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Causes for the underreporting of adverse drug events by health professionals: a systematic review

CAUSAS DE LA SUBNOTIFICACIÓN DE LOS EVENTOS ADVERSOS A MEDICAMENTOS POR LOS PROFESIONALES DE LA SALUD: REVISIÓN SISTEMÁTICA

CAUSAS DE SUBNOTIFICAÇÃO DE EVENTOS ADVERSOS A MEDICAMENTOS POR PROFISSIONAIS DA SAÚDE: REVISÃO SISTEMÁTICA

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ABSTRACT

Objective: Identifying the main causes for underreporting of Adverse Drug Reaction (ADR) by health professionals. **Method**: A systematic review carried out in the following databases: LILACS, PAHO, SciELO, EMBASE and PubMed in the period between 1992 and 2012. Descriptors were used in the search for articles, and the identified causes of underreporting were analyzed according to the classification of Inman. **Results**: In total, were identified 149 articles, among which 29 were selected. Most studies were carried out in hospitals (24/29) for physicians (22/29), and pharmacists (10/29). The main causes related to underreporting were ignorance (24/29), insecurity (24/29) and indifference (23/29). **Conclusion**: The data show the eighth sin in underreporting, which is the lack of training in pharmacovigilance. Therefore, continuing education can increase adherence of professionals to the service and improve knowledge and communication of risks due to drug use.

RESUMEN

Objetivo: Identificar las causas de la subnotificación de la Reacción Adversa a Medicamento (RAM) por profesionales de la salud. **Método**: Revisión sistemática realizada en las bases de datos LILACS, PAHO, SciELO, EMBASE y PubMed, cuyo período de revisión fue de 1992 a 2012. Se utilizaron descriptores para buscar los artículos. Las causas de subnotificación identificadas fueron analizadas de acuerdo con la clasificación de Inman. **Resultados**: Se identificaron 149 artículos, de los cuales 29 fueron seleccionados. La mayoría de los estudios fueron realizados en hospitales (24/29) para médicos (22/29) y farmacéuticos (10/29). Las principales causas relacionadas a la subnotificación observadas fueron: la ignorancia (24/29), la inseguridad (24/29) y la indiferencia (23/29). **Conclusión**: Los datos evidencian el octavo pecado de la subnotificación, que es la falta de formación en farmacovigilancia. Por lo tanto, la educación continua puede aumentar la adhesión de los profesionales al servicio y mejorar el conocimiento y la comunicación de riesgos del uso de medicamentos.

RESUMO

Objetivo: Identificar as causas de subnotificação de Reação Adversa a Medicamento (RAM) por profissionais da saúde. **Método**: Revisão sistemática realizada nas bases de dados LILACS, PAHO, SciELO, EMBASE e PubMed, cujo período de abrangência foi de 1992 a 2012. Foram utilizados descritores para buscar os artigos. As causas de subnotificação de RAM identificadas foram analisadas de acordo com a classificação de Inman. **Resultados**: Identificaram-se 149 artigos, dos quais 29 foram considerados elegíveis. A maioria dos estudos foi conduzida em hospitais (24/29), para médicos (22/29) e farmacêuticos (10/29). As principais causas relacionadas à subnotificação observadas foram: a ignorância (24/29), a insegurança (24/29) e a indiferença (23/29). **Conclusão**: Os dados evidenciam o oitavo pecado da subnotificação, que é a falta de formação em farmacovigilância. Assim, a educação permanente pode aumentar a adesão dos profissionais ao serviço e melhorar o conhecimento e a comunicação dos riscos associados ao uso de medicamentos.

DESCRIPTORS

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DESCRIPTORES

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INTRODUCTION

Spontaneous reporting of adverse drug events (ADEs) comprise the primary method for detecting signs in pharmacovigilance, because they are effective for identifying serious unexpected adverse drug reactions (ADRs), medication errors, therapeutic ineffectiveness and inconsistencies in drug quality, besides its low cost[1].

It is estimated that between 5% and 10% of ADR are reported[2-4]. Thus, the main limitation of the passive method of analysis of drug safety is cases underreporting[5], which decreases the sensitivity for detecting ADE, making it difficult to estimate the frequency of occurrence, as well as assessing the severity and impact on the health of drug users[6].

For improving the voluntary adhesion of health professionals in the assessment of drug safety, and to increase rates of ADR reporting, some actions are necessary. It is important to identify the causes that lead to underreporting of problems related to the use of drugs by health professionals, in order to establish strategies that will be developed for encouraging the communication of risks associated with drug use and provide safety guarantees for patients. In this context, the objectives of this study were: 1) identifying the manuscripts that analyzed the causes associated with poor adherence of health professionals to the passive method of pharmacovigilance service and, 2) proposing strategies designed to improve the rates of spontaneous reporting of ADR.

METHOD

The systematic review was carried out in the databases of LILACS, PAHO, SciELO, EMBASE and PubMed, looking for items to answer the guiding question: What causes that health professionals do not realize the pharmacovigilance notification?

The search strategy used was based on the PRISMA Statment[7], using the following health descriptors: *Surveillance of Marketed Products* AND *Adverse Drug Reaction Reporting Systems* AND *Attitude of Health Staff*. The following keywords were also used to complement the search: *ADR*, *underreporting of ADRs*, *notification rate of ADRs*, *adverse drug reactions (ADRs)*, *under-reporting of ADRs* and *attitudes and reporting behavior*.

The technique of content analysis was used for selecting the articles[8]. The initial reading of all articles identified by the elaborate search technique was done (N=149), covering the period between 1992 and 2012. The goal was to eliminate the articles that were not in English, Portuguese or Spanish; unavailable manuscripts; reviews; educational interventions; editorials; letters to the editor; news; comments; as well as results that were dissertations, thesis or abstracts published in conference proceedings or scientific journals.

The selected articles were subjected to content analysis and those not assessing the causes related to the underreporting of ADR by health professionals were eliminated. The analysis of the articles were developed by two reviewers (FRV and SGP), with eventual disagreements resolved through discussion.

The variables of interest were defined through a content analysis involving the following criteria: year of publication, country in which the study was carried out, the study method (epidemiological approach), instruments and methodology used for assessing the cause of underreporting, level of health care, professional category included in the study, adherence to the survey (response of professionals participating in the study), and the causes of underreporting according to the criteria described by Inman WHW[9]. He was the first to present a list of seven attitudes related to the causes of underreporting, calling them the *seven deadly sins*:

1) complacency (believing that serious ADRs are well documented when the drug is released in the market);

2) fear of getting involved in a lawsuit (legal process);

3) guilt for having been responsible for the damage observed in the patient;

4) ambition of group and publish case series or financial benefit;

5) ignorance on how to describe the notification (believing that only serious and unexpected ADRs must be reported);

6) insecurity about reporting suspicions of ADR (belief that there should be notification only if there is certainty that the damage was caused by the use of specific medication);

7) indifference, that is, lack of interest, time or other excuses related to postponing the notification of damage due to drug use.

RESULTS

In total, 149 potentially relevant articles were identified on the evaluated database. After reading the abstracts, 117 articles were eliminated for not fitting the inclusion criteria. After content analysis, four articles were eliminated (Chart 1) and 29 were considered eligible for the study (Chart 2).

It was observed that most of the studies (N=16) were carried out in the European continent, especially at tertiary level of health care (N=24) for physicians (N=22) and pharmacists (N=10). The experimental method most widely used for identifying the causes was the cross-sectional,

observational (N=24), with the questionnaire as the most used instrument (N=26). The response rate of the study subjects was greater than 50% in 21 studies, although three studies did not report these data. The main causes related to underreporting of adverse drug reaction were ignorance (N=24), insecurity (N=24) and indifference (N=23). No causes different than those established by Inman WHW have been identified[9]. However, the data show the eighth sin of underreporting, which is the lack of training in pharmacovigilance.

Chart 1 - Studies excluded of the review after content analysis and rationale for not meeting the inclusion criteria

Author	Rationale
Bäckström et al.[10]	Estudio de intervención que evaluó el efecto de incentivo económico sobre la tasa de notificación espontánea de RAM.
Granas et al.[11]	Educational intervention study assessing the effect of an educational program on pharmacovigilance for pharmacists in Norway. They observed that lack of trust, time and knowledge about how to report an adverse reaction could prevent them from reporting.
Giraldo-Matamoros et al.[12]	Study of active search for ADRs reported by nurses in the pharmacovigilance system of Extremadura, a region of Spain. However, it did not analyze the factors related to non-adherence of this professional category in the pharmacovigilance system.
González-Rubio et al.[13]	Retrospective study that analyzed the notifications of the primary sector in Spain. The paper justifies that underreporting may have occurred due to ignorance and insecurity, but did not evaluate this data with health professionals.

Chart 2 - Studies that analyzed the causes related to underreporting of adverse drug events.

Study (year of publication)	Location Country	Methods					Results	
		Method	Professional category	Level of health care	Sample size	Instruments	Adherence (%)	Causes of underreporting
Bateman et al.[14]	England	Cross-sectional, Observational	Physicians	Tertiary	1600	Pre-structured questionnaire by mail	74%	complacency (1) fear of litigation (2) ambition (4) insecurity (6) indifference (7)
Belton et al.[15]	United Kingdom	Cross-sectional	Physicians	Primary, secondary and Tertiary	500	Pre-structured questionnaire by mail	57%	complacency (1) fear of litigation (2) ambition (4) insecurity (6) indifference (7)
Belton and The Europen Pharmacovigilance Research Group[16]	Member Countries of the European Union	Cross-sectional	Physicians	Primary	Uninformed	Pre-structured questionnaire Uninformed	Uninformed	complacency (1) fear of litigation (2) culpa (3) ambition (4) ignorance (5) insecurity (6) indifference (7)
Cosentino et al.[17]	Italy	Cross-sectional	Physicians	Primary	350	Pre-structured questionnaire by mail	59,10%	ignorance (5) insecurity (6)
Eland et al.[18]	Holland	Cross-sectional	Physicians	Primary, secondary and tertiary	1984	Pre-structured questionnaire Uninformed tertiary	68,40%	fear of litigation (2) ignorance (5) insecurity (6) indifference (7)
Williams et al.[19]	Ireland	Cross-sectional, observational	Physicians	Primary and tertiary	400	Pre-structured questionnaire by mail	39,50%	complacency (1) fear of litigation (2) ignorance (5) insecurity (6) indifference (7)
Bäckström et al.[20]	Sweden	Cross-sectional	Physicians	Primary and tertiary	1274	Pre-structured questionnaire by mail	58,70%	complacency (1) ignorance (5) insecurity (6) indifference (7)

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Study (year of publication)	Location Country	Methods					Results	
		Method	Professional category	Level of health care	Sample size	Instruments	Adherence (%)	Causes of underreporting
Figueiras et al.[21]	Spain	Case-control	Physicians	Primary	692	Pre-structured questionnaire by mail	Not reported	complacency (1) ignorance (5) indifference (7)
Green et al.[22]	United Kingdom	Cross-sectional	Pharmacists	Tertiary	600	Pre-structured questionnaire by mail	53,70%	fear of litigation (2) ambition (4) ignorance (5) insecurity (6) indifference (7)
Hasford et al.[23]	Germany	Cross-sectional	Physicians	Primary, secondary and tertiary	1315	Pre-structured questionnaire by email	61,30%	complacency (1) fear of litigation (2) ignorance (5) insecurity (6)
Li et al.[24]	China	Cross-sectional	Physicians, nurses and hospital administrators	Tertiary	2000	Pre-structured questionnaire Uninformed	85,00%	complacency (1) guilt (3) ambition (4) ignorance (5) insecurity (6) indifference (7)
Herdeiro et al.[25]	Portugal	Case-control	Physicians	Primary and tertiary	859	Pre-structured questionnaire by mail	46,20%	complacency (1) ignorance (5) insecurity (6) indifference (7)
Vallano et al.[26]	Spain	Qualitative	Physicians	Tertiary	208	Focus group discussions and analysis of transcripts	100%	fear of litigation (2) ignorance (5) insecurity (6) indifference (7)
Herdeiro et al.[27]	Portugal	Case-control	Pharmacists	Primary and tertiary	314	Pre-structured questionnaire by email	86,80%	complacency (1) ignorance (5) insecurity (6) indifference (7)
Aziz et al.[28]	Malaysia	Cross-sectional	Physicians	Primary and tertiary	415	Face-to-face pre-structured questionnaire (survey)	84,30%	ignorance (5) insecurity (6)
Okezie et al.[29]	Nigeria	Cross-sectional	Physicians	Tertiary	220	Pre-structured questionnaire Uninformed	91%	ignorance (5) insecurity (6)
Ekman et al.[30]	Sweden	Cross-sectional	Physicians	Tertiary	1201	Pre-structured questionnaire by mail	54%	complacency (1) ignorance (5) insecurity (6) indifference (7)
Nichols et al.[31]	Canada	Qualitative exploratory	Pharmacists and physicians	Tertiary	36	Focus groups with pharmacists and pre-structured surveys with physicians	100%	insecurity (6) indifference (7)

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Study (year of publication)	Location Country	Methods					Results	
		Method	Professional category	Level of health care	Sample size	Instruments	Adherence (%)	Causes of underreporting
Oshikoya et al.[32]	Nigeria	Cross-sectional	Physicians	Tertiary	120	Pre-structured form	82,50%	guilt (3) ambition (4) insecurity (6) indifference (7)
Passier et al.[33]	Holland	Cross-sectional	Physicians	Primary	1490	Pre-structured questionnaire by mail	47%	fear of litigation (2) ignorance (5) indifference (7)
Vessal et al.[34]	Iran	Cross-sectional	Pharmacists	Primary and tertiary	200	Pre-structured questionnaire	55%	complacency (1) fear of litigation (2) ignorance (5) insecurity (6) indifference (7)
Gavaza et al.[35]	United States	Cross-sectional	Pharmacists	Primary and tertiary	1500	Pre-structured questionnaire by mail	16,40%	fear of litigation (2) ambition (4) ignorance (5) insecurity (6) indifference (7)
Su et al.[36]	China	Cross-sectional	Pharmacists	Tertiary	288	Face-to-face structured questionnaire	85,40%	complacency (1) ignorance (5) insecurity (6) indifference (7)
Bello & Umar[37]	Nigeria	Cross-sectional	Physicians	Tertiary	61	Pre-structured questionnaire Survey	Uninformed	fear of litigation (2) ignorance (5) insecurity (6)
Desai et al.[38]	India	Cross-sectional	Physicians	Tertiary	426	Pre-structured questionnaire Uninformed	61%	ambition (4) ignorance (5) indifference (7)
Gavaza et al.[39]	United States	Cross-sectional	Pharmacists	Primary and tertiary	1500	Pre-structured questionnaire by mail	26,40%	indifference (7)
Oreagba et al.[40]	Nigeria	Cross-sectional	Pharmacists	Primary	400	Face-to-face pre-structured questionnaire	83%	ignorance (5)
García et al. [41]	Venezuela	Cross-sectional	Pharmacists y physicians	Primary, secondary and tertiary	913	Face-to-face questionnaire	65,40%	ignorance (5) insecurity (6) indifference (7)
Pernas et al. [42]	Portugal	Cross-sectional	Physicians, nurses and pharmacists	Primary and tertiary	80	Pre-structured questionnaire	100,00%	complacency (1) fear of litigation (2) guilt (3) ambition (4) ignorance (5) insecurity (6) indifference (7)

DISCUSSION

The pharmacovigilance underreporting is a global reality evidenced by the identified studies, which were carried out in 17 different countries, and a multicenter study conducted in the European Union. However, it was observed that most of the analyzed publications (N = 17) were carried out in Europe (Germany, Spain, Holland, England, Ireland, Italy, Portugal, UK, Sweden). Such fact can be explained based on the tradition of these countries in the Program for International Drug Monitoring of the World Health Organization. In 1968, due to the presence of national ADR registration systems in Ireland, Holland, Sweden and the UK, these nations were invited to send ADR records for the WHO, in order to assess the safety of drugs available in the pharmaceutical market[43].

However, most of the countries in America, Africa and Asia joined the program afterwards (in the 1990s and 2000), which leads to the assumption that pharmacovigilance activities are more recent hence, only few studies were identified. For this reason, there is a need to better understand the factors associated with underreporting of problems related to drug use, and encourage voluntary reports by health professionals in these countries or Latin American countries.

The main epidemiological method and technique of data collection verified in this review was the cross-sectional, observational study (N = 24), and use of self-reported questionnaires (N = 15). These are relevant strategies to encourage surveys of this nature, especially in developing countries such as those from Latin America, where only one study was identified. This is justified based on the benefits of cross-sectional studies, which are inexpensive, can be made in a short time frame, and are capable of creating research hypotheses to be investigated with more robust methodologies. Moreover, the identified papers that used this method obtained similar results in relation to the authors who carried out studies with larger level of evidence (case-control). A study[44] carried out the analysis of the characteristics of ADR recorded in the WHO-ADR database (Vigibase), correlating this information with the income profile of registrars countries. The authors found that the rates of notification are lower in low-income countries, probably due to lack of knowledge and experience[11,13]. This corroborates the necessity of encouraging studies in these countries with the use of cheaper methods.

Considering the application of self-reported questionnaires, the literature points the low rate of return of these instruments by study participants (mostly doctors) as the main limitation of this technique[45]. The loss of more than 20% of the sample hampers conclusions with data for other populations, in addition to other factors such as convenience and sample size, method of study and biased results, considering that professionals who voluntarily answered the questionnaire possibly showed greater interest in the area of pharmacovigilance. However, the application of questionnaire by mail or email facilitates data collection, especially when respondents are geographically spread. Given this, a search[46] proposed sending stamps for the responses and reminders of the return period to encourage subjects' adherence to the survey.

Despite the limitations of collection methods and techniques, the main causes of ADR underreporting found in the included studies were ignorance and insecurity. This has a strong correlation with professionals' low knowledge about the activities of analysis of drug safety. Such fact was the most common cause for non-adherence of professionals to pharmacovigilance service, confirming a study hypothesis that evaluated the condition of notifications.

Thus, the notifications of professionals may be encouraged by promoting educational interventions aimed at clarifying the importance of the practice. As well as the concepts and processes involved in these activities, namely: which ones should be recorded (any suspected adverse drug events), who can register, and the return to society (patient safety), health facilities (reduction of unnecessary costs) and the pharmaceutical market (control and regulation). Studies show that continuing education for health professionals are effective in changing attitudes and behavior in relation to registration of adverse drug events, notably ADR[47-48]. Hence, economic costs are optimized due to the incentive on rates of voluntary registration of ADR[20].

Another cause of underreporting frequently reported by physicians and pharmacists included in the study is indifference, mainly associated with the lack of interest in registration, lack of time for too many activities in the clinical routine, among others. As an attempt to solve this problem, the ADR reporting by the own users of drugs is a positive perspective[49]. In addition, making the access to registration forms easier and simplifying documents[1], would contribute to improve the notification rates of problems related to medication, as well as facilitating communication between registrars and pharmacovigilance centers (such as the Rede Sentinela, a project developed in Brazil that encourages pharmacovigilance activities in hospitals, aimed at enabling the analysis of safety, quality and effectiveness of medicines), and encouraging feedback from the results of reports [26,31,35].

Studies evaluating the attitudes of nursing staff[24,42] found that the lack of knowledge in completing the notification form, and the lack of time to report ADRs are the main causes of underreporting in this class. Therefore, strategies must be developed to improve the adhesion of these professionals to the pharmacovigilance service. As these professionals are responsible for administering medications and assisting by the bedside, they can contribute to identify suspected problems of safety and effectiveness of drugs[50], especially serious ADR[51] that are unexpected. Thus, the training and qualifications of nursing staff may allow the development of competencies and skills for behavior change in relation to the spontaneous reporting. A study[52] verified that the completion of training by nurses is essential to optimize their roles in pharmacovigilance actions. In addition, health institutions should strengthen nonpunitive management for the administration of risks associated with drug therapy.

Health institutions are changing the way they manage risk (from personal to systemic)[53], and encouraging the notification of adverse events to drugs by health professionals, in order to improve processes and not to identify the author, causing fear of punishment and retaliation in these professionals, which is a major barrier to promote the reporting of drug related problems. Thus, ensuring the confidentiality and secrecy of people reporting the data avoids their exposure and encourages their participation in the analysis of drug safety[54].

The great interest in compiling and publishing case series was one of the causes of underreporting less frequently mentioned by professionals, perhaps because this is more related to the interests of researchers associated with universities. However, all records resulting from scientific investigations should not be dissociated from the regulatory acts. Therefore, they should be given to regulatory health agencies for feeding the database, contributing to signal generation in pharmacovigilance and improving communication of the risks associated with drug use. Considering financial benefits, such as encouraging registration of ADR through salary increases or bonuses for example, is a questionable strategy, since no impact of this incentive was found on ADR reporting in a study carried out in a Spanish hospital[55].

Finally, it is necessary to know the causes that lead to non-compliance with pharmacovigilance service in order to strongly encourage the reporting of ADR by health professionals, because many strategies can be used and developed for reducing this problem to a minimum. Thus, the best action plan may be designed, considering the needs and aspirations of the people who report the cases, the available resources for strategies implementation and the frequency with which they should applied. Therefore, studies of this nature should be carried out primarily in the American continent to indirectly contribute with the harmonization of patient safety plans.

Finally, the underreporting causes often informed by health professionals are related mainly to the low knowledge of concepts and processes related to pharmacovigilance and to indifference regarding this service. Continuing education, easy access to the registration form and its simplification are strategies that can be developed to increase the registration rates of ADR by health professionals. Furthermore, low cost epidemiological methods (cross-sectional, observational type) are able to detect similar underreporting causes when compared with methods of higher levels of evidence. This allows that developing countries like those of Latin America carry out studies aimed at investigating the reasons associated with low adherence of health professionals to pharmacovigilance service and demystify prejudices about the consequences of underreporting.

The limitation of the study was that the data obtained may be underestimated because of the selection strategy. Five databases were consulted and the only articles considered eligible were those written in Portuguese, English and Spanish, plus eight articles not available to consultation, which were then eliminated from the review. In addition to that, every author had an own interpretation of the *seven sins of Inman*, which can have been different from those considered in this review.

CONCLUSION

This study allowed adding the eighth deadly sin in underreporting: the lack of training in pharmacovigilance for health professionals. However, qualitative studies are needed to better understand this phenomenon.

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