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SHORT COMMUNICATION

A Comparative Analysis of Three Online Drug-Drug Interaction Checkers: A Short Communication

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ABSTRACT

Objective: To assess the agreement among three different online drug-drug interaction (DDI) checkers for the detection of psychotropic drug interactions among dental patients in the state of Minas Gerais, Brazil. **Material and Methods:** Between January and December 2017, a cross-sectional study was conducted in Minas Gerais with data on pharmaceutical claims of psychotropic drugs prescribed by dental practitioners. Data from the Pharmaceutical Management System provided the drug dispensing history of the patients, allowing the identification of those on concomitant medication use. The occurrence of DDI was determined by entering the name of the drugs taken by each patient into Merative Micromedex®, Medscape®, and DrugBank. The degree of agreement among the three DDI online checkers was analyzed using the Fleiss' kappa test. **Results:** Overall, 797 dental patients were found to be taking some psychotropic medication with other drugs simultaneously. The number of patients with DDI varied according to Micromedex® (n= 366), Medscape® (n= 473), and DrugBank (n= 736). The agreement between the DDI checkers was poor (Fleiss' kappa: 0.165; p<0.001). **Conclusion:** The online DDI checkers assessed in this study showed variations in their ability to detect interactions and poor agreement among them.

Keywords: Dentistry; Psychotropic Drugs; Drug Interactions; Decision Support Systems, Clinical; Patient Safety.

Introduction

The prescription of multiple drugs has been on the rise due to increasing life expectancy worldwide and the growing prevalence of chronic diseases or multimorbidity. At the same time, as new therapeutic substances are available each year, the number of possible drug combinations is constantly climbing [1,2]. According to a national survey, around 20% of older adults in Brazil are exposed to at least five drugs at once [3]. While the use of several prescribed medications brings about therapeutic benefits, it also raises concerns about unwanted adverse effects, such as drug-drug interactions (DDI).

DDI occurs when the therapeutic effect of one drug is modified by the simultaneous or subsequent administration of other drugs [4]. Some evidence shows that DDI is associated with increased emergency visits, hospitalization, healthcare expenditure, and deaths [5-7]. Preventing interactions is crucial for patients' safety and optimal treatment outcomes. Hence, several online DDI checkers have been developed to assist prescribers in making evidence-based decisions concerning drug combinations, dosage adjustments, or substitutions [8]. Despite interaction checkers, studies have reported a substantial frequency of DDI in patients under dental care [9-12].

In the United States, it was estimated that 3.4% of all older adults with a dental visit in 2006 were prescribed drugs with the potential for a serious DDI [9]. A cross-sectional study in Iran evaluated the interactions between the medication used by elderly patients and the drugs frequently prescribed in dental care. As a result, a high percentage of interactions were identified, suggesting that dentists have a low awareness of DDI [10]. Similar findings were reported by de Oliveira et al. [11] in the South of Brazil. Additionally, 25% of patients who were prescribed psychotropic drugs by dental practitioners in Minas Gerais, Brazil, might have experienced some DDI [12]. Despite the relevance of the available literature, the majority of the studies assessed the occurrence of DDI based on a single interaction checker.

With the emergence of online numerals DDI checkers, it becomes necessary to investigate the agreement and consistency among these tools. However, no previous study of interacting drugs prescribed by dentists examined the level of agreement of such tools. Therefore, we aimed to assess the agreement among three online DDI checkers for detecting psychotropic drug interactions among dental patients in Minas Gerais, Brazil.

Material and Methods

Ethics Statement

This study was approved by the Research Ethics Committee of the *Universidade Federal de Minas Gerais* (Approval Number 2.701.715). We analyzed a public database from the State Health Department of Minas Gerais, and the identity of all participants remained anonymous. Thus, it was not necessary to request individual informed consent.

Study Design and Data Collection

A cross-sectional study was conducted between January and December 2017 in Minas Gerais. Secondary data analysis was performed from pharmaceutical claims in which patients were prescribed psychotropic drugs by dentists. Data was collected from the Pharmaceutical Management System (Sigaf), a State-level electronic software that records medication dispensing history, prescribed quantity, and dosage for individual patients [13].

All drugs registered in Sigaf were classified according to the Anatomical Therapeutic Chemical (ATC) Classification System and Defined Daily Doses (DDDs) assignment, 2023, developed by the World Health

Organization (WHO) [14]. Initially, we selected the records of dental patients who were prescribed drugs belonging to the following ATC subgroups: N02A (opioids), N03 (antiepileptics), N04 (anti-Parkinson drugs), N05 (psycholeptics), N06 (psychoanaleptics), and N07 (other nervous system drugs). Next, we retrieved all other drugs concomitantly prescribed by any other healthcare provider to those individuals. Since the occurrence of DDI relies on the concurrent use of at least two drugs, only individuals who were prescribed psychotropics by dentists, as well as other drugs during the same time, were deemed eligible for this study. Further details about the selection processes were published elsewhere [12].

Drug-Drug Interactions

DDI data from one commercial online checker and two other open sources were included in our evaluation: Merative Micromedex®, Medscape®, and DrugBank. Micromedex® interactions tool is a reliable DDI checker that provides comprehensive information on each interaction's severity, management, and level of evidence. It is administered by Merative, an American analytics and technology biomedical company that requires a subscription to access its resources [15]. Medscape® drug interaction checker allows healthcare professionals to screen for potential interactions between two or more substances. This tool displays the severity, probable mechanism of the interaction, and managing recommendations [16]. DrugBank started in 2006 in Canada as a free-to-access resource. The checker stocks detailed information about the severity, mechanism, and evidence of each potential interaction, helping to ensure safe and effective medication management [17].

To estimate the occurrence of DDI, the names of the drugs taken concomitantly by each patient were entered into Micromedex®, Medscape®, and DrugBank. If the online checker reported no interaction, it was coded as 0, indicating the absence of DDI. If at least one interaction was detected, it was coded as 1, indicating the presence of DDI. In Medscape®, 12 drugs registered by Sigaf were not included in the online checker; as such, in the cases in which those substances were prescribed, code 2 (No information) was assigned. Two researchers independently performed these procedures (DRA, AJSC), and consensus solved disagreements.

Outcome Measures

The outcome was the degree of agreement among Micromedex®, Medscape®, and DrugBank, determined by computing the number of participants with at least one DDI.

Statistical Analysis

Data was analyzed using SPSS v.26 (IBM Corp.). Descriptive statistics was employed to calculate the number of participants who presented DDI in either one, both, or all three online checkers. The results were plotted in a Venn diagram. Fleiss' kappa test was performed to determine the degree of agreement between Micromedex®, Medscape®, and DrugBank. The Fleiss' kappa coefficient of 0–0.2 indicates a poor agreement; 0.21–0.40, fair; 0.41–0.60, moderate; 0.61–0.80, substantial; and 0.81–1.0, almost perfect agreement [18]. A P-value lower than 0.05 was considered statistically significant. We ran a sensitivity analysis by estimating the agreement among the three online checkers after excluding the cases coded as 'No information.'

Results

Out of the 1,480 individuals who were prescribed psychotropic medication, 797 (53.8%) were found to be taking two or more drugs simultaneously. Therefore, the analysis of DDI was conducted on a sample of 797. A total of 750 participants were reported to have drug interactions. Nevertheless, significant variations were

observed, with DrugBank identifying twice as many cases of interactions compared to Micromedex®. Table 1 shows the frequency of DDI according to each assessed online tool. Some overlap was observed among the online checkers; 315 patients were identified as having DDI according to the three tools. Micromedex® alone detected 5 cases, Medscape® alone identified eight instances, and DrugBank alone detected 227 cases (Figure 1).

Table 1. Drug-drug interaction counts per drug information resource.

DDI online checker	Counts (n)
Merative Micromedex®	366
Medscape®	473
DrugBank	736

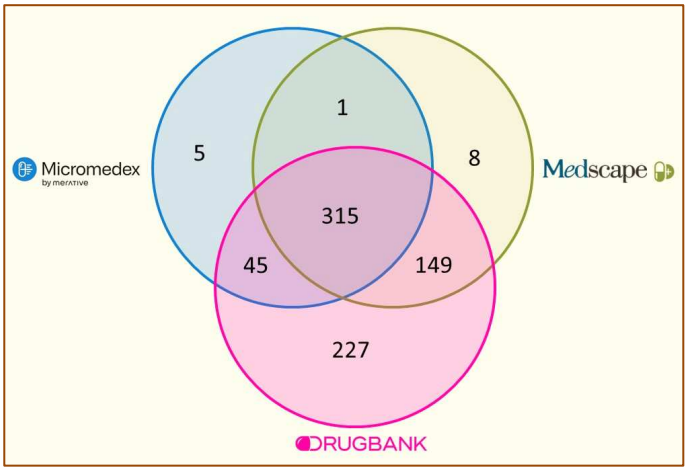

Figure 1. Venn diagrams illustrating the intersections of the Drug-drug interactions detected by the three online checkers.

The agreement on DDI among Micromedex®, Medscape®, and DrugBank was poor (Fleiss' kappa: 0.165; p<0.001). The results of the sensitive analysis also showed poor agreement among the three online interaction checkers (Fleiss' kappa: 0.193; p<0.001).

Discussion

This study presented findings on the agreement of psychotropic drug interactions included in three online DDI checkers. While there was some overlap in the number of patients with DDI, especially between Micromedex and Medscape, there were substantial discrepancies among the three online checkers. Also, the agreement among the studied tools could have been better, as assessed by the Fleiss' Kappa score.

There has been some interest in clinical decision support systems offering DDI guidance. These systems aim to optimize the use of medications by providing information, thereby helping healthcare professionals avoid drug combinations that might induce harm. Nonetheless, our research showed poor agreement among the assessed online DDI checkers. Similarly, Kontsioti et al. [19] investigated the concordance of clinical resources for DDI from three different countries, namely England, France, and the United States. The authors concluded that there needed to be more consistency in the information provided by various tools, which could have detrimental consequences for patient safety [19]. Some previous studies also suggested limited and poor agreement between DDI resources [8,20]. Such discrepancies may be explained by variations in the underlying databases, algorithms, and sources of information used to predict DDI [21].

The wide variations encountered in the DDI checkers pose challenges for healthcare professionals when making evidence-based decisions [21]. This is primarily due to the potential confusion that arises when conflicting information is provided by DDI resources, leaving providers needing clarification on which information to trust. Another issue is that some drugs or formulations are not licensed or have been discontinued in some countries (e.g., metamizole); as such, interactions involving those substances are not included in some DDI checkers [19,22]. Therefore, clinicians must carefully choose which DDI checker to use, critically evaluate the information and evidence provided, and then consider the relevance to each patient [8,21]. Furthermore, in some cases, it may be necessary to refer to multiple interaction resources or seek expert advice from a pharmacist, for instance [21].

This study has some limitations. First, we did not include books or compendiums of DDI. This is because electronic interaction tools are more commonly utilized in daily clinical practice, as they offer simplicity and convenience to providers. Second, our analysis focused on psychotropic drug interactions, and studies including other therapeutic groups are necessary for a broad understanding of this topic. Apart from the limitations to the best of our knowledge, this research is the first comparison of DDI checkers regarding dental-prescribed drugs. Moreover, a significant proportion of studies about interactions are conducted with data from a single service; we highlight that our analysis encompassed data from the entire state of Minas Gerais.

Conclusion

The online drug-drug interaction checkers assessed in this study showed variations in their ability to detect interactions, and there was poor agreement among them. These findings suggest the need for further research and improvement in the agreement of online tools for identifying drug-drug interaction to ensure patient safety and improve clinical decision-making.

Authors' Contributions

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AJSC	https://orcid.org/0000-0003-1905-4124	Methodology, Software, Formal Analysis, Investigation, Data Curation, and Writing - Review and Editing.
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All authors declare that they contributed to a critical review of intellectual content and approval of the final version to be published.

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Conflict of Interest

The authors declare no conflicts of interest.

Data Availability

The data used to support the findings of this study can be made available upon request to the corresponding author.

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