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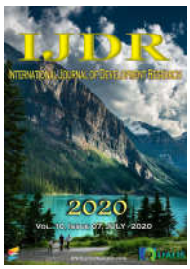

RESEARCH ARTICLE OPEN ACCESS

# EVALUATION OF THE SAFETY PROFILE IN OFFICIAL DRUG INFORMATION SOURCES IN BRAZIL, EUROPE AND THE UNITED STATES

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**ABSTRACT**

In this study, the completeness of the information on adverse reactions and poisoning management contained in the package inserts of the ten drugs most involved in drug morbidity and mortality was assessed, according to the 36th Annual Report, published by the American Association of Poison Control Centers, in 2018. These sources of information were compared to those contained in the clinical database UpToDate®, on the same drugs. The data were collected through online access to the electronic portal of Brazilian regulatory agencies, the National Health Surveillance Agency (ANVISA); from Europe, the European Medicines Agency (EMA); and the United States, the Food and Drug Administration (FDA). In total, 26 inserts were collected, 8 Brazilian, 8 European and 10 American. The results of the present study indicate that the leaflets of ANVISA and EMA, when compared with those of the FDA and the information contained in UpToDate®, present a shortage in the supply of relevant information that can help the health professional to identify and quickly manage the situation and little applicability. However, those of ANVISA proved to be superior when compared to those of EMA, regarding the completeness of the information. Therefore, it is up to the regulatory agencies to invest in strategies that guarantee the improvement of the quality of the information contained in the information sources, as well as improve its applicability in clinical practice, to allow a quick decision making, and consequently reducing the risks of negative clinical outcomes.



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## INTRODUCTION

In 1994, among a group of toxic agents studied, drugs were at the top of the causes of poisoning. Since then, drug poisoning has become a public health problem, in view of the trend towards an increase in the consumption of medicines by the world population. According to data collected over 20 years (1996-2006) by the National Toxic-Pharmacological Information System (SINITOX), 1,220,987 cases of drug poisoning were recorded in Brazil, of which 7,597 of these cases were fatal (OLIVEIRA *et al*., 2017).

Although patient-centered care is ideal for managing acute and chronic conditions, its application is not easy, and depends on breaking historical paradigms, which passively consider the patient and the doctor as responsible for their health (LE RESTE *et al*., 2013). Additionally, it highlights the difficulty of health professionals in applying scientific knowledge, since patients can present multiple comorbidities, and conflicting recommendations may exist. This fragmentation of care reduces the safety, effectiveness and efficiency of healthcare process (LE RESTE *et al*., 2013). The medicine leaflets act as informative guides for both patients and health professionals, which makes their use indispensable on a daily basis.

In addition, the package inserts represent important tools to reduce self-medication, alert about adverse reactions to medications and inform what should be done in case of accidental overdose and facilitate the dissemination of information about relevant drug interactions (ZARPELON *et al*., 2014). Adverse drug reactions (ADRs) are defined as an unintended response to a medication and usually results from doses used in the treatment of conditions, diagnosis and prophylaxis (LIMA *et al*., 2018). Knowing about the ADRs common to medicines becomes essential when it is intended to promote the provision of adequate health care, allowing the early identification and management of the situation. In addition, it is essential to know the clinical manifestations related to drug poisoning, whether accidental or not, as well as to know their management and clinical relevance of drug interactions. Advertising around drugs that do not need a prescription (over-the-counter – OTC), as well as the ease of acquiring them is one of the main factors responsible for the high rates of drug intoxications. The poorest people find these products a quick solution to relievetheir symptoms, once the access to a healthcare unit may be noit easy. Even though they are considered safe, OTC drugs pose a health risk when used incorrectly (COSTA *et al*., 2019). The pharmacist and other health professionals must offer dignified assistance to the population, through the promotion of actions that make the population aware of the rational use of medicines, of a safe dispensation, passing on all the necessary information to the patient, and, if necessary, guide the search for a health unit for a better evaluation (COSTA *et al*., 2019). Therefore, information about ADRs and management of drug intoxication must be present in a clear, objective and effective way in official sources of information on drugs, to allow quick decision making. Thus, considering this scenario, this study aims to compare the information contained in the national, European and American leaflets of the 10 drugs most involved in morbidity and mortality (according to the report published in 2018 by American Association of Poison Control Centers (AAPCC)) with the clinical database UpToDate® to identify critical points and improvements.

## METHODS

This study is an exploratory bibliographic research in which it was structured in two phases: the first phase was carried consist in the literature review was carried out by searching for articles in electronic databases. In the second phase, an exploratory bibliographic survey of the package inserts of the 10 drugs most involved in morbidity and mortality was carried out, according to the 36th Annual Report, published by the American Association of Poison Control Centers, 2018, on the electronic portals of the regulatory agencies in Brazil, Europe and United States, for further evaluation of the completeness and comprehensibility of the information contained in the topics adverse reactions and poisoning management, for health professionals. Search strategy: in the first phase, complete articles were used, available in the electronic databases: Scientific Electronic Library Online (SciELO) and PubMed (wich includes MEDLINE and PubMed Central databases). Electronic papers that contained the following words were included: adverse drug reactions, poisoning management and source of official information on medicines (official sources of information on medicines). The criteria for choosing the articles, due to their relevance to this study, included: articles dealing with the safety of pharmacotherapy, promoted by drug surveillance agenciesor population surveys of adverse drug events. These articles were reading the titles, abstracts and introduction, selecting those that best suited the proposed theme. The second phase, consisted of the collection of package inserts for health professionals, in Brazil, Europe and the United States, of the ten drugs listed. The package leaflet research was carried out on the electronic portal of the Health Surveillance Agency (ANVISA), Food and Drug Administration (FDA) and European Medicines Agency (EMA). The package inserts were obtained through electronic access from January 21 to February 27, 2020. Then, using the Microsoft Word 2013 tool, data on adverse drug reactions and intoxication management were organized in standardized tables (Appendix A and B In sequence, the clinical database UpToDate® was used to search for information about the profile of adverse drug reactions and management of intoxication of the listed drugs, and then to carry out a comparative analysis between the information contained in the package inserts of the drugs obtained in the electronic portals of ANVISA, EMA AND FDA. Finally, using Microsoft Word 2013, a table was created (Appendix C) to organize the data collected in the clinical database UpToDate®. Thesedata were collected between January 21 and February 22, 2020.

## RESULTS AND DISCUSSION

According to data collected by the NPDS and published in the "2018 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 36th Annual Report "the 10 drugs most involved in morbidity and mortality are (Table 1):

**Table 1. Medicines most involved in morbidity and mortality according to the 36th Annual Report, published by the AAPCC.**

| Drug | Nº of Exhibitions | Nº of Deaths | % Mortality |
|---|---|---|---|
| Fentanyl | 978 | 77 | 7,87% |
| Tranylcypromine | 25 | 1 | 4% |
| Clomipramine | 103 | 1 | 0,97% |
| Methadone | 962 | 9 | 0,94% |
| Amantadine | 110 | 1 | 0,91% |
| Doxepin | 671 | 6 | 0,89% |
| Colchicine | 256 | 2 | 0,78% |
| Tapentadol | 129 | 1 | 0,78% |
| Amitriptyline | 2397 | 14 | 0,58% |
| Morphine | 1106 | 5 | 0,45% |

Source: Adapted from GUMMIN, 2018.

**Table 2. Number of words contained in the topic of adverse reactions of the leaflets of ANVISA, FDA and EMA of the listed drugs**

| Drug | Anvisa | Ema | Fda |
|---|---|---|---|
| Fentanyl | 517 | 545 | 1023 |
| Tranylcypromine | 463 | - | 403 |
| Clomipramine | 734 | 634 | 1839 |
| Methadone | 234 | 421 | 435 |
| Amantadine | 334 | 54 | 265 |
| Doxepin | - | - | 288 |
| Colchicine | 119 | 176 | 626 |
| Tapentadol | - | 525 | 943 |
| Amitriptyline | 163 | 446 | 442 |
| Morphine | 245 | 492 | 518 |

Source: Author, 2020.

**Table 3. Number of words contained in the topic on management of intoxication of the leaflets of ANVISA, FDA and EMA of the listed drugs**

| Drug | Anvisa | Ema | Fda |
|---|---|---|---|
| Fentanyl | 208 | 180 | 313 |
| Tranylcypromine | 122 | - | 215 |
| Clomipramine | 506 | 539 | 770 |
| Methadone | 106 | 191 | 255 |
| Amantadine | 477 | 183 | 442 |
| Doxepin | - | - | 602 |
| Colchicine | 201 | 133 | 313 |
| Tapentadol | - | 269 | 315 |
| Amitriptyline | 606 | 476 | 663 |
| Morphine | 270 | 66 | 339 |

Source: Author, 2020.

**Table 4. Number of words contained in the topics adverse reactions and intoxication management, of the 10 drugs listed, available in the clinical database UpToDate**

| Drug | ADR | IM |
|---|---|---|
| Fentanyl | 605 | 625 |
| Tranylcypromine | 107 | - |
| Clomipramine | 829 | 2645 |
| Methadone | 216 | 1306 |
| Amantadine | 411 | - |
| Doxepin | 375 | 2645 |
| Colchicine | 122 | - |
| Tapentadol | 407 | 1306 |
| Amitriptyline | 257 | 2645 |
| Morphine | 749 | 1306 |

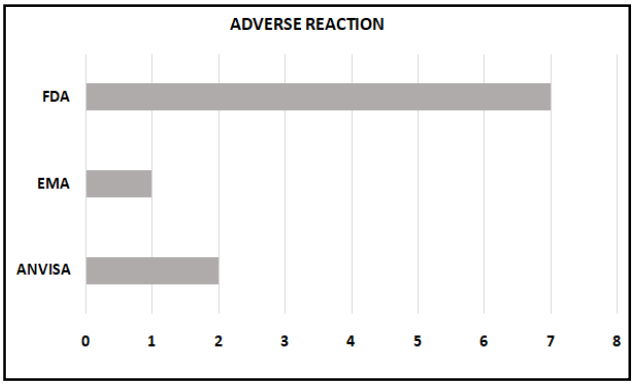
Source: Author, 2020.

In total, 26 inserts were collected, 8 Brazilian, 8 European and 10 American. Of the 10 drugs listed, only the doxepine package inserts, which are discontinued in Brazil and tapentadol, which is not a registered product in the country, were not collected on the ANVISA website. EMA, which is the agency that regulates the leaflets of all countries, member states, of the European Union (EU) makes available, on its electronic portal, a tool that gives access to national registries of medicines authorized in EU countries, through providing links to the agency's electronic portal in each country. Thus, the package inserts used in the research, for data collection, were obtained through the electronic portal of the agency that regulates medicines in Portugal, the National Authority for Medicines for Health Products (INFARMED), I.P. Of the 10 drugs, it was possible to collect only 8 package inserts on the INFARMED portal, since doxepine and tranylcypromine are not registered in Europe. In the FDA's electronic portal, all the package inserts for the drugs listed were obtained. In the UpToDate® database, information was collected on the adverse reactions of all ten drugs listed, but in the item "intoxication management", only information on seven drugs was collected, since there is no information on three drugs in the clinical base: tranylcypromine, amantadine and colchicine. Now, therefore, the necessary material (Appendices A, B and C) was obtained for comparative analysis between the data collected from the inserts of the three regulatory agencies with the data from one of the most important clinical bases today, due to the impact it has been causing in health environments.

The FDA had a greater volume of content on the topic "adverse reactions" in 70% of the package inserts of the listed drugs, with largest difference in volume found, in relation to the EMA and ANVISA package inserts, in the drug "fentanyl" (Table 2).

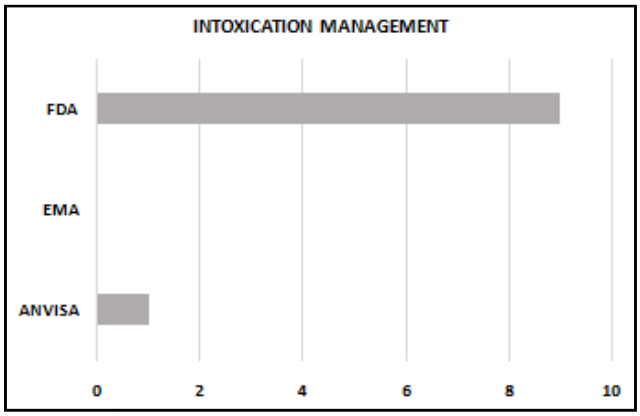
In the topic on intoxication management, the FDA presented a greater volume of content in 90% of the package inserts of the drugs listed, with the biggest difference found in the drug "amitriptyline", in relation to the inserts of other regulatory agencies (Table 3). Table 2 - Number of words contained in the topic of adverse reactions of the leaflets of ANVISA, FDA and EMA of the listed drugs. For a more detailed comparison on the provision of information to the health professional between the data from official sources of information on medicines and those collected in UpToDate, the number of words contained in the topics adverse reactions and poisoning management was analyzed. According to table Table 4, the FDA package inserts for tricyclic antidepressants (clomipramine and amitriptyline) had a higher volume of content. According to Table 2, 70% of the information on the topic "adverse reactions", contained in the package inserts collected on the FDA's electronic portal (Graph 1), presents a greater completeness when related to those of ANVISA and EMA. According to Table 3, on the topic "poisoning management", it is found that 90% of the information contained in the FDA drug package inserts is more complete (Graph 2). When comparing the data collected in the leaflets of ANVISA, EMA and FDA with those data collected in UpToDate®, there is that in the topic "adverse reactions" the FDA presents a greater completeness in 50% of the drugs, while the UpToDate, 30% ( Graph 3). In the topic "poisoning management", UpToDate presents a greater completeness in 70% of the medications (Graph 4).

**Graph 1. Volume of content contained in the item on adverse reactions in the leaflets of ANVISA, EMA and FDA**



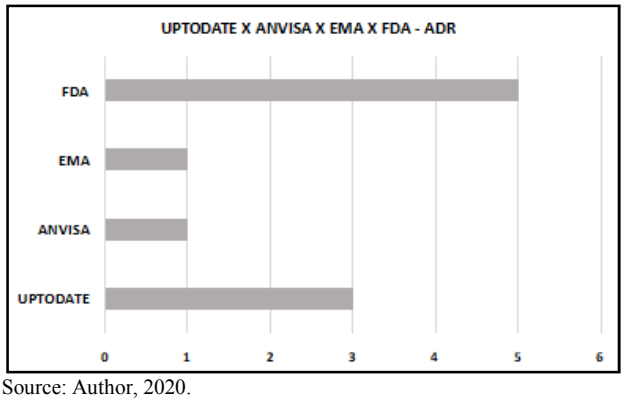

Source: Author, 2020.

**Graph 2. Volume of content contained in the item on poisoning management, in the leaflets of ANVISA, EMA and FDA**



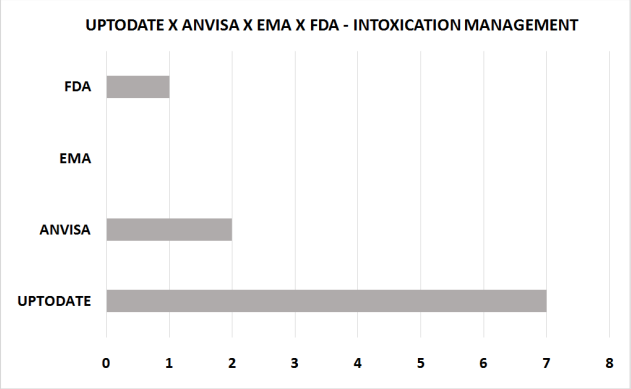

Source: Author, 2020.

**Graph 3. Comparison of the volume of content contained in the item on adverse reactions between the leaflets of ANVISA, EMA and FDA and UpToDate**




Source: Author, 2020.

**Graph 4. Comparison of the volume of content contained in the item on poisoning management between the leaflets of ANVISA, EMA and FDA and UpToDate**




Source: Author, 2020.

As the data on doxepine was only collected on the FDA and UpToDate® website, a comparison was made, according to the number of words contained in each topic, and it was seen that the UpToDate® contains more information about doxepin as much about the adverse reactions profile and clinical management in case of intoxication by this medication. It was also seen that in 100% of the leaflets collected on ANVISA's electronic portal, at the end of the topic "adverse reactions", a communication channel is presented to clarify any doubts and request additional information. This also occurs in 7 out of 8, collected on the EMA website. In the package inserts collected on the FDA portal, there is no informed communication channel. When analyzing all tables and graphs 1, 2 and 3, it was noted that both the FDA and UpToDate provide information on adverse reactions and management of intoxication in a more detailed and specific way than the package inserts for ANVISA and EMA medications. This is perhaps due to the FDA and UpToDate® updating the information frequently as new scientific evidence emerges. However, according to Graph 4, it is noted that ANVISA is ahead of the FDA and EMA, in terms of poisoning management, behind only UpToDate®. In addition, it is also possible to observe that UpToDate provides information about the management of drug intoxication in a very applicable and complete way than the information contained in the leaflets of ANVISA, EMA and FDA. All leaflets collected have many similarities, ranging from the format in which they are arranged to the content of the information.

However, they differ, mostly, by the volume of information provided in the sources of official information about medicines. Nevertheless, despite the historical evolution of the regulation of official information on medicines for health professionals, there are still scientific flaws, such as the deficiency in updating information, as well as omission or lack of integrity of essential information. Such reasons end up leading to disbelief, and, consequently, to the disuse of a source of medication information so important for health professionals and patients (FUNCHS; HIPPIUS; SCHAEFER, 2006). All drugs, in turn, have a risk-benefit profile that must be evaluated before prescribing. The potential benefits of a drug are assessed through clinical studies to determine positive outcomes. However, most of these studies are not large enough to define the overall safety profile of the drug. Post-marketing studies are essential for long-term safety assessment. Therefore, the more data contained in an information leaflet, the better for the health professional, with regard to the management of clinical practice. During the research, it was seen that UpToDate basically adopts the same clinical management in cases of drug intoxication by drugs of the same class. For this reason, some drugs presented in table 4, contain the same number of words in the topic "intoxication management". It was also noted that UpToDate is a clinical database that provides a lot of relevant information to health professionals, with regard to the management of drug intoxication. More than 80 studies demonstrate the impact of this clinical source on improving patient care and hospital performance (UPTODATE, 2019).

Nowadays, more than ever, healthcare service providers are being challenged to implement resources and tools with a proven positive impact on results, safety and patient experience, reducing costs through improvement and efficiencies. About 90% of academic medical centers in the United States use UpToDate as an effective approach to improving patient health (UPTODATE, 2019). The analysis of information on adverse reactions is complex. The degree of importance of the adverse reactions mentioned, according to the frequency or severity, was not analyzed. However, it is possible to observe that ANVISA and EMA are concerned with providing a communication channel at the end of the item "adverse reactions" of all package inserts, making sure that the health professional does not have only the information leaflet as an alternative for handling the clinical practice. The clinical management of intoxications, is fundamental to obtain a positive clinical outcome for the patient. Therefore, access to practical and quality information is essential for health professionals to act with precision and speed, to avoid fatalities.

The lack of strategies for improving the clinical applicability of the package inserts and the frequency of updating the information are obstacles faced concerning obtaining positive clinical outcomes. Regarding the clinical applicability, it was noticed that the UpToDate® presents more information applied to the clinical decision than ANVISA, EMA, while the FDA has more information related to clinical management, but less applicable. However, UpToDate® is a paid database, which makes it difficult for some health professionals to access quality information worldwide. Additionally, Brazilian health professionals, who do not have access to the information contained in official sources of medicines in other countries, either due to difficulties with their native language, or difficulties in accessing this information online, end up being harmed even more, considering that the information contained in the official sources of ANVISA is much less applicable in clinical practice. In carrying out this study, some limitations were found. Among them, the difficulty of identifying and comparing innovative information contained in the leaf lets collected from the three regulatory agencies, as well as the difficulty of identifying and comparing similar / equal information. However, in a later stage of this study, the IRaMuTeQ software, a visual interface capable of producing textual analysis, can be used to overco meth mentioned difficulties. The next steps in this study consist of the assessment of these official sources of medication through specific instruments for adverse reactions and intoxications, as well as the assessment of the clinical applicability of this information, and expand the search to other classes of drugs, such as Non-Prescription Drugs (MIP), for example.

## CONCLUSION

The present study demonstrated the need for frequent updating the reports of official drug information sources to guarantee the correct clinical decision making by health professionals The package insert has represented, in Brazil, the main material that provides information about drugs to users and the Health Surveillance Agency (ANVISA) is responsible for analyzing and approving the information material. The leaflets from EMA and ANVISA, when compared to those from the FDA and data from the clinical database UpToDate®, present a shortage in the supply of relevant information that can help the health professional in the identification and early management of the situation. Additionally, based on the problems found in the package inserts analyzed, it is believed that the legislation should be reformulated, with regard to the clinical applicability of the information, which could be presented in didactic leaflets for health professionals, in support of their clinical practice. Therefore, it is up to the regulatory agencies to invest in scientific contributions to obtain a significant improvement in the supply of reliable and secure information, to allow a quick decision making by health professionals, aiming to reduce the occurrence of negative clinical outcomes.

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