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QT interval prolongation: the relevance of pharmacovigilance

The QT interval is an electrocardiographic measurement of myocardial repolarization. A prolonged interval is associated with an increased risk of developing potentially fatal ventricular arrhythmias. QT values greater than 500ms are associated with a high risk of *torsades de pointes* or polymorphic ventricular tachycardia. Multiple factors can contribute to QT prolongation, including genetic susceptibility, electrolyte disturbances, and the use ofcertain medications.

In fact, several classes of medications, **such as antiarrhythmics, antipsychotics, antidepressants and some antibiotics**, have been implicated in prolongation of the QT interval. These medications induce QT interval prolongation through diverse mechanisms. For example, quinolones and macrolides such as moxifloxacin and erythromycin, respectively, block cardiac potassium channels, leading to delayed ventricular repolarization. A type of interaction of particular relevance is that between drugs with the potential to prolong the QT interval and which are metabolized by **cytochrome P450 3A4** and drugs that inhibit the latter.

Prevention of QT interval prolongation associated with drug iatrogenesis is essential for reducing the risk of potentially fatal arrhythmias. It is crucial to identify **patients at increased risk** due to genetic factors or pre-existing conditions such as heart failure or congenital long QT syndrome. Regular assessment of the QT interval in patients who are prescribed medications that affect cardiac repolarization can be accomplished through simple methods such as resting 12-lead ECG and Holter monitoring.

Early detection of this ADR should lead to **prompt intervention**: discontinuation or adjustment of the dose of the suspected medication should be considered, and electrolyte abnormalities, especially hypokalaemia and hypomagnesemia, must be corrected.

Reporting QT prolongation is essential for efficient pharmacovigilance, as the occurrence of QT prolongation may not be immediately apparent during clinical trials, which often exclude individuals with pre-existing heart disease. However, the late occurrence of torsades de pointes, of other arrhythmias, or even of sudden death, can all make it difficult to establish a clear causal relation, which partly explains underreporting of this QT interval prolongation.

Inês Jordão

Read more **here** about QT interval, medicines and risk of arrhythmia

INDEX CARD

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Compiled by Patrícia Catalão

Portal **RAM**

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Find answers to your questions about the ADR Portal here.

Next: We conclude the presentation of posters for the scientific program of the commemorative event of the 30th anniversary of INFARMED - **Pharmacovigilance: Involving the Citizen**. In this issue of the Boletim: data from pharmacovigilance related to counterfeit medications for erectile dysfunction and reviews of the safety profiles of immune checkpoint inhibitors, anti-TNFα agents, and tirzepatide. Finally, with multiple sclerosis as a case in point, a look at a common clinical difficulty: differential diagnosis between lack of efficacy and manifestation of the natural history of the disease.

THE ERA OF FAKE MEDICINES:
PHARMACOVIGILANCE DATA OF COUNTERFEIT MEDICINES USED IN ERECTILE DYSFUNCTION

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INTRODUCTION & AIMS: Substandard and falsified (SF) medicines are a public health problem almost overworld (1). SF medicines can be classified into 3 categories: substandard, unregistered/unlicensed, and falsified medicines. The regular use of SF medicines can lead to therapeutic failure or drug resistance as well as unknown adverse events, thus constituting a significant risk to the public health. There are several therapeutic classes that have been counterfeited mainly antiretrovirals. Notwithstanding, counterfeit medication used for the treatment of erectile dysfunction (ED) has also emerged in the illegal market. Among these SF medicines, sildenafil citrate is one of the most prevalent examples (2).

Herein, it is presented a brief analysis that aimed to identify and describe the cases (including the adverse drug reactions) related to counterfeit medication indicated for the treatment of erectile dysfunction (ED).

METHODS: This analysis was carried out based on EudraVigilance data for all Individual Case Safety Reports (ICSRs) obtained in the context of post-authorization monitoring for active substance(s) belonging to the ATC group G04BE used in the treatment of ED. The search was based on ICSRs which included at least one of the following preferred terms (PT): Counterfeit product administered; Product counterfeit; Product label counterfeit; Product packaging counterfeit; Suspected counterfeit product; Adulterated product; Product tampering or Suspected product tampering (3).

RESULTS & DISCUSSION: According to the EudraVigilance database, 77% ICSRs of counterfeit products were from non-European Union countries whereas 23% corresponded to European Union (EU) countries, mainly Germany. Most cases were reported on 2012/13 and only few were reported in the last three years probably due to the COVID-19 pandemics (**Fig.1**).

About 60% of ICSRs were considered as serious adverse drug reactions (ADR), among which 19.4% and 5.8% led to hospitalization and death, respectively (**Table 1**). Sildenafil followed by Tadafil were the most prevalent medicinal products that were reported. Nevertheless, it should be highlighted that only 29.7% of searched PT terms corresponded to "counterfeit product administered" while most cases (47.7%) were related to "suspected counterfeit product" which reveals that most data still need further investigation. About 46.5% ICSRs of searched PT terms were coded with "ineffective drug" or similar and 68% were coded with at least one physiopathologic adverse drug reaction (ADR), mainly headache, as reported in literature and product information of these therapeutic drugs.

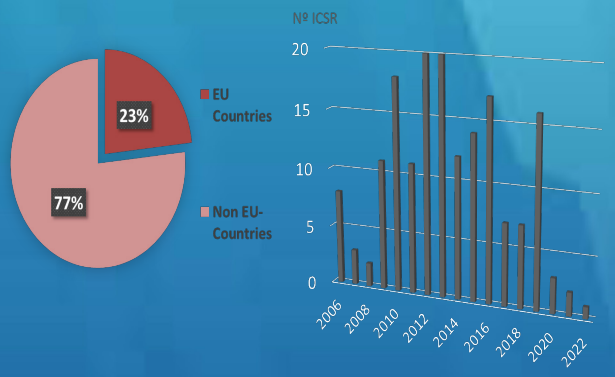

Fig.1. Representation of the number of ICSRs of counterfeit products for ED from EU and Non EU- countries since 2006 to 2022.

Table 1. Summary of main variables correspondent to searched PT of ICSRs of counterfeit products for ED from EU and Non EU- countries since 2006 to 2022 (Note: % Rounded values).

VARIABLES			%
Sex		Male	92.4
		Female	1.7
		Unknown	5.8
Seriousness		Yes	59.9
		No	34.3
		Not known	5.8
Seriousness criteria		Death	5.8
		Life risk	2.9
		Hospitalization	19.4
		Other	71.8
PT	***Counterfection***	Suspected counterfeit product	47.7
		Counterfeit product administered	29.7
		Product counterfeit	22.1
		Product Tampering	0.6
	Efficacy	Drug ineffective	46.5
	ADR	Headache	4.7
		Erection increased	2.7
		Dizziness	2.4
		Myocardial infarction	2.0
		Malaise	2.0
		Nausea	2.0
		Loss of consciousness	2.0
		Hypertension	1.7

CONCLUSION: Overall, these results showed that both counterfeit medicines used for ED and the respective ICSRs clearly deserve to be monitored. Nevertheless, there are still limited data regarding the prevalence of these medicines (among many others) and their impact in terms of ADR. Moreover, as many of those SF medicines (including herbal supplements formulated with this type of drugs) are ordered online and not always detected in customs besides several patients still do not report the ADR probably due to a stigma perspective, this reality represents a real challenge for pharmacovigilance monitoring. A special and shared effort should be undoubtedly welcome from all health authorities synchronized with other governmental systems in order to overcome this huge challenge and detect the SF medicines´ market at "real time", thus ensuring the main goal on public health – the use of safe medicines.

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Immune checkpoint inhibitors and cardiac events

A pharmacovigilance database analysis

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INTRODUCTION

The development of immune checkpoint inhibitors (ICIs) was a turning point in cancer therapy. ICIs rely on the immune system to be effective, and it is also through the immune system that their main adverse drug reactions (ADRs) arise [1]. In this context, myocarditis is relevant due to its relation to the mechanism of action, incidence, and difficulty of diagnosis. However, meta-analyses performed on cardiac toxicity induced by ICIs [2] showed that other cardiac disorders could have a higher incidence, redirecting the discussion.

OBJECTIVE

Contribute to this topic with the characterization and analysis of cardiac events reported to the Portuguese National Pharmacovigilance System and related to the use of ICIs.

METHODS

Retrospective analysis of individual case safety reports (ICSRs) reported to the Portuguese National Pharmacovigilance System, since 28 December 2010 (reporting date of the first ICSR of interest) until 30 November 2022.

ICSRs inclusion criteria:

- ICIs reported as suspect/interact drug;
- Had at least one ADR belonging to the primary MedDRA system organ class (SOC) "Cardiac Disorders".

The cardiac diseases reported were grouped into the categories used in clinical practice [3].

RESULTS

Total of 799 ICSRs

33 cases had at least one ADR encompassed by the primary MedDRA SOC "Cardiac Disorders" corresponding to a total of 38 ADRs.

21 types of cardiac disorders reported	
Arrhythmias	n=16 (42%)
Pericardial disorders	n=10 (26%)
Myocarditis	n=4 (11%)
Coronary artery disease	n=3 (8%)
Heart failure	n=2 (5%)
Cardiomyopathy	n=2 (5%)
Others	n=1 (3%)

31 (94%) ICSRs were classified as serious. Of these:

n=12 (36%) Clinically important
n=6 (18%) Hospitalization occurred or was extended
n=2 (6%) Assessed as life threatening
n=11 (33%) Patient died

CONCLUSIONS

- This study follows up on the possible association of ICIs and cardiac events other than myocarditis, with a higher impact than initially expected by their mechanism of action.
- The seriousness of cardiac ADRs and the progressive increase in patients on ICIs therapy reinforce the need for further studies on the mechanism and pattern of cardiac events manifestation in this setting.
- For this purpose, pharmacovigilance databases add an important complement to the safety analysis performed in clinical trials.

References: [1] Haanen J et al. Annals of Oncology. 2022; 33: 1217-1238; [2] Dolladille C et al; European Heart Journal. 2021; 42: 4964–4977; [3] Lyon R et al. European Heart Journal. 2022; 43: 4229–4361

The pharmacogenomic biomarkers and safety profile of immunosuppressive medicinal products anti-TNF-α

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Background: Anti-TNF-α agents are generally well tolerated, with minor common adverse effects and not needing drug discontinuation. However, serious adverse effects have occurred, the most common being of severe infections. Pharmacological therapy has side effects, which can lead to non-adherence to medication by users. Thus, it is important to ensure the efficacy and safety of this therapy. This is achieved by identifying pharmacogenomic biomarkers that can predict the response of these immunosuppressive medicines, preventing the occurrence of adverse reactions, toxicity, or lack of efficacy.

Objectives: The main goal of this project was to identify, describe, characterize and classify the scientific evidence associated with the use of pharmacogenomic biomarkers in the treatment of autoimmune diseases with anti-TNF-α agents.

Methods: The work was developed in two phases: i) a search for pharmacogenomic biomarkers in the summaries of products characteristics (SmPC) of anti-TNF-α agents; and ii) a systematic literature review based on the data obtained in the first phase, with the principal objective of finding studies in international literature that could describe and characterize the biomarkers founded before and possibly identifying other relevant biomarkers. The second phase is in process. Finally, the levels of evidence and recommendation grades will be classified for every study.

Results: As preliminary results, 7 anti-TNF-α agents (L04AB) were identified on the ATC/DDD Index 2023, but only 3 of them have marketing authorization in Portugal. In the phase I search, any pharmacogenomic biomarker was identified during the SmPC screening. For phase II, in the systematic literature review, the search is based on the following query: (((efficacy) OR (effectiveness)) AND ((safety) OR (surveillance) OR ("adverse drug reactions")) AND (("Tumor necrosis factor-alpha (TNF-alpha) inhibitors") OR ("anti-TNF-alpha") OR ("Anti-tumor necrosis factor (TNF)-alpha") OR ("anti-TNF-α drugs"))). The systematic review screening is in progress, with a view to identifying relevant information about pharmacogenomic biomarkers and classifying the evidence levels and recommendation grades.

Conclusions: Most pharmacogenomic variants are not studied or acknowledged by the pharmacogenomic tests and still need more scientific research that confirms their usefulness, namely to innovative medicines like anti-TNF-α agents. Besides, genotyping of patients is not common clinical practice. According to the potential biomarkers identified during the systematic literature review, a set of recommendations should be proposed.

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Tirzepatide: a systematic review

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Introduction

Type 2 Diabetes is a chronic and metabolic disease characterized by hyperglycemia due to inadequate insulin secretion or to insulin resistance . The ideal therapies are those capable of reducing blood glucose levels with a lower risk of hypoglycemia and weight gain

GLP-1 receptor agonists (GLP-1 RAs) have been first approved in 2005, which have proven very effective and now they are the first-choice injectable drugs for the treatment of Type 2 Diabetes

Type 2 Diabetes and Tirzepatide

More recently, it has been hypothesized that the combination of GLP-1 RAs with GIP receptor agonists (GIP RAs) would provide more effective glycemic control along with a significant weight reduction effect. A new drug – Tirzepatide -was developed based on a synthetic peptide that acts as an agonist of both GLP-1 and GIP receptors, producing a greater insulin response

Some studies have highlighted the safety and efficacy of two incretins in the control of glycemia and body weight. Since diabetes is a complex pathology, in many cases has associated co-morbilities, it is important to deepen the study of the safety of Tirzepatide to prevent and predict possible adverse events

Objectives

To define, evaluate and summarize information from relevant studies on Tirzepatide, its efficacy and any adverse events it may cause

This systematic review allows to have an updated summary of the scientific evidence about this new antidiabetic drug

Methods

A literature search was conducted in PubMed/Medline, up to February 20, 2023

Using the following medical subject heading terms and keywords: (tirzepatide) AND (“type 2 diabetes”) AND (“randomized controlled trial”)

A table and a concept map were created to summarize the collected data, following the PICO criteria

Results

Of the 174 items, 47 were selected as they corresponded to the selection criteria

Randomized controlled clinical trials or articles in which the safety profile of the drug was analysed in people with Type 2 Diabetes treated with Tirzepatide or other comparator agents

Treatment and severe adverse events were analyzed in all Randomized Controlled Clinical Trials and were compared with other antidiabetic agents or with a placebo

In most cases, the incidence of Tirzepatide effects was higher when compared to the placebo, but similar to the other antidiabetics

The adverse events encountered

Were, mainly, gastrointestinal ones with dose-dependent increased odds of nausea, vomiting and diarrhea, like those experienced by patients treated with GLP-1 RAs	Hypoglycemia has also been considered and occurred in some patients receiving Tirzepatide, with a lower incidence when compared with other drugs such as insulin glargine	Other adverse events included injection site reactions, pancreatitis, cholecystitis, hypersensitivity and mortality, all these had a low incidence and some of these events were not always attributable to the treatment

Conclusions

- This review is useful to have a general picture of the safety of the new antidiabetic drug Tirzepatide, approved in the United States in 2022.
- This review contributes to SDG 3 of the United Nations 2030 agenda.
- Since the only data available so far are the results of randomized controlled clinical trials , it is important to understand and know the possible adverse effects that may occur during the treatment.
- As the target patients are frail subjects, who often have pathologies related to diabetes that worsen the clinical situation, it is essential to minimize treatment-related and severe adverse events that can compromise the patient's health, such as severe hypoglycemia and pancreatitis.

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Disease manifestation or therapeutic ineffectiveness?

THE EXAMPLE OF MULTIPLE SCLEROSIS

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INTRODUCTION

- Multiple sclerosis (MS) relapses are triggered by a combination of several factors and often cause some anxiety in the patient [1], especially if they coincide with a recent change in therapy.
- When the manifestation of disease can result from several factors, it can be very difficult to differentiate the cases in which there is ineffectiveness of therapy [1].
- According to the rules for coding adverse drug reactions (ADRs) in pharmacovigilance, when a lack of efficacy is coded, its manifestation should not be coded at the same time.

This is a concern identified in clinical practice and pharmacovigilance.

METHODS

- Retrospective analysis of individual case safety reports (ICSRs) reported to the Portuguese National Pharmacovigilance System.
- Between 1 January 2011 and 31 December 2021.
- Criteria for inclusion of ICSRs:
  - At least one of the DMTs for MS was identified as a suspect/interacting drug;
  - Therapeutic indication included a MedDRA term encompassed by the high level term (HLT) "multiple sclerosis acute or progressive";
  - At least one ADR covered in HLT "multiple sclerosis acute or progressive" and/or HLT "therapeutic and non-therapeutic responses".

OBJECTIVES

Characterise and analyse the cases reported to the Portuguese National Pharmacovigilance System whose ADRs are the manifestation of the disease and/or the lack of efficacy of disease-modifying therapies (DMTs) in MS.

RESULTS

Total of 3,952 ICSRs

With at least one of the DMTs for MS identified as a suspect/interacting drug and its therapeutic indication included a MedDRA term encompassed by the HLT "multiple sclerosis acute or progressive".

The three drugs most reported were:

Interferon beta-1a (n=248)
Interferon beta-1b (n=123)
Fingolimod (n=99)

Of these cases:

633	Had an ADR only covered in HLT "acute or progressive multiple sclerosis"
22	Had an ADR only convered in HLT "therapeutic and non-therapeutic responses"
59	Had both HLTs

ICSRs classified as serious: 48% (n=343)
Principal seriousness criterion - **Clinical importance 68% (n=232)**

CONCLUSIONS

The difficulty to draw a line between what is a disease manifestation and what is an ADR of treatment ineffectiveness is reflected in the overlapping of adverse reactions codification.

This overlap adds "noise" to the pharmacovigilance system and could lead to interpretation biases.

This question is particularly relevant in MS and, in clinical practice, this may have implications in medication adherence and therefore in disease progression.

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INN Medicinal product	Target	Materials Online publication date
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Teriflunomida Sandoz	**Physicians:** neurologists	Guide
	Patients	Card 21-09-2023
Tremelimumab *Imjudo*	**Patients**	Card 12-10-2023

Compiled by Patrícia Catalão

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