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Farmacovigilância de medicamentos manipulados - Parte 2: notificações de eventos adversos e queixas técnicas no Brasil

Pharmacovigilance of compounded drugs - Part 2: Adverse event notifications and technical complaints in Brazil

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ABSTRACT

Introduction: Compounded drug is a pharmaceutical preparation obtained by a pharmacotechnical procedure from a prescription of a qualified professional intended for an individualized patient, or whose formula is registered in the National or International Form. **Objective:** To describe the profile of notifications related to compounded drugs, reported to the National Health Surveillance Notification System (Notivisa). **Method:** Descriptive exploratory study, retrospective to the period 2006-2016, of the notifications of compounded drugs reported to Notivisa. Data were recorded and analyzed using the Excel program, version for Windows 3.5.4. **Results:** Of a total of 108,400 notifications referring to medicines in the studied period, 335 (0.32%) were related to reports of compounded drugs. Technical complaints (QT) obtained 90.40% of the notifications, while adverse events (AE) obtained 9.60%. The Southeast region was the main notifier (66.00%), and the state of São Paulo was responsible for 54.00% of the total notifications. Hospitals were the institutions with the highest frequency of notification (81.00%). It was possible to evaluate the reasons that generated the notifications, of which the changes related to the aspect of the pharmaceutical preparation were the predominant among the QT, while for the AEs, the adverse drug reactions stood out. **Conclusions:** The occurrences observed in the pharmacovigilance of compounded drugs are specific to each product with its particularities, although, what is sought is a pattern. In this way, such observation can prevent the occurrence of damages to the population exposed to similar situations, if it is duly notified and widely disseminated.

KEYWORDS: Pharmacovigilance; Compounded Drug; Pharmaceutical Compounding Service

RESUMO

Introdução: Medicamento manipulado é a preparação farmacêutica obtido por procedimento farmacotécnico a partir de uma prescrição de profissional habilitado destinada a um paciente individualizado ou cuja fórmula esteja inscrita no Formulário Nacional ou Internacional. **Objetivo:** Descrever o perfil das notificações relacionadas aos medicamentos manipulados, reportadas ao Sistema Nacional de Notificação em Vigilância Sanitária (Notivisa). **Método:** Estudo exploratório descritivo, retrospectivo ao período de 2006-2016 das notificações de medicamentos manipulados reportadas ao Notivisa. Os dados foram registrados e analisados no programa Excel versão para Windows 3.5.4. **Resultados:** De um total de 108.400 notificações referentes a medicamentos no período estudado, 335 (0,32%) foram relacionadas a notificações de medicamentos manipulados. As queixas técnicas (QT) obtiveram 90,40% das notificações, enquanto os eventos adversos (EA) obtiveram 9,60%. A Região Sudeste foi a principal notificadora (66,00%) e o estado de São Paulo, responsável por 54,00% do total das notificações. Os hospitais foram as instituições com maior frequência de notificação (81,00%). Foi possível avaliar os motivos que geraram as notificações, das

quais as alterações relacionadas ao aspecto da preparação farmacêutica foram as predominantes dentre as QT, enquanto para os EA destacaram-se as reações adversas a medicamentos. **Conclusões:** As ocorrências observadas na farmacovigilância de medicamentos manipulados são próprias de cada produto com suas particularidades, embora o que se busque seja um padrão. Desta forma, tal observação poderá prevenir a ocorrência de danos à população exposta a situações semelhantes, se for devidamente notificada e amplamente divulgada.

PALAVRAS-CHAVE: Farmacovigilância; Medicamento Manipulado; Farmácia de Manipulação

INTRODUCTION

Compounded drugs are pharmaceutical preparations obtained from a prescription by a qualified professional, intended for an individual patient, and which establish in detail their composition, pharmaceutical form, dosage, and way of use[1,2,3]. It is called officinal preparation when it is prepared from a formula described in the National Form or in International Forms recognized by the Brazilian National Health Surveillance Agency (Anvisa). This type of medicine may also comprise a product obtained from the transformation of a pharmaceutical specialty, in exceptional circumstances when the raw material is unavailable on the market and due to the absence of the specialty in the dose, concentration, or pharmaceutical form compatible with the patient's clinical conditions, in order to adapt it to the prescription[4].

The compounded drug, like all drugs, must offer quality and safety in its use. Thus, Resolution of the Collegiate Board of Directors (RDC) No. 67, of October 8, 2007, from Anvisa[3,5], establishes good manufacturing practices (GMP) and guides the sanitary monitoring actions of these products in the market, from their production, commercialization, and use through sanitary control and pharmacovigilance.

Activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other possible drug-related problems consist of pharmacovigilance. This makes it possible to recognize the pattern of occurrences through reports and, thus, prevent damages and injuries that may occur. Among the occurrences of interest to pharmacovigilance, there are adverse events (AE) and technical complaints (TC), which can be caused by any drug[6].

Quality deviation is the departure from established quality parameters for a product or process. These may be related to physical, chemical, physical-chemical, or microbiological changes. General alterations are also included, such as: presence of foreign particles, lack of information on the label, registration problems, label or content change, cracks and bubbles in the packaging material[7,8].

AE is defined as the occurrence of any unwanted effect in human beings, resulting from the use of products under health surveillance, which may or may not be avoidable[7,8].

For the processing of AE and TC reports, the Health Surveillance Notification System (Notivisa) is used, implemented on the web platform since 2006.

The information generated by pharmacovigilance helps in health regulation actions aimed at minimizing risks and problems related to products, which are often only identified at the time of use. Thus, knowing the profile of reports related to compounded drugs helps to recognize the pattern of related problems to then develop preventive control policies, from obtaining the product to its use[9,10].

The objective of this study was to identify, quantify, and categorize the occurrences of AE and TC notifications related to compounded drugs received by Notivisa.

METHOD

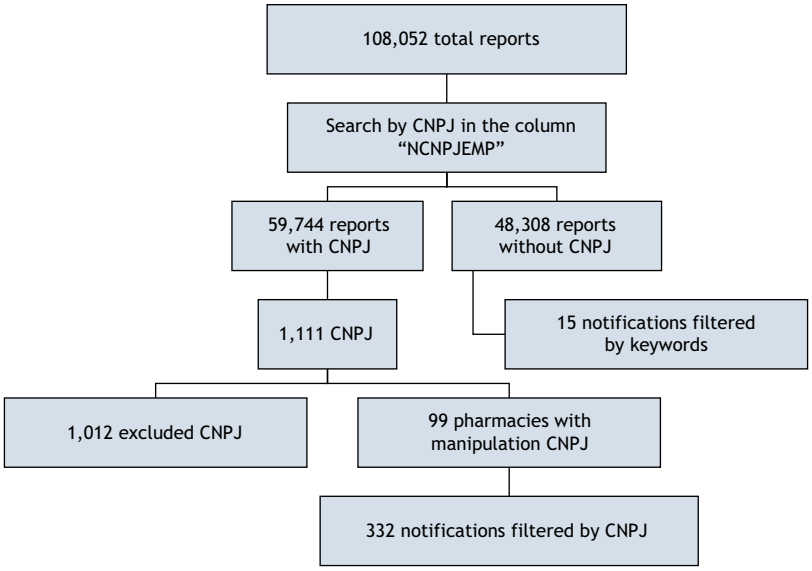
A descriptive exploratory observational study was carried out from January 2006 to August 2016, with a quantitative approach. The information was obtained from the notifications of manipulated drugs registered in the Notivisa database.

For the present study, notifications related to compounded products were extracted. Initially, a survey of the National Registry of Legal Entities (CNPJ) registered was carried out, searching for the Economic Activity Code number 47.71-7-02, which refers to the "Retail trade of pharmaceutical products, with manipulation of formulas". Of the 1,111 registered CNPJs, 99 CNPJs were found with the description of pharmacy with manipulation, totaling 332 notifications. In addition, a search was carried out, in the notifications without CNPJ, in the company's trade name column for the following words: manipulation(s), manipulated, masterful, and officinal and 15 more reports were found. By the sum of the research carried out, 347 reports were found, which became the object of study of this work (Figure 1).

The variables selected for the present study were: year of report (2006-2016); federation unit (UF) of the report; detailed description of reports and reported products; technical name of the reported product; notifying institution and CNPJ of the reported company. For a more detailed analysis of the data, the variables were created: region, notification category, reason for the occurrence, and physical form of the drug.

All reports related to drugs handled during the study period were included in the study. Notifications of products not related to compounded drugs were excluded.

Data were processed using the Excel program, version for Windows 3.5.4, processed using descriptive statistics, and presented



Source: Elaborated by the authors from data at Notivisa, 2021.
CNPJ: National Registry of Legal Entities.

Figure 1. Flowchart representing the search for notifications related to manipulated drugs.

as absolute and relative frequencies, mean, and standard deviation. For greater detailing of the data, analyzes were performed by crossing variables, and the results found were organized in tables and graphs.

Ethical aspects

The study was based on the analysis of secondary data from the Notivisa database, not directly involving human subjects. The evaluation was restricted to the aggregate analysis of the variables, keeping anonymous the subjects related to the notifications and the identification of the notifier, the patient and/or the company, a situation in which the evaluation by the research ethics committee is waived. The recommendations of the National Health Council (CNS) in its resolution No. 510 of April 7, 2016, were observed.

Study limitations

The Notivisa database has major limitations, as there is a notorious lack of specific information for characterizing the drugs handled. Furthermore, not every report or compounded drug company presented the search words in their description. In addition, there was a restriction regarding the search for health sciences descriptors in the electronic databases used, since there are no specific descriptors for pharmacy with manipulation, only for pharmacovigilance, which are well described.

RESULTS

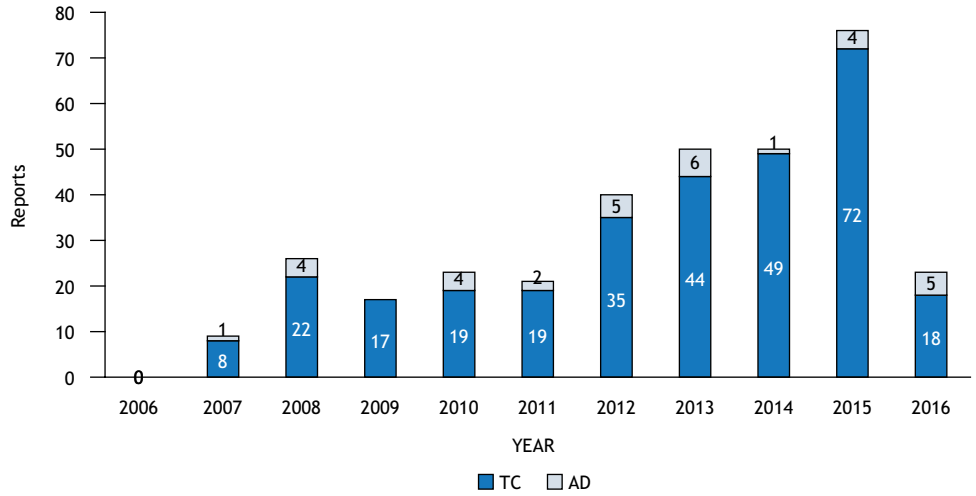
In the period from January 2006 to June 2016, Notivisa received a total of 108,052 drug notifications, of which 335 were related to compounded drugs, which corresponds to 0.31% of the total notifications. According to the inclusion criteria used, 335 notifications were part of the study. Among them, 32 AE and 303 TC were obtained. The amplitude ranged from 0 to 82 notifications in the period, with an annual average of 31.54 notifications and a standard deviation of 23.34.

Figure 2 presents the annual distribution of notifications stratified by type of notification. The data indicated that the TC for compounded drugs had a gradual growth, going from nine, in 2007, to 76, in 2015, with an average of 27.55 annual notifications. In 2016, there was not a considerable frequency, since Notivisa was discontinued for its adaptation to the World Health Organization (WHO), in the Uppsala Monitoring Center (UPP), for the creation of a new system called VigiMed. AEs, on the other hand, did not follow the growth similar to that observed in TC and varied from one notification, in 2007, to six notifications, in 2013, with an average of 2.91 annual notifications.

In the distribution of notifications by regions of Brazil, it was observed that the Southeast had the highest frequency (66.00%) of reports, followed by the Northeast (14.00%), South (14.00%), and Midwest (6.00%) regions. The North Region did not present reports for the studied period (Table 1).

It was possible to analyze the nature of the reporting institutions (Table 2) and it was found that the hospitals made 271 (81.00%) notifications; Anvisa carried out 30 (9.00%); municipal and state Sanitary Surveillance made 16 (5.00%); compounding pharmacies made five notifications (3.00%); universities reported six events (2.00%); others with four notifications (1.00%) and health secretariats, three notifications (1.00%).

As for the characteristics of the occurrences related to the types of report (TC and AE), the Notivisa user manual was used,



Source: Health Surveillance Notification System (Notivisa), Anvisa/Ministry of Health.

Figure 2. Distribution of frequency adverse events and technical complaints reports on compounded drugs, according to the years of the period 2006-2016, Brazil.

Table 1. Distribution of frequency adverse events and technical complaints reports on compounded drugs, according to the Regions of the period 2006-2016, Brazil.

Region	Type of report			
	AD	TC	n	%
North	0	0	0	0.00
Northeast	4	44	48	14.30
Midwest	2	18	20	6.00
Southeast	18	204	222	66.30
South	8	37	45	13.40
Total	**32**	**303**	**335**	**100.00**

Source: Health Surveillance Notification System (Notivisa), Anvisa/Ministry of Health.
AE: adverse event; TC: technical complaint.

Table 2. Distribution of frequency adverse events and technical complaints reports on compounded drugs, according to the nature of the notifying institution of the period 2006-2016, Brazil.

Type of notifying institution	Type of report			
	AD	TC	n	%
Anvisa	9	21	30	**8.90**
Compounding pharmacy	0	5	5	**1.50**
Hospital	20	251	271	**80.90**
Health Department	0	3	3	**0.90**
University	1	5	6	**1.80**
City and state Health Surveillance	1	15	16	**4.80**
Others	1	3	4	**1.20**
Total	**32**	**303**	**335**	**100.00**

Source: Health Surveillance Notification System (Notivisa), Anvisa/Ministry of Health.
AE: adverse event; TC: technical complaint.

classifying the TC into four categories: changes in appearance, packaging, functionality, and registration. AEs were divided into two categories: absence/reduction of effect and adverse drug reactions (ADE) (Table 3).

Of the 303 notifications corresponding to TC, 109 (36.00%) were related to changes in the appearance of the product, 19.00% of which were caused by the presence of particles or foreign bodies in the product. Then, the most frequent TC were problems related to packaging in 84 (27.80%), functionality in 66 (21.80%), and registration in 44 (14.50%). As for AE (32), ineffectiveness was described in 81.00% of the notifications and ADE in 19.00%.

DISCUSSION

The data obtained showed that the notifications of compounded drugs contributed with less than 0.50% of all reports registered in Notivisa. A similar result was found by Lima et al.[12], who analyzed the profile of notifications of products based on plant species and found a frequency lower than 1.00% for these products. It was not possible to compare this result with international data, however they indicated a low number of notifications, compared to other drug notification profiles found in Brazilian studies[11,12].

The historical distribution showed great differences between the number of notifications in the years studied, not reproducing a homogeneous distribution pattern, whose dispersion is verified by the proximity of the standard deviation in relation to the average of notifications in the period. However, it was possible to notice a gradual growth in the number of notifications in the period, with the exception of the year 2016, which contributed with only half of the year for the analysis.

This result corroborates other studies that analyzed the profile of notifications of herbal medicines[12], medicines in a hospital

Table 3. Distribution of frequency of reports on compounded drugs according to the characteristics of technical complaints.

Characteristics of technical complaints	AF (n)	RF (%)
Aspect	**109**	
Foreign body/Particles/Precipitate	57	18.81
Changes in color, stain, smell	24	7.92
Appearance different from described or usual	19	6.27
Handling error or GMP failure	9	2.97
Package	**84**	
Changes to the label, packaging	57	18.81
Irregular packaging	27	8.91
Funcionality	**66**	
Leak	39	12.87
Amount less than labeled lack of medication in the package	27	8.91
Register	**44**	
Raw material suspected of being unregistered	12	3.96
Suspected other irregular practices	11	3.63
Produção irregular em lote	11	3.63
Irregular Company Operating Permit	5	1.65
Irregular marketing	3	0.10
Counterfeit product suspected	2	0.66
Total	**303**	**100.00**
Characteristics of adverse events	AF (n)	RF (%)
Absence or reduction of effect	26	81.00
Adverse drug reactions	6	19.00
Total	**32**	**100.00**

Source: Health Surveillance Notification System (Notivisa), Anvisa/Ministry of Health.
AF: absolute frequency; RF: relative frequency; GMP: good manufacturing practices.

environment[11], and health products, under the scope of techno-surveillance[13] and cosmetovigilance[14]. The increase in the number of notifications sent to Notivisa may denote greater organization of the national system, as well as greater awareness of the notifier for the need to report such occurrences to the health surveillance. There is also the possibility that some occurrences have been investigated and concluded by state or municipal Health Surveillance bodies to be included in the Notivisa system[15].

It was verified in this study a predominance of TC to the detriment of AE. This result is very similar to that obtained in the work carried out by Lima et al.[16], who developed a study in a sentinel hospital, whose most reports (70.00%) were related to TC related to quality deviations and 9.00% to AE. These data are also in agreement with the study carried out by Bezerra et al.[17], in which it was observed that 55.00% of the reports were related to TC and 8.00% to ADE. It is likely that the ease of visualizing the quality deviation before using the drug by the patient favors detection and, therefore, notification. AEs, on the other hand, are difficult to identify, either due to factors related only to the patient, or due to the drug and its interference in the body[16].

Regarding the distribution of notifications by regions, it was found that the Southeast Region concentrated the largest amount of TC and AE reports, and this is also the region where 48.90% of the hospitals associated with the Sentinel Network are accumulated. Furthermore, 28.20% of the hospitals in the network are located in the state of São Paulo, which shows the importance of the active participation of hospitals not only in pharmacovigilance but also in techno-surveillance[13].

Sentinel hospitals were created as a strategy for the implementation of pharmacovigilance in the hospital environment. Thus, these institutions have organized and professional infrastructure responsible for risk management of health technologies used in the hospital environment[11]. This fact could explain the greater number of TC records from these hospitals, since they need to notify the drug to be exchanged by the compounding pharmacy, in order not to compromise the hospital budget, and that the use of products with quality deviation also reflects on the hospital onus, impacting the institution's general budget[18].

On the other hand, compounding pharmacies were the reporting institutions with the lowest frequency observed. This result indicates a very timid participation of this professional segment, and it is probably necessary to raise the awareness of notifying professionals in order to improve the monitoring of these products. It is noteworthy that RDC No. 67/2007[3] establishes the competence and obligation of the pharmacist who works in the compounding pharmacy to carry out pharmacovigilance in the magistral environment.

Regarding the causes that motivated the notifications, about 70.00% of the TC were related to visually detected changes in appearance, packaging, and functionality, which could impair the correct performance of the drug being handled. Since, in general, such changes do not negatively reflect the competence of the professional or the notifying institution, this fact may have favored the greater sending of notifications, especially by referring the responsibility directly to the compounding pharmacy that produced the drug[16,17,18].

Considering the reasons attributed to the drug aspects, the following were reported: presence of foreign bodies, particles, or precipitates, insoluble materials in solution, precipitates of different textures, and evidence of microbiological growth. In this group, sensory aspects were observed, such as: odors that were not characteristic of the products, stains of different colors, changes in the product's color, such as darkening or lightening of the drug's color, or even non-inherent colors.

According to Andrade et al.[19], notifications about changes in color, stains, and smells can occur due to microbiological

changes. Therefore, it should be noted that the high microbial load can compromise stability, leading to a loss of efficacy due to the degradation of the active ingredient or due to alteration of the physicochemical parameters of the medicines, which can compromise consumer acceptance and even lead to problems of bioavailability of magistral preparations.

In this category, notifications related to changes in texture or dosage form were also verified, in addition to those attributed to manipulation errors or absence of GMP (9.10%), among which: compounding of volume greater than prescribed, compounding of concentration different from that prescribed by the medical team, lack of input in the product due to compounding failure.

It is noteworthy that the error of concentration of the active can exacerbate adverse effects, as well as the absence of active produce the ineffectiveness of the product, in which both situations mean therapeutic damage to the patient[20,21,22]. An example of a fatal outcome illustrative of this type of situation was described by Yano et al.[20], who reported an overdose, about 20 times higher than the maximum recommended dose of the drug colchicine in capsules handled by compounding pharmacies in the city of São Paulo. In this episode, the patients, after using the drugs, had acute digestive hemorrhage caused by the overdose of this active, culminating in death, since it has a narrow therapeutic index, and the therapeutic dose is very close to the toxic dose.

The reports related to changes in packaging and labels contributed to 18.80% of the total TC, among which were verified: lack of information on the label (expiry date, batch, patient's name, active ingredient, concentration, dosage, and indication of use) or wrong information on the label/packaging (pharmaceutical form, patient's name, indication of use).

Yano et al.[22] analyzed six compounded drug labels and found that in 100% of them there was at least one item in disagreement with the legislation regarding the wording, verifying: two addresses, lack of the patient's name, lack of the prescriber's name, lack of the route of administration, inappropriate phrases for dosage, abbreviated drug names, common plant name without the scientific name, lack of the company's CNPJ, among others.

Both packaging defects and changes described for drug labeling indirectly affect the quality of the drug, which may compromise patient treatment, due to lack of information as well as the lack of functionality of the packaging.

Regarding functionality, a large percentage (12.90%) of reports of leakage in the primary packaging was verified, exposing the drug to the external environment, changing its partial function, due to the loss of volume or quantity of the product. In some cases, the drug's loss of function can be attributed to the degradation of the active by contact with the outside environment (temperature, humidity, luminosity, oxygen) or to microbiological contamination.

Functional TCs were demonstrated in another similar study. Pissatto et al.[23] verified great variation in the quality of handled fluoxetine capsules in terms of average weight, content, and content uniformity, and all samples were outside the pharmacopoeial limits for content uniformity. The present study also identified reports of suspected irregularities in the registration in 14.50% of the listed notifications. Among these, there were notifications of prohibited substances in the country, dispensation of controlled drugs without a special prescription, and of drugs without proof of efficacy.

It is emphasized here the importance of ensuring that all raw materials, as well as industrialized products that enter the production process of compounded drugs, contain authorization for registration with the Brazilian sanitary agency, as well as the quality analysis report of the manufacturing laboratory, in order to ensure adequate traceability of the final compounded product[3]. Anvisa is responsible for monitoring the safety profile of medication use, intervening, and applying sanitary measures such as suspension, prohibition, interdiction, and the recall of irregular medicines that are available on the market[3].

AEs were also observed in the total number of notifications studied, representing approximately 10.00% of the records of manipulated medicines, among which the following stand out: therapeutic ineffectiveness or reduction of the pharmacological effect and adverse drug reactions (ADR).

Ineffectiveness may occur due to a reduction or absence of the expected pharmacological effect, caused by problems with the quality of the drug or also by drug interactions, inappropriate use, resistance, or tolerance of the patient to the drug[7]. ADRs, on the other hand, are defined as harmful or unwanted effects that occur after the administration of doses of drugs normally used in humans for the prophylaxis, diagnosis, or treatment of disease[7].

In the present study, therapeutic ineffectiveness was more frequent than ADR. This result differs from the findings of other similar studies that found among the AEs, which were the most prevalent ADRs in a hospital environment[12,13,24]. It is important to emphasize that ADRs are inherent to the therapeutic use of drugs[7]. Thus, these adverse reactions are expected to occur in greater volume than other drug-related problems, which was not observed in this study, a fact that may also indicate underreporting of this type of ADE.

CONCLUSIONS

Data on compounded drugs were scarce and difficult to extract, however, it was possible to identify, categorize, and quantify the records of TC and AE notifications for these products, based on Notivisa records.

The number of notifications gradually increased during the period studied, with the Southeast Region of Brazil being the one that most contributed with reports to the System, with the sentinel hospital standing out as the main reporting institution.

Among the main reasons that generated the notifications, alterations related to the aspect of the pharmaceutical preparation for TC were predominant, while for adverse reactions, ADE stood out.

Considering that the compounded drugs can be mostly personalized pharmacotechnical preparations, sanitary regulation has been hard established, since such drugs do not undergo clinical and biopharmaceutical tests. Thus, although each preparation is unique, differing from others in its composition, the pattern of response sought in pharmacovigilance is related not only to individual actives, but also to their association with other drugs and vehicles used, as well as its excipients, which can change in each formulation and generate an unexpected, undescribed, and clinically important AE. Such observation, if notified and widely publicized, could prevent the occurrence of harm to the population exposed to similar situations.

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Author's Contributions

Pimenta TL, Passos MMB - Conception, planning (study design), acquisition, analysis, data interpretation, and writing of the work. Monteiro MSSB - Acquisition, analysis, data interpretation, and writing of the work. Oliveira DR, Freitas ZMF – Writing of the work. All authors approved the final version of the work.

Conflict of Interests

The authors inform that there is no potential conflict of interest with peers and institutions, politicians, or financial in this study.