



Original Research

Language does not come “in boxes”: Assessing discrepancies between adverse drug reactions spontaneous reporting and MedDRA[®] codes in European Portuguese

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Abstract

Background: The description of adverse drug reactions (ADRs) by health care professionals (HCPs) can be highly variable. This variation can affect the coding of a reaction with the Medical Dictionary for Regulatory Activities (MedDRA[®]), the gold standard for pharmacovigilance database entries. Ultimately, the strength of a safety signal can be compromised.

Objective: The objective of this study was to assess: 1) participation of different HCPs in ADR reporting, and 2) variation of language used by HCPs when describing ADRs, and to compare it with the corresponding MedDRA[®] codes.

Methods: A retrospective content analysis was performed, using the database of spontaneous reports submitted by HCPs in the region of the Southern Pharmacovigilance Unit, Portugal. Data retrieved consisted of the idiomatic description of all ADRs occurring in 2004 (first year of the Unit activity, $n = 53$) and in 2012 ($n = 350$). The agreement between the language used by HCPs and the MedDRA[®] dictionary codes was quantitatively assessed.

Results: From a total of 403 spontaneous reports received in the two years, 896 words describing ADRs were collected. HCPs presented different levels of pharmacovigilance participation and ADR idiomatic descriptions, with pharmacists providing the greatest overall contribution. The agreement between the language used in spontaneous reports and the corresponding MedDRA[®] terms varied by HCP background, with nurses presenting the poorer results than medical doctors and pharmacists when considering the dictionary as the gold standard in ADRs' language.

Conclusions: Lexical accuracy and semantic variations exist between different HCP groups. These differences may interfere with the strength of a generated safety signal. Clinical and MedDRA[®] terminology training should be targeted to increase not only the frequency, but also the quality of spontaneous reports, in accordance with HCPs' experience and background.

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Introduction

Pharmacovigilance, as defined by the World Health Organization (WHO), is the science and activities related to detection, assessment, understanding and prevention of adverse drug reactions (ADRs).¹ Several methods are available to improve knowledge on ADRs,² of which spontaneous reporting (SR) has been considered an effective way to collect such information.³ It enables health care professionals (HCPs), and recently also patients, to voluntarily submit new information about serious or unknown ADRs.^{2,4,5} One of the major limitations of SR is under-reporting; being estimated that fewer than 10% of all ADRs are reported.⁶ Nevertheless, SR is the most widely used method to detect ADRs by pharmacovigilance systems worldwide.^{2,4,5,7} It is also the recommended system in the European Union.^{2,8}

An important pharmacovigilance activity is the coding of reported ADRs in SR.⁹ It requires reading and interpreting the reported information and its coding by using a special dictionary.^{1,10} The use of the Medical Dictionary for Regulatory Activities (MedDRA[®]) is mandatory in the European Union and Japan.^{11–13} MedDRA[®] is a large terminology covering medical signs, symptoms, syndromes and diagnoses, social conditions, surgical and medical procedures as well as clinical investigations. It comprises of 26 vertical axes, the system organ classes (SOCs), divided by High Level Group Terms (HGLT), Preferred Terms (PT), and finally, Lower-Level Terms (LLT).⁹ The spontaneous reports about ADR come generally as free idiomatic text. Information is then coded into MedDRA[®] terms and the following procedures facilitate the detection of a signal.^{12,14} A pharmacovigilance signal, as defined by the WHO, is a reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented.¹⁵ To generate a signal, more than a single report is required and the strength of it is dependent on the event and quality of the information made available. Pharmacovigilance databases are retrieved and statistical methods are applied to calculate possible associations between ADRs and a drug. All signals are deemed worthy of investigation, and if the data retrieved are inconclusive, other methods to assess the validity of the information are needed. These can be post-marketing surveillance studies, which generally take some time to produce results, therefore delaying the triggering of regulatory action.

Signal detection is an essential part of drug safety surveillance. The goal of signal detection is to identify ADRs that were previously considered unexpected, and help regulatory agencies to take action in a way that protects patients.¹⁶

The language used to describe ADRs can have an impact when choosing the appropriate code. In this sense, language plays an important role in the description of ADRs, since it can add uncertainty to the signal generation process. The Lower-Level Terms (LLT) correspond to the greatest linguistic variation and are the ones used to code ADRs. Case reports are stored in databases that constitute putative knowledge on suspected ADRs.¹¹ The detection of relationships between a combination of terms and levels of the MedDRA[®] dictionary has received researchers' attention, contributing to the solution of semantic entanglements.^{8,11,12}

HCPs participating in pharmacovigilance systems have their own education, current lexicon and ethos, which is embedded in the societal and individual frames. The way to use language in ADR spontaneous reports is not necessarily uniform, even when using standardized procedures.^{8,12} Coding activities are described as time-consuming, deriving from the natural ambiguity of the reported information. Clarity is needed to remove ambiguity and to be able to transform information into a code with biomedical relevance.⁸

The aim of this study was to investigate the participation of different HCP in ADR reporting. From that analysis, variations in the language used by the different will also be assessed, controlling for independent variables, such as the pharmacovigilance system maturity.

Methods

Study design

The study was designed as an exploratory retrospective content analysis of spontaneous ADRs reports.

Data source

The data retrieved consisted of all spontaneous reports submitted by HCPs during the years 2004 and 2012 and registered in the Portuguese Southern Pharmacovigilance Unit (UFS) ADR database. This Unit was established in 2004, and it covers the southern administrative districts of Portugal. The database is kept in both electronic and paper formats. In this Unit, two

pharmacovigilance officers trained by the Maintenance and Support Services Organization, the organization responsible for MedDRA[®], perform the tasks of receiving the incoming spontaneous reports, analyzing and providing the initial codes to be attributed to the ADRs. These ADRs have a causality assessment performed by an expert (usually a clinician), which includes validation of reports interpretation and subsequent final validation of the MedDRA[®] codes.

The reports contain the idiomatic description of the ADR, HCP identification (profession and gender), origin of the report and setting of the notification. Patient's age, gender, concomitant medication and the outcome of the ADR are also available. The study addressed language variation in reports sent in by different HCP, thus data extraction focused on the verbatim of the original reports, plus the corresponding MedDRA[®] codes that were attributed. Some ADR descriptions corresponded directly to MedDRA[®] codes, while other accounts needed to be interpreted by pharmacovigilance officers.

Each MedDRA[®] code can be composed by one single term, or up to several conjoint terms. Spontaneous reports wording were compared with the awarded MedDRA[®] codes. Only prosodic words, i.e. those with semantic content, were analyzed. Reflecting the lexical and semantic discrepancies, a dichotomous key to describe the univocal correspondence between each ADR clinical description and the coded MedDRA[®] term was built. This key corresponded to an agreement index, with the value 0 representing an imperfect fit, while 1 represented a perfect fit, the index being a simple mean of all analyzed reports. In other words, the outcome evaluated is the exactness of the words describing the ADR compared with the MedDRA[®] code that was awarded: if the spontaneous report wording was exactly the same as the MedDRA[®] code given, then the index equals 1. The study was based on the quantitative fit between ADR wording and the MedDRA[®] codes used; therefore no assessment of the verbatim content was attempted.

For the data extraction, a matrix with several parameters was developed. This matrix included information about the type and gender of HCP, detailed origin and report presentation, verbatim of the ADR, agreement between the ADR description and MedDRA[®] code, discrepant words and age and gender of the patient. The data extracted were independently checked by two researchers and then coded by one researcher. After the reports were coded, the consistency of

the information was checked by the other researcher, and a consensus was reached on the final classification to be attributed to the cases. All personal identification data were already encrypted, guaranteeing the complete anonymity of all participants. Nonetheless, the data was handled with strict confidentiality, within the usual requirements for pharmacovigilance data.

Study data were statistically analyzed using SPSS[®] v20 (IBM Corporation), through descriptive statistics with a type I error level of $P < 0.05$. To evaluate the influence of variables, (such as the notification geographical origin (district) and HCP working setting and professional background) non-parametric statistics were employed (Mann–Whitney U and Kruskal–Wallis χ^2).

Results

This study made a comparison between the ADR reports of 2004 and 2012. There are clear differences between the two years: 2004 was the first year that the pharmacovigilance unit collected ADR reports, while in 2012 the system already had greater maturity. The expected results will take into consideration the different proportions of information of the two years in analysis. One of the derived objectives of the study was to perceive the maturity of the pharmacovigilance system, especially regarding the language progression in both years.

A total of 403 reports were included in the study, 53 (13%) from 2004 and 350 (87%) from 2012. This corresponded to 130 and 766 reported ADRs, respectively (Table 1), i.e. 14.5% ADRs in 2004 and 85.5% in 2012. Community pharmacists had the highest relative ADR reporting activity in 2004 and 2012, although hospital pharmacists have become an almost as common source of reports in 2012 (relative reporting activity 16.9% vs. 13.4% in 2012, respectively). GPs contributed less to the system in 2012 than in 2004. The reports sent by nurses were more numerous in 2012.

By region, the District of Beja had the highest relative spontaneous reporting activity per 1000 inhabitants in 2004 (Table 1), but Faro was the greatest contributor in 2012, particularly in terms of reporting ADRs in prosodic words (Table 2).

Comparison of prosodic words and MedDRA[®] terms describing ADRs in spontaneous reports

For the two years in analysis, a total of 896 words describing ADRs were collected (Table 2).

Table 1

Number of spontaneous ADR reports submitted by health care professionals in 2004 and 2012 by professional group (reports per 100 professionals) and geographical region (reports per 1000 inhabitants in the region)

Number of spontaneous ADR reports	2004	2012
	<i>n</i> [Ratio 1 (%)]	<i>n</i> [Ratio 2 (%)]
Professional group^a		
General practitioners	16 [0.9 (30)]	16 [0.6 (4)]
Hospital specialists	12 [0.6 (23)]	38 [1.3 (11)]
Community pharmacists	37 [0.7 (42)]	153 [16.9 (44)]
Hospital pharmacists	0	121 [13.4 (35)]
Nurses	3 [0.1 (5)]	21 [2.2 (6)]
Dentists	0	1 (0)
Total	53 [100 (100)]	350 [100 (100)]
Geographic region^b		
Beja	22 [0.2 (42)]	37 [0.3 (11)]
Evora	10 [0.1 (19)]	77 [0.5 (22)]
Faro	20 [0.1 (38)]	216 [0.5 (62)]
Portalegre	1 [0.0 (1)]	20 [0.2 (5)]
Total	53 [100 (100)]	350 [100 (100)]

n = number of spontaneous ADR reports submitted in a given year (2004 or 2012); Ratio 1 Prof. Group = number of spontaneous ADR reports submitted by each group of health professionals working in the region covered by the Portuguese Southern Pharmacovigilance Unit (UFS) compared to the total number of each health professionals during the year 2004; Ratio 1 Geo. Region = number of spontaneous ADR reports submitted by each district in the region covered by the Portuguese Southern Pharmacovigilance Unit (UFS) compared to the total number of inhabitants in that region during the year 2004; Ratio 2 is equivalent to Ratio 1, but in 2012.

^a Portuguese Ministry of Health.^{16,17}

^b Portuguese National Census.^{18–21}

The agreement between the language used in spontaneous reports and the corresponding MedDRA[®] codes varied by professional background (Table 2, Fig. 2), with nurses presenting the worst results. The total of prosodic words to describe ADRs submitted by health professionals from each geographical location are also presented in Table 2.

No statistically significant associations were found in 2004, while in 2012 there were significant influences on the agreement index from professionals' setting (Fig. 1), background (Fig. 2) and geographical location (Fig. 3), respectively, a Kruskal–Wallis χ^2 of 23.167 ($P < 0.001$), 10.362

($P = 0.035$) and 30.575 ($P < 0.001$). It was possible to confirm that working within the community pharmacy and the hospital setting (Fig. 1), as well as in the Évora District (Fig. 3), presents an agreement index significantly higher than other work settings and locations. All health care professionals performed above the mid score (50%) in their ADR descriptions performance, except for nurses (Fig. 2).

Linguistic data

In 2004, HCPs used on average 6.6 prosodic words (SD = 3.6) to describe a single ADR, whilst in 2012 that number increased to 7.5 words (SD = 6.5) (Table 3). In 2004, the number of prosodic words needed on average to produce one single MedDRA[®] code was 1.60 (SD = 0.70), while in 2012 that number increased to 1.83 words (SD = 0.79). The contribution per HCP group in the number of words to describe an ADR also changed in the two years in analysis: in 2004, community pharmacists were the ones sending the higher total number of words, followed by general practitioners (GP), hospital medical specialists, and finally nurses. As for 2012, community pharmacists continued to be the biggest group to provide lexical volume, followed by hospital pharmacists, hospital medical specialists, GPs, nurses and dentists.

Despite the number of different words used to describe ADRs, there was still the need for the pharmacovigilance officers to complement or clarify ambiguous information from spontaneous reports. In 2004, there was a need to add 1 additional MedDRA[®] code, while in 2012 there was a need to add 22 new codes to the general classification of the ADRs received (Table 3).

Discussion

General findings

This study compares two distinct years, with a time difference of 8 years. A direct comparison can be made between the two, as the exact same data was collected in the same way for both years. Nevertheless, some caution is needed, since the number of practicing HCPs is different, having increased in 2012.^{17,18} Also, the first year of pharmacovigilance unit work should differ from 8 years later, when more training in drug safety is expected, with a correspondent rise in the number of reported ADRs. Some other factors, such as occasional safety problems from the drugs in the

Table 2

Distribution of prosodic words and MedDRA[®] terms describing ADRs in reports according to professional background and geographical region

	2004			2012		
	Total ADRs in prosodic words ^a	Total ADRs in MedDRA [®] codes ^b	Number of MedDRA [®] codes & agreement index [1 (%)] ^c	Total ADRs in prosodic words ^a	Total ADRs in MedDRA [®] codes ^b	Number of MedDRA [®] codes & agreement index [1 (%)] ^c
Health care professional	Per 100 professionals (%)	Per 100 professionals (%)		Per 100 professionals (%)	Per 100 professionals (%)	
GP	187 (10.0)	55 (3.0)	39 (30.0) [29 (18.8)]	256 (8.8)	66 (2.3)	34 (4.4) [24 (3.1)]
Hospital specialist	159 (8.5)	50 (2.7)	30 (23.1) [18 (13.8)]	970 (33.5)	144 (5.0)	84 (11.0) [48 (6.3)]
Hospital pharmacist	0 (0)	0 (0)	0 (0) [0 (0.0)]	1855 (205.6)	502 (55.6)	265 (34.6) [155 (20.2)]
Community pharmacist	477 (69.3)	89 (12.9)	54 (41.5) [32 (24.6)]	1996 (221.3)	564 (62.5)	335 (43.7) [202 (26.4)]
Nurse	38 (0.9)	15 (0.3)	7 (5.4) [3 (2.3)]	640 (12.1)	119 (2.2)	46 (6.00) [39 (5.10)]
Dentist	0 (0)	0 (0)	0 (0) [0 (0.0)]	18 (3.9)	5 (1.1)	2 (0.26) [0 (0.0)]
Total	861 (100)	209 (100)	130 (100)	5735 (100)	1400 (100)	766 (100)
Geographical region	Per 1000 inhabitants n (%)	Per 1000 inhabitants n (%)		Per 1000 inhabitants n (%)	Per 1000 inhabitants n (%)	
Beja	168 (0.7)	46 (0.2)	24 (18.5) [11 (8.5)]	686 (2.9)	150 (0.6)	82 (10.7) [66 (8.62)]
Évora	371 (2.2)	76 (0.5)	53 (40.8) [37 (28.5)]	1244 (7.3)	306 (7.3)	169 (22.1) [99 (12.9)]
Faro	319 (0.8)	86 (0.2)	52 (40.5) [33 (25.4)]	3463 (7.7)	871 (1.9)	472 (61.6) [234 (30.5)]
Portalegre	3 (0.03)	1 (0.1)	1 (0.3) [1 (0.7)]	342 (2.9)	73 (0.6)	43 (5.6) [19 (2.5)]

^a Total ADRs in prosodic words ($n = 861$) correspond to the total number of prosodic words presented in the spontaneous reports submitted by healthcare professionals ($n = 403$).

^b Total ADRs in MedDRA[®] codes corresponds to the total number of MedDRA[®] codes present at the spontaneous reports submitted by healthcare professionals adjusted by the codification process of the pharmacovigilance unit.

^c Agreement index: the mean value attributed to the perfect fit between prosodic words and a MedDRA code, with 0 representing imperfect fit and 1 perfect fit, and distributed by percentage of total amount of codes per each professional group.

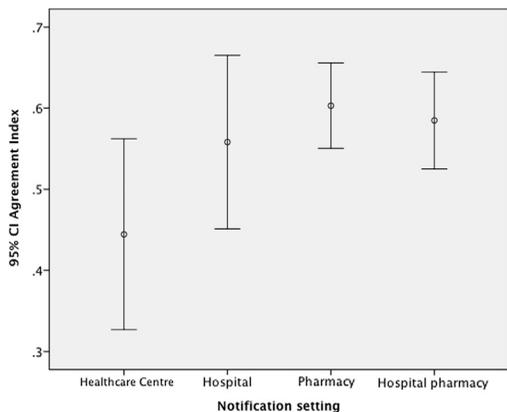


Fig. 1. Agreement index versus notification setting in 2012.

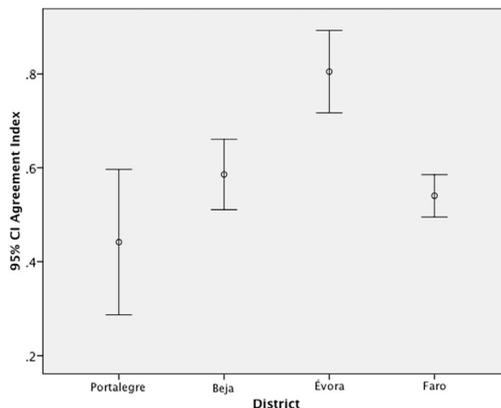


Fig. 3. Agreement Index versus district of notification in 2012.

market or the fact that some groups of HCPs might receive different influences to report, might also affect the results.

The pharmacovigilance system in Portugal is made of decentralized units. The change to a decentralized model was supposed to encourage a more direct contact with HCPs, provide training and strengthen cooperation with universities.¹⁹ The number of spontaneous ADR reports submitted by HCP has been increasing in Portugal in the past few years, reaching a national total of 2696 reported ADRs in 2012.²⁰ In the period of 2009–2011, the number of SR registered rose by 39%.²⁰ This trend was also clear in the region covered by the present study; during this period the number of reported ADRs increased six-fold.

The region in analysis had an index of 155.8 reports per million inhabitants, higher than the

national index of 110.4 reports per million inhabitants.²⁰

Comparing both years, there are some differences to take into account: in 2004, medical doctors were the group that most reported, followed by pharmacists. In 2012, this situation was inverted, with pharmacists providing over two-thirds of reports. The participation of nurses and other HCP was low for both years in analysis.

For this study, pharmacists were divided in two distinct groups: community and hospital pharmacists. The contribution of hospital pharmacists was especially noteworthy in 2012, taking into account that in 2004 there was no report coming from this group. This might be a result of better pharmaceutical training, and the fact that professionals are more aware of drug-related issues.²¹

Medical doctors have been decreasing their participation in the SR system. Possible reasons might be a lack of specific training in drug safety, too much time consumed in administrative tasks

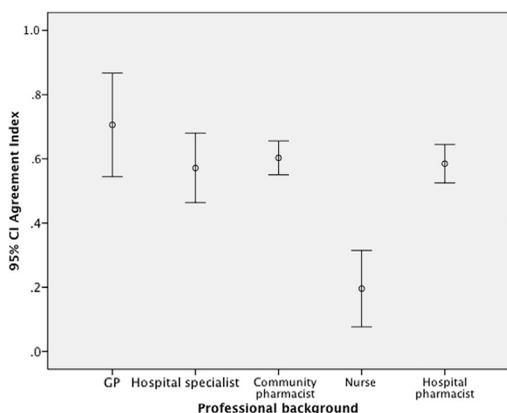


Fig. 2. Agreement Index versus professional background in 2012.

Table 3
Linguistic data in prosodic words describing 1 ADR and 1 MedDRA[®] code and additional codes needed in 2004 and 2012

	2004 Mean (SD)	2012 Mean (SD)
Prosodic words need to describe 1 ADR	6.6 (3.6)	7.5 (6.5)
Prosodic words forming 1 MedDRA [®] code	1.6 (0.7)	1.8 (0.8)
Additional MedDRA [®] codes added	1	22

or indifference.²² Ideally, the pharmacovigilance centre would provide more training actions. Some studies have suggested that there is a need for repeated specific training in order to maintain the reporting ratios.⁵

In both years, nurses provided a low number of reports. The involvement and encouragement of nurses, the largest group of active professionals by number, can bring immediate value in reporting.^{23,24} It is also noteworthy that nurses are reporting in a smaller number in this region when compared to others in Portugal, where this group is the biggest provider of spontaneous reports.²⁰ Other HCPs, such as dentists, presented a frequency of reporting and an agreement index that are not representative of their potential input. Their participation could be improved knowing they work with particular treatments, such as topical medications and medical devices.^{25,26}

Linguistic accurateness in reporting

Spontaneous reporting shows a high degree of linguistic variation to describe ADRs. Ideally, HCPs would use more clinical terminology with less resource to common jargon. Sometimes bizarre or complex ADRs descriptions do not fit into a simple single description, considering the dictionary as the gold standard in ADR language. Due to the nature of the MedDRA[®] dictionary, a clearer use of words by HCPs could help the pharmacovigilance coders to choose the right term for coding an ADR, therefore increasing the strength of a safety signal.

The linguistic congruity to describe ADRs decreased from 2004 to 2012, while it seemed to improve if the ADR reporter was located in a city near to the pharmacovigilance unit (placed in Lisbon). The city of Évora is an example of this (Fig. 3). Although other factors might also explain this result, especially in 2012, such as a larger population of HCPs and more health-related infrastructures, i.e. district hospitals, health care centers and pharmacies.^{17,18} More production and input is expected to also decrease the agreement between dictionary terms and verbatim accounts, due to probable lexical variety and less chances of linguistic accuracy.

A statistical association was found between the setting and the agreement index. Public health care institutions, in particular health care centers, performed worse than community pharmacies. Actually, community pharmacists showed a slight increase in the accuracy of language used from

2004 to 2012 (Table 2). As an example, in 2012 community pharmacists described 564 ADRs that were equivalent to 335 MedDRA[®] codes, being the largest contributors. The agreement index of these ADRs corresponded to 26.4% of the words provided to describe ADRs. These results confirm Portuguese pharmacists concerns with medicines outcomes and safety issues,²¹ which is not necessarily the practice in other European Union countries (e.g. Denmark).^{4,27,28} Sometimes regarded as an “incomplete” or somehow limited profession, having to deal with non-patient and health care oriented issues (e.g. management and stock activities), pharmacists confirm their good position to gather information about ADRs.^{26,29} Results show that pharmacists lexical variety in describing ADRs was high (Table 2), even if this may not correspond necessarily to an overall valuable input. However, as pharmacists deal with less serious types of ADRs, which are supposedly easier to describe, a higher agreement index was expected.

Medical doctors working in health care centers or hospitals have a high probability to come in contact with ADRs,³⁰ particularly those working at hospital level who have contact with patients being treated with newly marketed drugs. Furthermore, several hospitalizations are due to ADRs.³¹ A good agreement between spontaneous written language used to describe ADRs and MedDRA[®] codes coming from medical doctors was expected, as they are expected to be the HCPs who make the most use of clinical jargon.^{5,21} In 2004, GPs described 55 ADRs equivalent to 39 MedDRA[®] codes, with an agreement index of 18.8%. Comparing to 2012, GPs described 66 ADRs, which were coded into 34 codes, with an agreement index of 3.1% for the words provided. Doctors and nurses were the HCPs that showed a greater variation of the agreement index (Fig. 2) between years. This variation might be not only from the different ADRs that these HCPs encounter, but may result from a more complex description of the reactions.²³ Potential lack of awareness of how to complete a spontaneous report, and other factors such as lack of time or diffidence, might as well be to blame.²² Both HCP groups only slightly increased their general participation from 2004 to 2012, despite the growth in the number of working staff and a higher pharmacovigilance visibility (Table 1). In fact, a significant percentage of active HCPs did not submit spontaneous reports.^{17,18} There are reasons to believe that the curriculum

of medical doctors might not have sufficient emphasis in the detection and mitigation of ADRs as a health-related hazard.³²

An additional point in language accuracy concerns is the need for extra MedDRA[®] codes. In 2012, there was a need for more codes introduced by the pharmacovigilance officers to complement the reactions description (Table 3), which is maybe another sign that the clarity of the description is not guaranteed and/or the ADR was not totally covered. Another aspect is the increase in the amount of words needed to code for one ADR (Table 3); not only were more words used, but also there was a higher deviation (i.e. less agreement or accuracy). This shows that the description of the reactions might have proved harder and/or HCPs needed to make use of different words not directly related to MedDRA[®]. A higher number of HCPs reporting in 2012 did not directly translate into a higher accuracy in the direct translation from ADR description into a MedDRA[®] code. This might mean that HCP training, specifically the focus given to reporting of ADRs, is not being translated into better quality of language used in the reports.

Potential issues from using MedDRA[®]

Medical terminologies provide the database blocks upon which are built various methods for detecting signals of new adverse reactions to medicines.⁹ The MedDRA[®] dictionary presents an extensive number of choices within its hierarchy, influencing the number of records listing for ADRs. A direct interpretation of the ADR description and its translation into the MedDRA[®] lingo should introduce limited variation and error in the process of language evaluation made by pharmacovigilance officers, even if officers can usually search for data entry confirmation.⁸ However, the MedDRA[®] dictionary presents an extensive number of choices within its hierarchy, influencing the number of records listing for ADRs. A direct interpretation of the ADR description and its translation into the MedDRA[®] lingo should introduce limited variation and error in the process of language evaluation made by pharmacovigilance officers, even if officers can usually search for data entry confirmation.⁸ However, spontaneous reporting is prone to semantic variation due to its free text modality and there is a degree of specificity of some MedDRA[®] terms, making the correct selection more challenging.³³ This natural

variation might impact on the detection of some security signals, but the quality of the language plays an important part in helping to reduce the background 'noise.' Without questioning the scientific validity and usefulness of the MedDRA[®] dictionary, especially when recognizing its jargon complexity and the dialectal boundaries in spontaneous reporting, it seems clear that all Portuguese professionals should be encouraged to use a more technical description of ADRs.

Despite the political willingness to increase health care professionals' information in the field of drug safety,^{3,19,34} present results indicate that the quality of the language to report ADRs might have deteriorated. The increasing number of common language words and less accurate medical jargon suggest HCPs may have problems when selecting the right MedDRA[®] terms.³³ As an example, if we consider a possible signal of neuropathy, depending on how the individual cases have been reported, these could be represented in many different ways. Single reports of each might fail to reach the threshold required to be recognized as a signal. There are more than 25 different MedDRA PTs containing the word 'neuropathy.'⁹ Although education on medicines risk surveillance is the cornerstone for good quality reporting, active reporting both in quantity and quality is crucial and must become part of continuing medical education and clinical governance.³⁵ In this sense, HCPs might have a need to be better trained in using the specific fields of the spontaneous reporting forms, making an effort on clinical language and MedDRA[®] terms use. One practical implication of the present work is to initiate the development of a compilation of an alphabetical list of ADR-specific terms in the form of a glossary. This, together with a tailored training for each HCP group, should contribute to HCPs reporting with greater lexical accuracy.

Although professionals may be to blame, the dictionary itself raises usage issues. For instance, when introducing further codes to describe the ADRs, the pharmacovigilance centers select terms that should always fall in the lowest level (LLT).³³ The dictionary guidelines state that it may be appropriate to select more than one term, in order not to lose specificity.³³ Although no qualitative investigation was performed, it is possible that some codes were mandatory to be added by the pharmacovigilance unit to adjust for the type of ADRs reported. In this sense, MedDRA[®] responsible organizations should investigate and promote the right balance between standardization

and the dictionary functioning to HCPs needs and capacities. Signal generation is an evolving discipline. It needs to be set in the context of existing variations in approach to signal generation between different organizations and the gap which exists between language and the appropriate MedDRA[®] code. Studies are needed to compare the way in which identical data sets coded with MedDRA[®] and with other terminologies would function in generating and exploring signals using the same methods of detection and evaluation. To support signal generation a terminology should facilitate recognition of medical conditions by using terms which represent unique concepts, providing appropriate, homogenous grouping of related terms. It should allow intuitive or mathematical identification of adverse events reaching a threshold frequency or with disproportionate incidence, permit identification of important events which are commonly drug-related, and support recognition of new syndromes.⁹

The rolling of the new European Union legislation on pharmacovigilance means that both HCP and patients alike will be involved in drug safety regulation. New online tools to report ADRs and an emphasis on quality of reporting have been highlighted.^{7,13} Further evaluations should determine if MedDRA[®] is not only serving its own purposes, but also truly allowing for a proper classification of ADRs. Ultimately, it should also be a factor of reassurance in an active detection of safety signals.

Conclusion

This exploratory study found spontaneous reporting in a Portuguese region to have grown since its beginning in 2004 to the present, with variations in spontaneous ADR reporting frequency and language accuracy between HCPs. There was a considerable contribution from pharmacists, especially at the community level. The study has some limitations, namely the difference in the amount of active HCPs reporting ADRs, which makes it more difficult to assess the validity of the information. Further studies involving a bigger time frame would be required to validate the results. Nevertheless, it showed that the use of language can be a constraint, adding to uncertainty in the choice exist of ADR terminology.

The quality of language in spontaneous reports is a factor to consider in order to have strong drug safety signals. The structure of MedDRA is multi-

axial, so that terms may be present in more than one SOC location at the same level in the terminology. Improvements in the MedDRA[®] dictionary should be devised, adjusting the term organization to facilitate the HCP and patient truthful and thorough participation. Further studies are required to assess the impact of language variation and corresponding MedDRA[®] codes, as safety signals generated might be weaker. These could help health authorities when evaluating the safety profile of drugs and the regulatory action. Recent initiatives to improve reporting such as online reporting and increase HCP participation need to be linked with continuing education and training.

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