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*RESEARCH ARTICLE*

# Evaluation Of Mobile Applications For The Detection Of Potencial Drug Interactions

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**ABSTRACT**

In chronic diseases, such as rheumatoid arthritis (RA), the affected patients tend to have a higher risk of developing comorbidities and demand therapy with a wide variety of drugs (polypharmacy), so the phenomenon of drug interactions can arise in people with RA. The aim of this study was to analyze the available mobile applications which presented the functionality of drug interactions and adverse drug reactions. The sample consisted of 23 adults diagnosed with RA. Of the 1030 drugs distributed by the pharmacy, only the ten most frequent drugs were compared in pairs in three applications. The mean age of the patients was 59.4 years, with a median of 61 years. The vast majority of patients were women, 20 (87%). A greater risk was observed for the variables: family member with cardiovascular disease (Odds ratio=1.87) and allergic reaction to drugs or food (Odds ratio=1.55). A predominance of potential severe risk for drug interactions (20 alerts) was observed. The Drugs.com app was the most sensitive. It was concluded that the use of these devices for decision making as an instrument for prescription and therapeutic follow-up should be used in the older persons with rheumatoid arthritis.
**Keywords:** Rheumatoid arthritis; Drug interactions; Adverse drug reactions; Mobile apps; Older persons

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## INTRODUCTION

Due to the autoimmune and inflammatory nature of Rheumatoid Arthritis (RA), there is the possibility of the development of other associated diseases such as: coronary heart disease, atherosclerosis in the carotid arteries, peripheral vascular disease and cerebrovascular accident (CVA). Other common diseases are: congestive heart failure, type 2 *diabetes mellitus* and osteoporosis [1].

Although there are different drugs that are already used for the treatment of RA, new drugs have appeared in recent years, including the so-called biological drugs and small molecules that inhibit cytoplasmic signaling. These resources, associated with positive strategies (fixed therapeutic goals, aiming for the disease remission), have brought a better quality of life for patients, reducing the number of severe deformities and functional disability [2].

The Polypharmacy phenomenon consists of the simultaneous use of multiple medications, occurring especially among the older persons, putting this population at risk by increasing drug interactions [3]. In addition, the chances of developing adverse drug reactions (ADRs) are also included in this population, due to alterations in renal function, decreasing the excretion of metabolites and further aggravating this whole scenario [4].

Elderly primary and secondary care patients in the United States of America (USA) are more subject to drug interactions than the patients of other age groups. Some statistical studies suggest that the amount of ADRs can be much higher, since many cases are underreported, *i.e.*, they are not considered serious. This fact can represent a much more problematic picture in public health, since it increases the costs and the duration of hospital admissions [5].

Drug interactions occur when one or more drugs are administered simultaneously, interacting with each other. There are two main types of drug interactions: pharmacokinetics and pharmacodynamics. The interactions of the first type can affect the bioavailability (absorption, distribution, metabolism) of drugs. On the other hand, in pharmacodynamic interactions, the action between drugs can be synergistic or antagonistic, and can occur at the pharmacological receptor level or at the signaling level, affecting different signaling pathways or effector levels [5].

According to WHO, pharmacovigilance is defined as the science and activities related to the identification, evaluation, understanding and prevention of adverse effects or any other problems related to the use of medicines [6].

Spontaneous reporting systems provide an extensive and appropriate field for detecting new adverse effects of drug interactions in the post-marketing period [7]. Other studies have shown that the spontaneous reporting of patients is one of the great trends of the present day, making pharmacovigilance systems more proactive [8].

In Brazil, from the mid-2000s, a notification method for Health Surveillance, known as Notivisa [9], was implemented for the first time. Data were collected using an electronic notification form available online. In 2018, it was replaced by the new notification system in Health Surveillance known as Vigimed [10].

The use of mobile applications available on digital platforms in order to assess potential drug interactions is a tool of increasing interest for the scientific community and health professionals. There are several applications that need to be evaluated regarding the quality of the information, as they work as instruments for the practice of prescription, and can prevent drug interactions and ADRs in RA patients. Thus, the main objective of this study is to evaluate mobile applications for detecting potential drug interactions and adverse drug reactions for patients with RA.

## MATERIAL AND METHODS

A cross-sectional and prospective study was carried out at a pharmacy of a public health unit, belonging to the 11th Regional Health Department in the state of Paraná [11]. Only adult patients with rheumatoid arthritis were invited. The sample initially consisted of 30 patients; however, with the loss of 7, the study was conducted with a total of 23 participants. The study period was from January 1 to

December 30, 2018. The names of the drugs distributed during this period were collected and classified according to the classification of the Anatomical Therapeutic Chemical (ATC) Code System [12]. In order to collect the information, a form adapted from the protocol for the treatment of AR [13], validated and standardized by the researcher, was used.

The sociodemographic variables (age and sex) and the clinical characteristics of the patients were analyzed statistically (frequency, percentage, probability, odds ratio, p-value) using the software R, version 3.6.0. The names of the drugs distributed to the participants during the study period were collected during the interviews and also in the secondary databases of the pharmacy. All the participants signed an informed consent form. This research was approved by the research ethics committee of the State University of Maringá (UEM) under registration no. 2,278,630. The ten most frequent drugs collected in the interviews and in the secondary bases of the pharmacy were compared in pairs in three mobile applications (apps): IBM Micromedex drug interaction version 3.1, Medscape version 6.6, and Drugs.com version 2.9.7. The apps were purchased on the Google Play digital platform. Two of them were obtained for free (Medscape app and Drugs.com app) and one under license (IBM Micromedex app).

The potential drug interactions generated were classified according to the alerts emitted by the applications: a) potential severe risk for interaction - when the words "major", "contraindicated" or "serious" were present in the alert; b) potential moderate risk for interaction - when the words “moderate” or “monitoring” were present in the alert; and c) potential low risk for interaction - when the words "low" or "minor" appeared in the alert. The device used to verify the applications was a moto g (6) play with Android version number 9. The study was performed in a wireless network environment.

## RESULTS AND DISCUSSION

When analyzing the data obtained, it should be noted that the average age of the patients was 59.35 years and the median was 61 years, with 13 patients (56.5%) being considered as older adults, with age group ranging from 61 to 85 years. Twenty participants (87%) were female. The associated diseases observed were: 13 occurrences for Arterial Hypertension (57%); 10 for Dyslipidemia and Osteoporosis (43%); 4 for Chronic Obstructive Pulmonary Disease (COPD) (17%), and 1 occurrence of Sexually Transmitted Infection (STI) (4%).

When asked about having a family member with symptoms for RA and about having changed their drug treatment, 8 (35%) of the interviewed patients answered “yes” for both variables.

When asked about having a family member diagnosed with cardiovascular disease, 15 (65%) patients responded “yes” and 14 (61%) added the fact that they have already had an allergic reaction to medication or food. When questioned, only 2 (9%) patients reported having undergone a cardiac procedure or surgery (table 1).

**Table 1: Variables of the clinical characteristics of patients with rheumatoid arthritis participating in the study (n=23)**

| Variables | n | % | P | CI95% | Odds ratio | p value |
|---|---|---|---|---|---|---|
| Family member with arthritis symptoms | 8 | 35 | 0.34 | [0.16;0.57] | 0.53 | 0.21 |
| Family member diagnosed with CVD | 15 | 65 | 0.65 | [0.42;0.83] | 1.87 | 0.21 |
| Allergic Reaction to Drugs or Food | 14 | 61 | 0.60 | [0.38;0.80] | 1.55 | 0.40 |
| Treatment changes for RA | 8 | 35 | 0.34 | [0.16;0.57] | 0.53 | 0.21 |
| Cardiac surgery or procedure | 2 | 9 | 0.08 | [0.01;0.28] | 0.09 | $6.60e^{-5}$ |

n: frequency. P: probability. CI: confidence interval. CVD: cardiovascular disease. RA: Rheumatoid Arthritis

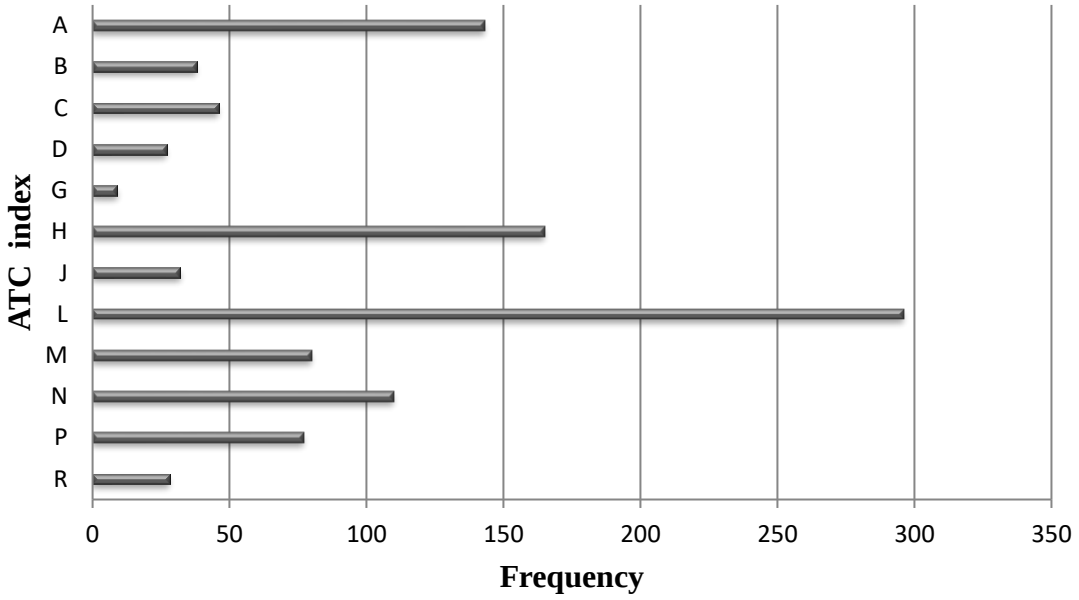
In the statistical analysis of the probabilities of events regarding rheumatoid arthritis, the variable procedure or cardiac surgery presented a much lower odds ratio when compared with the other variables of the patients’ clinics. This result reflects a small chance that patients have developed heart disease over the years with the diagnosis of RA.

As this is a study with a small sample and a short duration, this research does not reflect the results of other researchers and authors that reveal a greater risk for patients with RA to develop cardiovascular diseases [14-16]. Our result reinforces that RA patients, despite having undergone a surgical procedure, consume a large amount of medications.

Regarding the probability for the variables family members with heart disease and allergic reaction to drugs or food, the following Odds ratio values were observed: 1.87 and 1.55, respectively. This finding reflects phenomena that are more likely to occur in this population studied.

The 1030 drug records collected from patients during the study were classified according to the rules of the Anatomical Therapeutic Chemical (ATC) Code System and are represented in table 2: 296 drugs belonging to group L (Antineoplasics and immunosuppressants); 165 drugs in group H (Systemic hormonal preparations, excluding sex hormones and insulins); 143 drugs belonging to group A (Digestive system and metabolism); and 110 drugs in group N (Nervous system).

**Table 2: Frequency of drugs distributed to the research participants during the study period, according to the ATC classification (WORLD, [s/d]a)**




Index: A - Digestive system and metabolism; B - Blood and hematopoietic organs; C - Cardiovascular apparatus; D - Dermatological; G – Genito-urinary tract and sex hormones; H - Systemic Hormone preparations, excluding sex hormones and insulins; J - General anti-infectives for systemic use; L - Antineoplasics and immunosuppressants; M - Skeletal muscle system; N –Nervous System; P - Antiparasitic products; R - Respiratory system.

Records with a frequency higher than 50 and lower than 100 were: 80 drugs in group M (Skeletal muscle system) and 77 in group P (Antiparasitic products). Drugs with a frequency lower than 50 were classified, but they were not analyzed in this study (groups B, C, D, G, J and R).

Only the ten most frequent drugs were classified according to ATC by pharmacological groups: 151 (14.6%) selective immunosuppressants; 114 (11.1%) glucocorticoids; 91 (8.8%) proton pump inhibitors; 75 (7.28%) aminoquinolone; 55 (5.34%) derived from propionic acid; 54 (5.24%) tumor necrosis factor inhibitor; 51 (4.95%) thyroid hormones; 50 (4.85%) folic acid analogs; 41 (3.98%) interleukin inhibitors, and 30 (2.91%) for other analgesics and antipyretics.

The drug with the highest frequency of distribution was Leflunomide (group L), with a total of 151 (14.6%). Leflunomide is representative of the group of selective immunosuppressants (synthetic MMCD). The second most frequent medication was Prednisone (group H) with 114 (11.07%). It is representative of the group of corticosteroids for systemic use. These results corroborate with the drugs

indicated in the protocols for drug treatment of RA [17]. Then, the third most distributed drug was Omeprazole (group A) with a total p of 91 (8.83%) units. Omeprazole is representative of proton pump inhibitors.

Considering a total of 34 alerts of drug pairs with potential for drug interaction, a predominance of potential severe risk for drug interactions (about 20 alerts for the drug pairs) was observed. The distribution of the alerts was as follows: a) the Medscape application presented a total of 13 alerts of potential for interaction, being 8 pairs of drugs with potential severe risk for interaction, 3 pairs with potential moderate risk for interaction and 2 pairs with potential low risk for interaction; b) the Drugs.com application showed a total of 16 alerts of potential for interaction, being 8 pairs of drugs with potential severe risk for interaction, 7 pairs with potential moderate risk for interaction and 1 pair with potential low risk for interaction, and c) the IBM Micromedex application presented 5 alerts of potential for interaction, being 4 pairs of drugs with severe risk for interaction and 1 with moderate level (table 3).

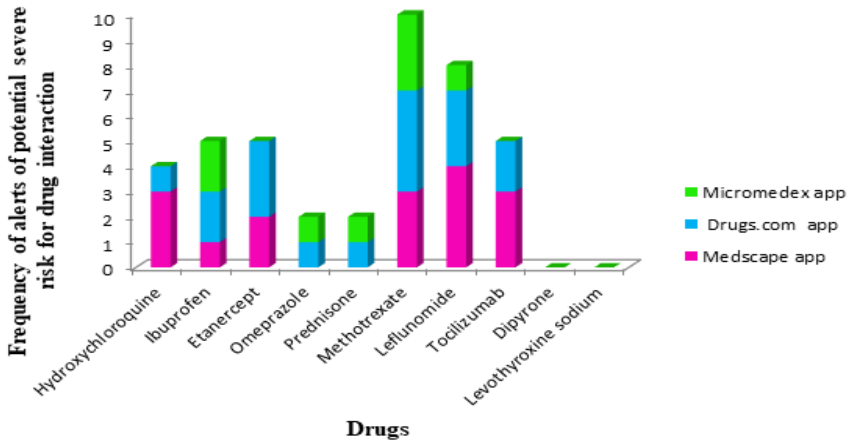
**Table 3: Frequency of alerts of potencial drug interaction generated by the ten most distributed drugs during the study, by severity level in mobile device applications:**

| | Severity Level | | |
|---|---|---|---|
| Apps | Severe risk | Moderate risk | Low risk |
| Medscape app | 8 | 3 | 2 |
| Drugs.com app | 8 | 7 | 1 |
| Micromedex app | 4 | 1 | 0 |

The Medscape and Drugs.com apps obtained the same number (n=8) of drug pairs with potential severe risk for interaction. The Drugs.com app obtained the highest amount (7) of alerts for potential moderate risk for drug interaction. In this study, no alert of low potential for drug interaction was observed in the IBM Micromedex app. The most observed pairs of drugs were: Ibuprofen and Methotrexate; Ibuprofen and Prednisone; Leflunomide and Methotrexate, and Omeprazole and Methotrexate.

A more detailed analysis of the frequency of the combined drug pairs was performed for the potential severe risk for drug interaction in the three apps (table 4). A total of 17 pairs were found for potential severe risk for interaction in the Drugs.com app, 16 pairs of drugs in the Medscape app, and 8 pairs in the IBM Micromedex app. The drug pairs that generated a several potential risk of interactions were divergent between the three apps.

**Table 4: Frequency of alerts of potential severe risk for drug interaction generated by the tem most widely distributed drugs during the study on mobile device applications.**




Among the combined drug pairs, Methotrexate (group L) presented the highest frequency, with a total of 10 alerts for potential severe risk of drug interaction in the three apps, with 4 alerts in the Drugs.com app, 3 alerts in the Medscape app and 3 other alerts in the Micromedex app. The drug Leflunomide (group L) showed a total frequency of 8 alerts for a potential severe risk for drug interaction,

being: 4 alerts of potential severe risk for interaction in the Medscape app, 3 in the Drugs.com app, and 1 in the Micromedex app.

Although Methotrexate is not the most widely distributed drug during the study period, we understand that patients with RA are not assured with prescriptions free of drug interactions, and may develop consequences such as decreased renal clearance due to increased serum levels of Methotrexate and Ibuprofen pairs (table 5), damage to the nervous and hepatic systems and in bone marrow function Leflunomide and Methotrexate pairs (table 6); in addition to toxicity due to the serum increase of methotrexate and its metabolites Omeprazole and Methotrexate pairs (table 7).

**Table 5 - Description of Drug Interaction Alerts in the *Medscape* application**

| Drugs Pairs | | Severity | Description | Affected Mechanism |
|---|---|---|---|---|
| Hydroxychloroquine | Etanercept | 1 | Increase in the Immunosuppressive Effect Risk of infection | - |
| | Leflunomide | 1 | Increase in the Immunosuppressive Effect Risk of infection | - |
| | Methotrexate | 2 | Increase in the level of methotrexate Decrease in the clearance of methotrexate | - |
| | Tocilizumab | 1 | Increase in the Immunosuppressive Effect Risk of infection | - |
| Ibuprofen | Leflunomide | 3 | Increase in the effect of Ibuprofen | Hepatic metabolism of the CYP2C9/10 enzyme |
| | Methotrexate | 1 | Increase in the level of methotrexate | Decrease of Renal Clearance |
| | Prednisone | 2 | Both increase the toxic effects Risk of gastric ulcer | Pharmacodynamic synergism |
| Levothyroxine | Omeprazole | 3 | Decrease of the levels of Levothyroxine | Increase of gastric pH |
| Etanercept | Leflunomide | 1 | Both increase the toxic effects Risk of infection | - |
| Leflunomide | Tocilizumab | 1 | Both increase the immunosuppressive effects Risk of infection | - |
| | Methotrexate | 1 | Leflunomide increases methotrexate toxicity | Pharmacodynamic synergism |
| Omeprazole | Methotrexate | 2 | Increase in the level of methotrexate | Decrease of Renal Clearance |
| Methotrexate | Tocilizumab | 1 | Both increase the immunosuppressive effect Risk of infection | - |

Legend: 1 - Severe risk; 2 – Moderate risk; 3 – Low risk; (-) not observed. Source: Elaborated by the authors.

The pairs of drugs that contain Ibuprofen (group M), Etanercept (group L) and Tocilizumab (group L) presented a total of 5 alerts for a potential severe risk for drug interaction. For Ibuprofen, both the Drugs.com and Micromedex apps detected 2 alerts for a potential severe risk for interaction. For Etanercept, the Drugs.com app detected 3 alerts for potential severe risk, whereas the Medscape app indicated only 2 alerts. Tocilizumab generated 3 potential alerts in the Medscape app for severe risk and the Drugs.com app indicated 2 alerts. Hydroxychloroquine (group P) obtained 4 total alerts of potential severe risk for interaction: 3 alerts by the Medscape app and only 1 by the Drugs.com app. The medications Omeprazole (group A) and Prednisone (group H) had 2 total alerts for potential severe risk generated by the apps Drugs.com and Micromedex.

The drug Sodium Levothyroxine (group H) did not present any potential severe risk for the combined drug interactions. The drug Dipyrone also did not show any type of potential drug interaction because this drug is not available in the USA. Since the biological MMCD drugs (Tocilizumab and

Etanercept) cannot be prescribed together, according to the current protocols [17], the representatives of these classes were not combined in pairs in the apps.

**Table 6 - Description of Drug Interactions alerts in the *Drugs.com* application**

| Drugs Pairs | | Severity | Description | Affected Mechanism |
|---|---|---|---|---|
| Hydroxychloroquine | Etanercept | 2 | Increased damage to the nervous system | - |
| | Leflunomide | 1 | Decrease of the number of blood cells | Bone marrow functions |
| | Tocilizumab | 2 | Increased damage to the nervous system | - |
| | Methotrexate | 3 | - | - |
| Ibuprofen | Leflunomide | 1 | Increased liver damage when taken with Ibuprofen | - |
| | Methotrexate | 1 | Increased blood levels and side effects of Methotrexate | - |
| | Prednisone | 2 | Increased Inflammation in the gastrointestinal tract | - |
| Etanercept | Leflunomide | 2 | Decrease of the number of blood cells | Bone marrow functions |
| | Methotrexate | 1 | Increased risk of serious and potentially fatal diseases | - |
| | Prednisone | 1 | Increased risk of serious and potentially fatal diseases | - |
| Leflunomide | Tocilizumab | 1 | Decrease of the number of blood cells | Bone marrow functions |
| | Methotrexate | 1 | Nervous system injury<br>Liver damage<br>Impaired bone marrow function | - |
| | Prednisone | 2 | Risk of serious infections | - |
| Methotrexate | Tocilizumab | 2 | Liver damage | - |
| | Omeprazole | 1 | Increased blood levels and side effects of Methotrexate | - |
| | Prednisone | 2 | Increased blood levels and side effects of Methotrexate | - |

Legend: 1 - Severe risk; 2 – Moderate risk; 3 – Low risk; (-) not observed

In the analysis of the documentation generated by the apps (description of the type of event resulting from the phenomenon of drug interaction and the affected mechanism), we could observe: Medscape provided 13 reports of description and 6 of mechanisms; Drugs.com provided 15 reports of description and 3 of mechanisms; Micromedex provided 5 reports of description and 4 of mechanisms. The Drugs.com app obtained the highest amount of description of interactions, despite having the lowest amount of reports of affected mechanisms.

In this research, the Drugs.com app was the most sensitive of the three apps selected, generating 16 pairs of drugs with alerts for potential drug interactions. According to the detailed analysis for severe risk, the Drugs.com app detected 17 alerts of combined drug pairs. It also proved to have the greatest amount of information about the description of the event, despite having described the lowest amount of mechanisms affected when compared with the other two apps.

Our results followed the same line of studies carried out by other researchers [18], who also evaluated applications available on digital platforms. The Drugs.com app was rated with 4.06 (good level), a result obtained using the MARS tool (Mobile App Rating Scale) [18]. This tool classifies several aspects, such as the drug interaction checker and the quality of information in the content present in the mHealth apps. It is, therefore, a reliable measure of the quality of health applications [19].

**Table 7 - Description of Drug Interaction Alerts in the application IBM *Micromedex Drug Interactions***

| Drugs Pairs | | Severity | Description | Affected Mechanism |
|---|---|---|---|---|
| Ibuprofen | Prednisone | 1 | Increased risk for gastrointestinal ulceration or bleeding | Additive effects |
| | Methotrexate | 1 | Increased risk of methotrexate toxicity (Leukopenia, Thrombocytopenia, Anemia, Nephrotoxicity and Ulcerative mucosa) | Decrease of release of methotrexate |
| Levothyroxine | Omeprazole | 2 | Decreased effectiveness of levothyroxine | Decreased absorption of levothyroxine |
| Methotrexate | Leflunomide | 1 | Increased exposure to methotrexate and increased risk of hepatotoxicity and bone marrow toxicity | Inhibition of demetotrexate mediated transport by leflunomide or activation of its metabolite |
| | Omeprazole | 1 | Increased concentration of methotrexate and its metabolites and increased risk of toxicity by methotrexate and its metabolites | - |

Legend: 1 - Severe risk; 2 – Moderate risk; 3 – Low risk; (-) not observed

The results reported in some articles corroborate our findings and explain that the high sensitivity of Drugs.com is due to the fact that it contains a larger database, including Micromedex, the only app under license in this study [20].

The smartphones or tablets, very present in daily clinical practice, offer an increasing number of mobile applications, promoting a wide effective change in health care. Their immediate and on-the-go access support clinical decisions, benefiting health professionals [21-22].

In none of the apps the functionality of reporting the ADRs for health professionals or for regulatory bodies was observed. This fact was already evidenced in other studies [18], in which this functionality is proposed in order to improve public health services through the monitoring of ADRs and potential drug interactions.

Post-marketing surveillance must be continuous. However, there is a greater need for monitoring by health professionals, as several studies have shown that, in order to detect a wider range of ADRs, it is necessary that all health agents are involved [6].

Our study, when evaluating mobile applications with the functionality of verifying potential drug interactions, contributed to explain the different potentials for drug interactions generated by different classes of drugs, such as drugs for RA treatment, analgesics and pump protons inhibitors.

We emphasize that this study analyzed the potential drug interaction of the medications most distributed to patients during a determined period of time. Drugs that were not analyzed but collected in the interviews, such as over-the-counter or otherwise purchased, had a frequency lower than 50 and were not analyzed.

The RA patients studied are not free from real drug interactions, and may develop an ADR as the decrease in the desired treatment effect, or even the increased toxicity of the drug.
Evidently, only some of the potentials for drug interactions can result in real adverse events; however, researchers have identified as causes of risk for ADR in older persons patients: age, female gender and the polypharmacy phenomenon [23].

Further studies should be conducted in order to evaluate mobile apps with the functionality of checking the potential for drug interaction, due to the growing offer on digital platforms, thus guaranteeing accurate and quality information for an excellent prescription and pharmacotherapeutic follow-up.

Technological innovation in the health field thus allows an immediate acquisition of information and an efficient and safe applicability, and should be conceived as an important tool for the practice of drug prescription and for effective therapy for patients.

## CONCLUSION

The use of decision-making apps as a tool for prescription and therapeutic follow-up can be indicated for individuals with rheumatoid arthritis due to concomitant diseases, to the high range of different drugs, to the increased risks to polypharmacy and to the possible emergence of drug interactions and severe adverse reactions.

Advertising campaigns in traditional and digital media could be created in order to make the population aware of the potential risks of drug interactions and adverse drug reactions, resulting in proactive and defenders of healthier lives users.

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