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From the Editor

In this issue, we continue to publish the works presented at the INFARMED event **Pharmacovigilance: Towards an Integrated Approach**, including studies on the role and intervention profile of **community pharmacies** and of a **hospital adverse reactions clinic**, as well as a reflection on collaboration between **hospital pharmaceutical services** and **regional pharmacovigilance units**. Another interesting study analyzed the attitudes of **dentists** towards reporting adverse drug reactions.

Also in this issue, a brief narrative review on the adverse reaction profile of the opioid **fentanyl**.

Note: Only posters presented in English or with a version in English are published in this issue. For the remainder, please refer to the Portuguese language edition.

Fentanyl: Adverse reactions

In 1986, the World Health Organization (WHO) developed an **analgesic ladder** to provide appropriate pain relief for cancer patients, which includes fentanyl.

This ladder has undergone changes over the years and is currently applied not only in the treatment of cancer pain, but also of acute and chronic non-oncological painful conditions, such as degenerative diseases, musculoskeletal disorders, neuropathic pain disorders, among others. The WHO analgesic ladder continues to be a simple and palliative approach that can reduce pain in around 70% to 80% of patients.

Fentanyl is a powerful analgesic, classified as a strong opioid medication which, being more potent than morphine, is often administered and prescribed in case of severe pain or used together with other anesthesia medications. It has a rapid onset of action and its effects generally last less than one or two hours. It can be administered by intravenous injection, transdermal patches, or orally.

Worldwide, the distribution of opioid analgesic prescriptions is highly variable. Recent years have seen a global increase in the prescription of opioid analgesics, but only the US and Canada are in an "epidemic" situation, while European numbers are much lower. In Portugal, the consumption of fentanyl has strict rules. However, in recent years, the number of prescriptions has increased, making it the **fourth opioid analgesic most commonly sold** in pharmacies, usually in patches or tablets.

INDEX CARD

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Opioids have a profile of adverse reactions that is characteristic of their class, including the potential to induce **physical dependence**. Though this should always be considered, it should not limit the treatment of patients with significant pain.

There are other adverse reactions that may occur when taking opioid medications, including fentanyl (see SPC). The most frequently observed are dizziness, nausea, vomiting, sedation and sweating. The most feared adverse effect of fentanyl is **respiratory depression** due to decreased sensitivity to carbon dioxide, leading to reduced respiratory rate and potentially causing anoxic brain injury and death. This risk decreases when, in the context of anesthesia, the airway is protected by an endotracheal tube. The risk is greater in groups with specific conditions, such as patients with obstructive sleep apnoea.

Another complication that is related to fentanyl **overdose** includes the so-called **wooden chest syndrome**, which quickly induces complete respiratory failure by paralyzing the chest muscles.

Fentanyl poses an exceptionally high overdose risk in humans since the **amount required to cause toxicity is unpredictable**. In its pharmaceutical form, in a recent review by **Cheema E et al (2020)** most overdose deaths attributed exclusively to fentanyl occurred at mean serum levels of 0.025 µg/mL, with a range of 0.005–0.027 µg/mL. According to the profile published online by the **European Union Drugs Agency (EUDA)**, in contexts of consumption of multiple substances, blood concentrations of fentanyl of approximately 7 ng/mL or more have been associated with mortality. More than 85% of overdoses involved at least one other medication and there was no clear correlation showing at what level the combinations were fatal. Part of the increase in mortality does not involve prescription fentanyl, rather being related to **illicitly produced fentanyl, which is mixed or sold as heroin**.

In Portugal, 197 cases of ADRs to fentanyl have been reported so far, most with concomitant medications, and including three cases of overdose. There are reports of some cases of drug addiction, either through use with other drugs or as a prescribed drug for analgesia. According to the Portuguese Institute for Addictive Behaviours and Dependencies (ICAD), 11 of the cases were recorded in 2023 and one of them in 2024, and in eight cases fentanyl was used together with other drugs.

Psychotropic drugs and narcotics such as fentanyl, despite being associated with illicit acts, play an important role in medicine, as long as they are used correctly and appropriately. As some of the most controlled substances in the world, monitoring their use and the occurrence of adverse effects is of the utmost importance

Cristina Mousinho

Selected links:

1. https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/10500/5699%3B
2. https://www.cdc.gov/niosh/topics/fentanyl/risk.html
3. https://www.deco.proteste.pt/saude/medicamentos/noticias/fentanilo-quando-usar-quais-riscos
4. https://www.euda.europa.eu/publications/drug-profiles/fentanyl_en
5. https://health.ucdavis.edu/blog/cultivating-health/fentanyl-overdose-facts-signs-and-how-you-can-help-save-a-life/2023/01
6. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6848196/
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9. https://sigarra.up.pt/reitoria/pt/pub_geral.pub_view?pi_pub_base_id=279129

What do they mean?

ADR	Adverse Drug Reaction
EMA	European Medicines Agency
MA	Marketing Authorization
PL	Patient Information Leaflet
PRAC	Pharmacovigilance Risk Assessment Committee (EMA)
SmPC	Summary of Product Characteristics

ADVERSE DRUG REACTIONS REPORTED BY COMMUNITY PHARMACISTS IN THE LAST 6 YEARS – *A LANDSCAPE ANALYSIS*

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INTRODUCTION

According to the European Medicines Agency (EMA), an adverse drug reaction (ADR) is a noxious and unintended response to a medicine.[1] Community pharmacists (CP), due to their accessibility and frequent interaction with patients, are in a unique position to detect and report ADRs.

AIM

To analyze the individual case safety reports (ICSRs) made by Community Pharmacists to the Portuguese National Pharmacovigilance System (NPS) in the last 6 years.

METHODS

Study Design

- **Observational, Retrospective (01.2018 to 12.2023)**
- **ICSR from Community Pharmacists** (directly to the NPS)

Macro Analysis

- **Number of ICSRs made by Community Pharmacists per year of participation in the NPC**
- **Seriousness of the ICSR**

Demographic Analysis of Patients

- **Age**
- **Gende**

Medicines Analysis

- **ATC Classification***

**Anatomical Therapeutic Chemical*

(Note: Each report may contain more than one suspected medicine, which was counted individually. Thus, the number of ATC codes may be higher than the number of reports.)

ADRs Analysis

- **SOC Group***

**System Orgam Class*, the highest level of MedDRA coding

(Note: If the same report contained more than one adverse reaction belonging to the same MedDRA SOC group, it was counted only once.)

- **ADR described or not in the Summary of Product Characteristics (SmPC)**

Statistical Analysis

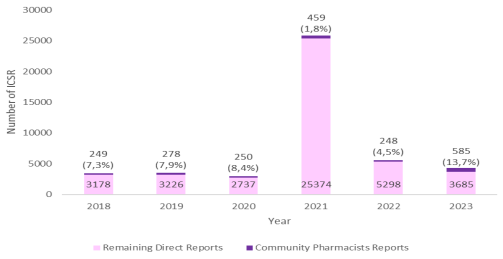
- Descriptive analysis was performed using the *software Statistical Package for the Social Sciences®* (IBM SPSS Statistics) 29.0 version.

RESULTS

Macro Analysis

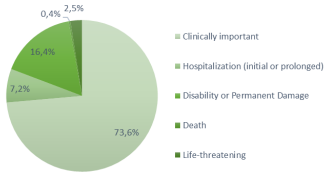
Over six years, the Portuguese NPS collected 34722 ICSRs, of which **2069 (5.9%) were carried out by Community Pharmacists.**

Graphic 1: Number of ICSRs per year



The most reported cases were serious (57.6%), and **the most frequently mentioned seriousness criteria were: "clinically important" (73.6%), "disability or permanent damage" (16.4%), and "hospitalization" (7.2%).**

Graphic 2: Seriousness criteria



Demographic Analysis of Patients

The **median age is 63 years** [IQR 25%: 46; IQR 75%: 73], with **women being the population group with the most reported ICSRs (70.7%)**.

Medicines Analysis

The following table shows the **5 most frequently involved ATC** codes in the reported adverse reactions.

ATC	%
J - Antiinfectives for Systemic Use	32,4%
N - Nervous System	19,0%
C - Cardiovascular System	15,4%
A - Alimentary tract and metabolism	9,3%
M - Musculo-Skeletal System	7,3%

Table 1—Five ATC codes most frequently involved in ICSRs reported by Community Pharmacists in the last 6 years

ADRs Analysis

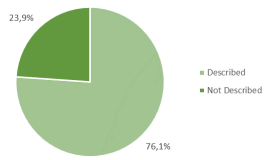
Table 2 shows the **top 10 most reported SOCs**:

SOC	%
General disorders and administration site conditions	23,2%
Gastrointestinal disorders	18,5%
Nervous system disorders	14,0%
Skin and subcutaneous tissue disorders	13,4%
Musculoskeletal and connective tissue disorders	6,9%
Respiratory, thoracic and mediastinal disorders	4,1%
Psychiatric disorders	3,4%
Eye disorders	2,7%
Vascular disorders	2,3%
Product issues	1,6%

Table 2—Top 10 most reported SOCs in ICSRs by Community Pharmacists in the last 6 years

Regarding the description of ADRs in the SmPC, **23.9% were not listed** at the reporting date.

Graphic 3: ADR described or not in the SmPC



DISCUSSION

The analysis of ICSRs by Community Pharmacists reinforces the vital role of these professionals in monitoring the safety profile of marketed medicines. Evidence shows that there was global awareness regarding the administration of vaccines against COVID-19 among community pharmacists, with great concern about reporting ADR. It should also be noted that Community Pharmacists report serious ADRs and, in some cases, are not listed in SmPC, demonstrating that their participation is beneficial. Other studies[2,3] conducted within this professional group mention similar data regarding the most reported drug groups and the most affected SOC by ADRs. Additionally, they mention that the close relationship between Community Pharmacists and patients allows for detecting rare, serious, or specific ADRs in particular population groups.

CONCLUSION

The national data collected may also enable the identification of benchmarks that drive the evolution of the NPS, promoting the increasing participation of Community Pharmacists. Furthermore, their contribution not only improves the safety and efficacy of medicines but also facilitates the early detection of potential associated risks, allowing Regulatory Agencies and healthcare professionals to take appropriate measures to mitigate these risks.

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3. Y. M. Yu, W. G. Shin, J. Y. Lee, S. A. Choi, Y. H. Jo, S. J. Youn, et al..Patterns of Adverse Drug Reactions in Different Age Groups: Analysis of Spontaneous Reports by Community Pharmacists. PLoS One 2015 Vol. 10 Issue 7 Pages e0132916.

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Source: National Pharmacovigilance System – Portal RAM– INFARMED, I.P.

Impact of the activity of the adverse drug reactions clinic in a Tertiary Hospital

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INTRODUCTION

The Clinical Pharmacology Unit (UFC) of the Coimbra Local Health Unit (ULS Coimbra) is responsible for integrating and developing various activities in the field of Clinical Pharmacology, namely Pharmacovigilance. In January 2020, the creation of an external consultation on adverse drug reactions (ADRs) at the ULS of Coimbra was authorised. Traditionally, the reporting rate of suspected ADRs at hospital level has been low, for a variety of reasons, including lack of time, which is why there needs to be a continued commitment to promoting and facilitating reporting.

AIM

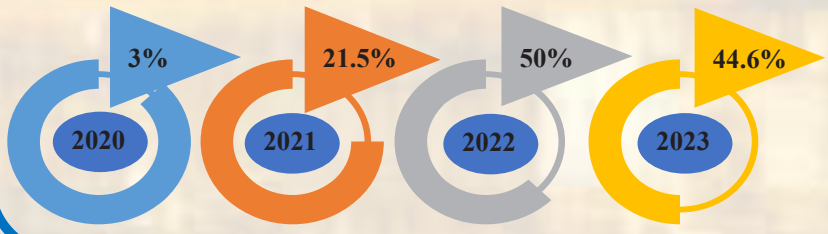
The Adverse Drug Reactions consultation aims to support doctors from the various hospital specialities, facilitating the reporting process and enabling clinical follow-up of patients when appropriate.

METHODS

All the notifications made by the ADR consultants between January 2020 and December 2023 were counted and compared to the total number of notifications made by the tertiary hospital in the same period.

RESULTS

Evolution of the percentage of notifications made by the UFC.



The influence of the ADRs consultation was not limited to making notifications in its consultation, but with the intensive training that was carried out in the services during 2023, it contributed to the hospital having an increase of more than 60 per cent in notifications in 2023 compared to the best previous years.

CONCLUSION

In view of the results presented, we are motivated to be more persevering and to be able to expand our activities, now to Primary Health Care.

This activity is also beginning to show evidence of its importance, particularly with regard to requests for collaboration/opinions for serious adverse reactions, which require more detailed assessment and trigger the need for possible dose adjustments and/or changes in the frequency of administration, as well as the need for rigorous monitoring of both signs and symptoms and parameters that can be assessed from complementary diagnostic tests.

LITERATURE

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	Patients	Card 28-06-2024
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Compiled by Patrícia Catalão