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Potential serious drug interactions in the hospital environment: Validation of warning messages for use in electronic prescription software

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Abstract

Objective: The present study has as its main objective the validation of alert messages, for prescribers, about possible serious drug interactions. **Methods:** This is a descriptive documentary study, using a hospital's medication list. The first step was identifying and analyzing potential serious drug interactions through the database on the website Drugs.com among the drugs on this list. The interactions identified were categorized into Medicines; Mechanism; Recommendations, and Action. The second step was the validation of the selected interactions. The validation was carried out using the Delphi Technique, in which the interaction bank was sent with a questionnaire to assess content and clinical utility for Brazilian professional specialists with expertise in the area. In the end, he tried to obtain at least a Content Validity Coefficient (CVCc) of at least 0.8 of agreement between the judges. **Results:** After the analysis, 330 possible serious drug interactions were selected in which they were validated. Regarding evaluating the interaction alerts content,, all the questions presented CVCc equal to or greater than 0.8 during the study. All 37 judges responded and participated in the validation process, who suggested adequacy of language, insertion of new interactions and standardization of messages. In addition, the jury was composed of a group of heterogeneous people, with several training areas, the highest proportion composed of masters (43.24%) and PhD (18.91%). **Conclusion:** The database was validated with a CVCc of at least 0.8 of agreement between the judges, considering the high prevalence of possible serious drug interactions, both in the hospital and in the outpatient setting. It can be implemented in electronic prescription software, helping to reduce the prevalence of these potential serious drug interactions and contributing to patient safety.

Keywords: drug interactions; validation study; delphi technique

Potenciais interações medicamentosas graves no ambiente hospitalar: Validação de mensagens de alerta para uso em software de prescrição eletrônica

Resumo

Objetivo: O presente estudo tem como objetivo principal a validação de mensagens de alertas, para os prescritores, sobre possíveis interações medicamentosas graves. **Métodos:** Trata-se de um estudo descritivo documental, sendo utilizado a lista de medicamento de um hospital. A primeira etapa foi identificação e análise de potenciais interações medicamentosas graves por meio da base de dados do site Drugs.com entre os medicamentos desta lista. As interações identificadas foram categorizadas em Medicamentos; Mecanismo; Recomendações e Ação. A segunda etapa foi a validação das interações selecionadas. A validação foi realizada por meio da Técnica de Delphi, em que foram enviado o banco de interações com um questionário de avaliação de conteúdo e utilidade clínica para especialistas profissionais brasileiros com expertise na área. Ao final procurou obter no mínimo um Coeficiente de Validade de Conteúdo (CVCc) de pelo menos 0,8 de concordância entre os juízes. **Resultados:** Após a análise foram selecionados 330 possíveis interações medicamentosas graves, as quais foram validadas. Em relação a avaliação do conteúdo dos alertas das interações todos os quesitos apresentaram CVCc igual ou superior a 0,8 durante o estudo. Ao todo 37 juízes responderam e participaram do processo de validação, que sugeriram adequação da linguagem, acréscimo de interações, padronização de mensagens. Além disso, o júri foi composto de um grupo de heterogêneos, com diversas áreas de formação, sendo a maior proporção compostas por mestres (43,24%) e doutores (18,91%). **Conclusão:** Considerando a elevada prevalência de possíveis interações medicamentosas graves, tanto no âmbito hospitalar como no ambulatorial, o banco de foi validado com um CVCc de pelo menos 0,8 de concordância entre os juízes. Podendo ser implantado em um software de prescrição eletrônico auxiliando na diminuição da prevalência dessas potenciais interações medicamentosas graves e contribuindo para a segurança do paciente.

Palavras-chave: interações medicamentosas; estudo de validação; Técnica Delphi



Introduction

In the 20th century, Brazil underwent a sociodemographic transformation process characterized by a reduction in mortality and an increase in society's life expectancy.^{1,2} Population aging underlies the increase in the number of older adults, which is related to the increased consumption of medications and polypharmacy.^{3,4,5} In addition to that, hospitalized patients use more medications when compared to other health settings. Consequently, the probability of adverse events increases with the number of medications prescribed.⁸

The National Health Surveillance Agency (*Agência Nacional de Vigilância Sanitária*, ANVISA) characterizes drug interaction as a pharmacological, toxicological, clinical or laboratory response caused by the combination of a drug with other medications. The interaction can result in an increase or reduction of the therapeutic effectiveness or even in the emergence of new adverse events, impairing safety in medication use.⁹

The concomitant use of multiple drugs presents higher risks of adverse reactions and drug interactions, which can lead to severe consequences for patient safety. In addition to that, problems arising from interactions between drugs are significant and are associated with 0.6% to 4.8% of the hospitalizations.¹⁰ Another study shows a 6.5% prevalence of the admissions associated with a Drug-related Adverse Reaction (ADR), directly leading to admission in 80% of the cases. In general, the interactions represent 16.6% (from 15% to 19%) of the ADRs.¹¹

A Brazilian study identified that the prevalence of potential drug interactions in older adults in a high-complexity hospital was 87.8%. In relation to the severity of the drug interactions, 1,102 (85.6%) were classified as moderate; 176 (13.7%) as severe; and 10 (0.7%) as contraindicated.¹² A meta-analysis revealed that 33% of the general ward patients and 67% of the intensive care patients experienced at least one potential drug interaction during their hospitalization.¹³ In contrast, 48.3%¹⁴ and 53.4%⁴ of the outpatients undergoing monitoring experienced potential drug interactions. It is also known that 96% of the patients on polypharmacy undergoing outpatient treatment present at least one potential drug interaction.¹⁵

In 2017, the World Health Organization (WHO) launched a global initiative to reduce by 50% the serious and preventable drug-related harms in all countries over the next five years.¹⁶ Therefore, this study aims at validating warning messages about potential serious drug interactions for an electronic prescription software. The messages will be validated with the Delphi Technique. The technique consists of a systematized method of judging information, which is useful to obtain expert consensus on a given topic. It is carried out through validations articulated in rounds on an issue where there is little evidence or agreement.¹⁷ Finally, the results of this analysis can contribute to the development of strategies, such as the inclusion of warning messages in an electronic prescription software, which minimize the potential negative effects of the interactions and better manage patients in the clinical practice.

Methods

A documentary and descriptive study was conducted

List of medications and study locus

The list of medications used to analyze potential serious drug interactions in this study corresponds to the list of medications selected from a medium-complexity philanthropic hospital located in the metropolitan area of the city of Belo Horizonte, in the state of Minas Gerais. The list had 194 medications and was prepared by the Pharmacy and Therapeutics Commission, together with the hospital's clinical staff. This hospital has 109 beds for the care of patients from the Unified Health System (*Sistema Único de Saúde*, SUS) and from private health plans. It has outpatient, orthopedics, maternity, Intensive Care Unit (ICU), pediatrics and surgery units. The dispensing system uses individualized dose per hour and per 24 hours, depending on the sector.

Stages for conducting the study

In order to attain the objectives, the study was conducted in two stages, namely:

Stage A: identification and analysis of the potential severe drug interactions

The first stage consisted in identifying the potential serious drug interactions and was carried out through the database of the "Drugs.com" website, the largest independent and most visited website for information about medications, freely accessed on the Internet. The platform presents content for the lay and professional audience, in addition to underpinning the information by describing the bibliographic references of all the interactions mentioned. It is important to highlight that serious drug interactions are those with potential risk of death, threat to life, hospitalization or prolonged hospitalization; significant or persistent disability; congenital anomaly or clinically significant event.¹⁸

To analyze the interactions, all the medications included in the hospital's list were registered in the "Drugs.com" website. The following filters were applied after registration: "professional scope" and "serious interactions", for generation, followed by a report with this information: potential drug interactions, clinical impact, mechanism and clinical management.

For data analysis and interpretation, a database was built in the form of spreadsheets, for use in the clinical practice, with the aid of Microsoft Office Word 2016, containing the following information for each interaction pair: Interaction, Mechanism, Recommendations, Action.

In a future stage, this information will be entered into the hospital's electronic prescribing system so that warning messages are generated when prescribing medications, in order to assist the clinician in decision-making and to improve patient safety in the use of medications. The following are understood as warning messages: Information organized in order to draw the user's attention regarding certain conduct.

During the analysis of the interactions identified, the information was categorized and systematized as follows:

- Medications involved in the Drug interaction;
- The Mechanism of the interaction;
- Recommendations that will be inserted in the electronic prescription software warnings;
- And, finally, the Action that the physician can follow, which will be categorized into: Generally avoid, contraindicated, close monitoring, dose adjustment.



Stage B: Validation of the selected interactions

Considering that the interactions identified are described in English, and that they come from studies carried out in different countries and care settings, the content of the warning messages was validated by experts (Brazilian professionals with expertise in the area) using the Delphi Technique.^{19,20,21}

To carry out this stage, the professionals received the interaction database with the respective information of interest and a questionnaire to assess the content of the information regarding language adequacy and clinical usefulness. The professionals were officially invited via email;²² after acceptance, they received the validation questionnaire and text messages also via e-mail, with a 15-day response period. Likert-type scales, with positive values from 0 to 10, where 0 represents “strongly disagree” and 10 “strongly agree”, were developed and converted into agreement percentages from 0% to 100%.²³ At the end of each question, an optional field for comments by the specialist was made available, in addition to the possibility of issuing an opinion and adding suggestions considering the professional’s clinical and intellectual experience.

Also in this stage, after receiving all the answers from the professionals, the agreement percentage was estimated using the Content Validity Coefficient (CVC).²⁴ The questions assessed were the following: Suitable language; Quality of the content of the messages; Size of the messages; Relevance of the interactions; Mechanism or Effect; Quality of the recommendations for managing the interaction; Suggested action for managing the interaction; and Usefulness of inserting the warning messages. The CVC was calculated for each question assessed, following these stages: (a) calculation of the mean of the scores (Mx); (b) calculation of the initial CVC (CVCi), by dividing the mean by the maximum value that the item could reach; (c) calculation of the error (Pei), by dividing the number one (1) by the total number of professional evaluators, to the power of the same number of evaluators – the error aims at minimizing possible biases; (d) calculation of the final CVC (CVCc), from the subtraction of CVCi by Pei. The items with a CVCc above 0.8 were considered valid. The topics that did not reach the stipulated score were reformulated according to opinions and suggestions contained in the comments and sent back to the experts until a CVCc of at least 0.8 of agreement was reached in all the topics.

Ethical aspects

The project was approved by the Committee of Ethics in Research involving Human Beings of the Federal University of São João del-Rei (*Universidade Federal de São João del-Rei*, UFSJ) - Dona Lindu Midwest Campus (*Campus Centro Oeste*, CCO) CAAE: 12092019.0.0000.5545.

Results

Altogether, 161 medications from the hospital’s list were found on Drugs.com and included in the research. After the analysis, 330 possible severe drug interactions were selected. Therefore, a database was created with the information collected so that, in a future time, such information <https://ufsj.edu.br/portal2-repositorio/File/nepefac/GUIA%20INTERACOES%20FINAL%20>

corretto.pdf be incorporated into the hospital’s electronic prescription system.

After the stage of identification and analysis of the potential serious drug interactions, 60 judges were invited to validate the information collected. Of these, 37 answered the invitation and participated in the validation phase. The collaborators’ profile was mostly from the Pharmacy area (n=30; 81.0%), followed by Nursing (n=4; 10.8%) and Medicine (n=3; 8.1%). It is worth noting that 27 (73%) were post-graduates in their respective areas (Table 1).

Table 1. Profile of the participants in the validation of the warning messages.

Highest Academic Degree	(%)
PhD	18.9
MS	43.2
Specialist	10.8
Graduate	13.5
Undergraduate student	13.5

In relation to the assessment of the content of the messages, all the questions presented CVCc values equal to or greater than 0.8 during the study (Table 2). However, some topics were reformulated according to the suggestions sent by the judges, with the intention of improving comprehension and the content linked to the messages. This process resulted in the inclusion of 11 drug interactions and in the change of three actions that the judges considered relevant. Considering the suggestions made by the judges (Table 3), a compilation of considerations was carried out, which were partially or not accepted by the researchers, due to the need for homogeneity and concise construction of the database so that it would be feasible for the clinical practice.

After analysis using the Delphi technique, validation and construction of the database were completed, as shown in Figure 1.

In relation to the profile of the possible drug interactions, the main medications involved were Amiodarone (n=31; 9.1%), Methadone (n=28; 8.2%), Tramadol (n=28; 8.2%), Fentanyl (n=23; 6.7%) and Citalopram (n=23; 6.7%). The main actions proposed in the warnings were the following: “close monitoring” (n=161; 47.35%) and “avoid association with” (n=127, 37.3%).

Table 2. Final Content Validity Coefficient (CVCc) of the judges’ evaluations.

Topics referring to the messages	CVCc
Quality of the content of the messages	0.94
Size of the messages	0.90
Relevance of the interactions	0.92
Mechanism or Effect	0.94
Quality of the recommendations to manage the interaction	0.90
Action suggested to manage the interaction	0.91
Usefulness of inserting the warning messages	0.97

Figure 1. Examples of the database:

Interaction	Mechanism or Effect	Recommendations	Action
Clarithromycin x methylprednisolone	Increase of the carbazepine plasma concentration.	If concomitant use is necessary, reduce by 50% the daily dose of methylprednisolone	Adjust the dose
Omeprazole x Clopidogrel	Omeprazole inhibits CYP2C19, which metabolizes the clopidogrel pro-drug, and this reduces the cardioprotective effect of clopidogrel.	Consider the possibility of deprescribing omeprazole. If a proton pump inhibitor is needed, replace with pantoprazole	
Amiodarone x Chlorpromazine	They can cause dose-related QT interval prolongation.	Avoid the association, unless it is expected that the benefits outdo the risks. If the association is necessary, monitor electrocardiogram, hyperkalemia and hypomagnesemia.	Avoid the association
Ciprofloxacin x Haloperidol	QT interval prolongation, which can result in additive effects and increase the risk of ventricular arrhythmias	If it is really necessary to use haloperidol and there is no other alternative, Monitor closely, especially if in parenteral administration and in high doses.	Monitor closely
Loperamide x Clopidogrel	Increased plasma concentration and adverse effects of loperamide	Do not exceed the recommended dose and frequency of loperamide. Monitor: torsades de pointes, dizziness, palpitation, abnormal heart rhythm, shortness of breath or syncope	Monitor closely

Table 3. Examples of the suggestions made by the judges during message validation

Suggestions made by the specialists after correcting the messages	Suggestion accepted (Yes/No/Partially)
Language adequacy	Yes
Adding interactions	Yes
Standardization of actions	Yes
Change of action	Yes
Adjust the size of the messages to the dynamics of the clinical practice	Partially
More detail in the recommendations	Partially
Expand the description of the interaction mechanism	No

For the analysis, participants who obtained technical qualification in the area were invited. In addition to knowledge and experience, the judges had to be willing to participate in the assessment processes and stages in the Delphi Technique.²⁶ It is believed that a heterogeneous group with different training levels and areas makes it possible to obtain satisfactory results in the construction and validation of warning messages about drug interactions.^{31,32} After analysis by the judges, the database became clearer, more robust and concise.

Thus, this project validated warning messages of possible serious drug interactions to later include them in an interaction assessment software program. Other studies suggest that an electronic monitoring program coupled with a pharmaceutical intervention produced a significant reduction in the frequency of drug interactions.³³

The study has as limitations the use of only a single database for the analysis of the interactions, considering that the information sources presented heterogeneous data profiles.³⁴ Another limitation was the fact that the medications analyzed came from only one list of a single hospital. On the other hand, the study used an open-access database, adapted to the Brazilian reality, in addition to employing three different categories of professionals with variable clinical experience, which enabled a review in several spheres. Finally, it is believed that this study may come to improve patient safety and minimize drug interactions, with the possibility of resulting in the best treatment for the patient in line with shorter hospitalizations and costs for the hospitals.

Discussion

The study enabled the creation of an information database to identify potential and serious drug interactions for analysis of prescriptions in the hospital environment. The development of electronic systems, such as the creation of software to assess possible drug interactions in a prescription, can be an alternative to minimize the risk of these events.^{25,26,27} The organization of the technical-scientific content is essential for the construction of these tools.

In this study, to validate the information obtained, the suggestions made by a panel of experts were considered, using the Delphi Technique, to reach consensus regarding the form and content of the warning messages, with a minimum CVCC of 0.8 of agreement on all the topics. Other studies also employed the CVC as part of this technique to validate the instrument and its items, since it can measure the proportion of judges who are in agreement on such items and, therefore, verify the ability to accurately measure the phenomenon to be studied.^{28,29}

The Delphi technique has been widely used in health research,²⁰ especially because it is an organizational research tool with enormous power today in the context of the health services.³⁰ In view of the proposed technique, even with the judges' considerations, the researchers did not conduct a second Delphi round. This was justified by the fact that all CVCC values have reached at least 0.8 of agreement, considered not necessary.

Conclusion

This study allowed assembling a set of warning messages of possible severe drug interactions validated by specialists, to later introduce them into an electronic prescription software program. Using the Delphi technique, all items obtained a CVC above 0.8, the cutoff point recommended for each topic to be validated.

Considering the results obtained, the messages present themselves as an important tool to guide the medical course of action in the prescription process. It can be implemented in an electronic prescription software program, helping to reduce the prevalence of these potential serious drug interactions and contributing to patient safety. New studies involving the execution of the software must be carried out in order to assess its feasibility, applicability, reproducibility and effectiveness.

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Colaboradores

The authors declare that they are aware of the final version of the article, guaranteeing the accuracy and integrity of the information herein expressed.

1. Project conception or data analysis and interpretation: VCF; GCF LAS and AOB

2. Writing of the article or relevant critical review of the intellectual content: VCF; GCF; LAS and AOB

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Conflict of interest statement

The authors declare that there are no conflicts of interest regarding this article.

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