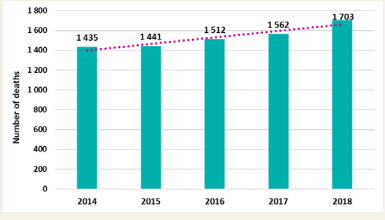


Fig. 1 – Number of violent or ignored cause deaths involving psychoactive medicines

The mean age of decedents with violent or ignored cause deaths has been increasing, from 61.0 years in 2014 to 64.0 years in 2018, with 62% of deaths occurring in males. About 26% of deaths were intentional.

The total number of anxiolytics, hypnotics and sedatives (benzodiazepines and analogues) involved in fatal cases has decreased, from 1 343 in 2014 to 1 160 in 2018; prescription opioids (strong and weak) show an opposite trend (64;132 in 2014, to 151;218 positive toxicology reports in 2018), as well as antidepressants (548 in 2014, to 710 in 2018) – Figure 2.

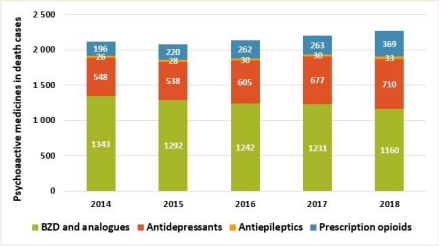


Fig. 2 – Psychoactive medicines involved in death cases

Death data are in line with sales data of these therapeutic groups, with benzodiazepines declining and opioids increasing their sales in the 5-year period (Figure 3).

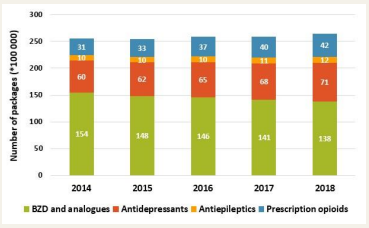


Fig. 3 – Sales data of psychoactive medicines

A moderate positive relationship between psychoactive medicine deaths and sales data was found (Pearson r = 0.412; p = 0.010).

In 4.8% of the studied deaths, the autopsy confirmed the medicine's contribution to the fatal outcome.

In 20% of deaths there was polydrug use, 14.2% with alcohol (75% males; 28% older than 65 years) and 4.2% with illegal drugs (N=323, 78% males), of which 48% with cocaine and 58% with cannabis (Figure 4).

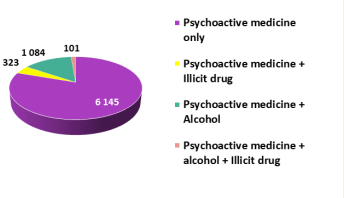


Fig. 4 – Distribution of deaths according to type of psychoactive substances involved

Diazepam (5 810; 76%), tramadol (1 493; 20%) and alprazolam (1 262; 16%) were the active substances more frequently found in psychoactive medicine death cases.

Active substance	2014	2015	2016	2017	2018	Total	% of cases involving the active substance
Diazepam	1 199	1 132	1 242	1 151	1 086	5 810	76%
Tramadol	185	200	319	333	456	1 493	20%
Alprazolam	273	250	278	243	218	1 262	16%
Sertraline	141	157	265	267	261	1 091	14%
Lorazepam	176	157	150	144	128	755	10%
Ethyl loflazepate	180	160	150	124	116	730	10%
Trazodone	109	125	135	157	172	698	9%

Table 1 – Psychoactive medicines more frequently involved in death cases

Using sales data from HMR Portugal, the number of users of each active substance was estimated in order to calculate utilization-based death rates.

In 2018, tramadol, midazolam, diazepam and fentanyl had the highest utilization-based death rates (3 942, 1 194, 1 028 and 865 deaths/100 000 patients treated, respectively) – Figure 5. Morphine (for which a death rate of 10 073/100 000 patients was estimated) has been excluded from the analysis due to the fact that, being often administered in emergency medicine, its presence in forensic results of violent or ignored cause deaths can be partly attributed to use in emergency context, not indicating use by the decedent before death.

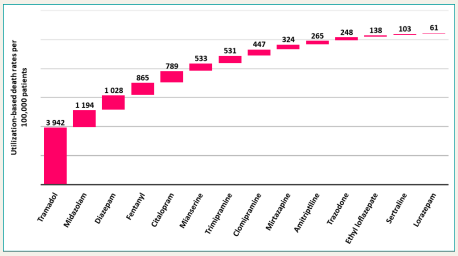


Fig. 5 – Highest utilization-based death rates by active substance

CONCLUSIONS

Our results, pointing to an increase in deaths involving psychoactive medicines in which 20% also involve other CNS-acting non-medicinal substances, like illegal drugs and alcohol, highlight the importance of using medicine-related morbi-mortality data as a tool to monitor medicines' misuse and increase the safety of their use.

Although no single source of information fully describes the acute harms associated with the misuse of psychoactive prescription medicines, using a variety of different sources can provide a good overview of the morbi-mortality consequences of prescription drug misuse.

The MisuMedPT project, which also includes a scoping review on misuse of medicines in the European Union, triangulates information on deaths involving psychoactive medicines with consumption data, hospital admissions and poisonings involving these medicines in Portugal. The main conclusions of the project will soon be shared with the scientific community.

Contact Information

Corresponding author: Ana Araújo
Email: ana.araujo@ff.ulisboa.pt

Adverse drug reactions of psychotropic drugs in children

A review of reports to the Portuguese National Pharmacovigilance System

Luísa Prada[1 2], João Fernandes[3], Catarina Santos[1 2], Daniel Caldeira[1 2], Márcia Silva[3] & Ricardo M. Fernandes[1 2]

[1] Laboratory of Clinical Pharmacology and Therapeutics, Faculty of Medicine, University of Lisbon, Lisbon, Portugal
[2] Institute of Molecular Medicine, Faculty of Medicine, University of Lisbon, Lisbon, Portugal
[3] INFARMED – National Authority of Medicines and Health Products- I.P., Directorate for Risk Management for Medicines, Lisboa, Portugal

INTRODUCTION

While there is a growing evidence favoring the treatment of pediatric patients with psychotropic drugs, a vast majority is prescribed "off-label" with entailing risks of under- or overdosing and unwarranted adverse effects (1-3). Further, there is still limited evidence regarding the safety profile of these medicines used across several indications in the pediatric population in daily clinical practice (4,5). Pharmacovigilance databases are a valuable tool to evaluate the safety profile of these drugs in pediatric patients in a real-life setting (6,7).

AIM

This study aims to assess Individual Case Safety Reports (ICSRs) reported with psychotropic medicines in both approved (on-label) and unapproved (off-label) indications in real life clinical practice, in the Portuguese pediatric population.

METHODS

Retrospective analysis of ICSRs of psychotropic drugs concerning patients 0-17 years old reported to the Portuguese National Pharmacovigilance System, between 1 June 2012 and 31 December 2021.

We focused our search on the following drug classes: Anatomical Therapeutic Chemical (ATC) groups N05A (antipsychotics), N05B (anxiolytics), N05C (hypnotics and sedatives), N06A (antidepressants), and N06B (psychostimulants, agents used for Attention Deficit Hyperactivity Disorder and nootropics).

We evaluated patients' demographic data, as well as characteristics and seriousness of adverse drug reactions (ADRs), stratified by age groups, and we assessed whether the use was on-label or off-label, based on the drugs´ approved indications or approved age group.

RESULTS

Between 1 June 2012 and 31 December 2021

A total of 212 ICSRs → With 601 ADRs

Patients' age varied from 0 to 17 years
(median: 12 years, interquartile range: 6).

Male patients
48,1 % (n=102)

Female patients
51,9 % (n=110)

The majority of the cases occurred in patients between 12 and 17 years (50,9%), of which 68 cases (63,0%) were classified as serious.

Most ICSRs were reported by physicians (66,0%), followed by other healthcare professionals (12,7%).

The most commonly reported drugs (43,4%) were psychostimulants (ATC group N06B).

Most reported MedDRA system organ class (SOC)	n (%)
"General disorders and administration site conditions"	76 (35,8)
"Psychiatric disorders"	75 (35,4)
"Nervous system disorders"	64 (30,2)

Most frequent MedDRA preferred terms (PT)	n (%)
"Off-label use"	43 (7,2)
"Drug ineffective"	25 (4,2)

- 92 (43,4%) ICSRs were assessed as off-label use, however, only 43 cases (46,7%) were coded with the PT "off-label use".
- 59 ICSRs related to psychotropic off-label use were classified as serious, representing 50% of the total serious cases (n=118, 55,7%).

CONCLUSIONS

- This study provides an overview of ADRs reported with psychotropic drugs in the Portuguese pediatric population.
- Our findings highlight the need to closely monitor off-label use of psychotropic drugs in children and adolescents.
- There is an urgent need for clinical trials to establish the efficacy and safety of drugs currently being used off-label in the pediatric population.

Literature

Acknowledgements

INFARMED – National Authority of Medicines and Health Products- I.P., Directorate for Risk Management for Medicines, Lisboa, Portugal, Laboratory of Clinical Pharmacology and Therapeutics, Faculty of Medicine, University of Lisbon, Lisbon, Portugal and Institute of Molecular Medicine, Faculty of Medicine, University of Lisbon, Lisbon, Portugal

Materiais Educacionais publicados na ficha do medicamento no Infomed

Clique nas hiperligações para consultar

DCI Medicamento	Público-alvo	Que materiais? Data de publicação *online*
Axicabtagene ciloleucel *Yescarta* **Brexucabtagene autoleucel** *Tecartus*	**Profissionais de saúde:** equipas multidisciplinares dos centros qualificados e responsáveis pela gestão de doentes sob terapêutica com estes medicamentis	**Guia sobre o manuseamento, modo de administração e recomendações para a recolha de amostras de neoplasias malignas secundárias** **Guia sobre a gestão de reações adversas neurológicas graves e de síndrome de libertação de citocinas**
	Doentes	**Cartão de alerta** 31-01-2023
Dexametasona *Ozurdex*	**Doentes**	**Guia** **Versão Áudio do Guia** 13-01-2023
Dostarlimab *Jemperli*	**Doentes**	**Cartão** 06-01-2023
Fentanilo *Fentanilo Sandoz comprimidos sublinguais*	**Médicos:** unidades de tratamento de dor, de cuidados paliativos; serviços de oncologia **Farmacêuticos:** farmácias comunitárias e hospitalares, com serviços de oncologia, dor ou cuidados paliativos	**Guia do prescritor e do farmacêutico**
	Doentes	**Guia do doente e do cuidador** 16-01-2023
Levonorgestrel *Jaydess, Kyleena e Mirena*	**Médicos:** ginecologia, obstetrícia e medicina geral e familiar (consultas de planeamento familiar)	**Guia para profissionais de saúde** 26-01-2023
Ranibizumab *Ranivisio*	**Doentes**	**Guia** **Audioguia** 26-01-2023
Vacina contra a cólera *Vaxchora*	**Profissionais de saúde:** consulta do viajante, centros de vacinação internacional e serviços farmacêuticos hospitalares que dispensem a vacina	**Guia para o médico**
	Doentes	**Guia da pessoa a vacinar/cuidador** 30-01-2023

Compilado por Patrícia Catalão