Analysis and Redesign of a Knowledge Database for a Drug-Drug Interactions Alert System

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Abstract

Physicians tend to ignore drug-drug interactions alerts. this is due to the large amount of irrelevant interactions displayed and the interface in which these alerts are shown. The high rate of clinically inadequate alerts produce “alerts fatigue”. This high number of incorrect alerts predisposes physicians to underestimate the electronic prescription systems as useful tools in their practice. We decided to analyze and redesign our drug-drug interactions alerting system knowledge database. In order to do so, we cleaned our knowledge database according to the clinical significance of drug-drug interactions. New drug interactions taxonomy was created in four levels based on clinical significance and the recommendations given in each single monograph of interaction. We proceeded to recategorize the alerts as Active, which present themselves to the physician interrupting the prescribing process, or Passive, which allow physicians to accept the recommendations, and adopt some action in order of minimizing the interaction risks.

Keywords:

Drug interactions, medical order entry systems, clinical decision support systems

Introduction

Errors in medicine, as well as in other human activities, occur frequently. Although most of them do not have harmful consequences, some cause injuries of varying degrees, and may even cause death. It has been reported that a fourth of those errors are related to medications [1]. Errors in medication lead to the so-called preventable adverse drug events [2]. Considering the different steps in the medication cycle (prescribing, transcription, dispensing, administrating, and monitoring), it is during prescribing that almost half of the errors occur [3]. The most common mistake during this step is related to a lack of knowledge of the drug and patient information [4]. Some of the errors during the prescription step are labeled drug-drug interactions (DDI) [5]. A DDI occurs when one drug affects the metabolism of a second drug, thereby producing adverse effects [6]. DDI occur frequently, but most of them do not lead to adverse events. It has been estimated that only 10 to 15% of these interactions have clinical significance [7]. The occurrence of these interactions varies according to the clinical setting (inpatient, emergency, outpatient) [8]. Evidence shows that physicians do not recognize these interactions 50% of the time, and one-third of the time in serious interactions [9, 10]. Published studies and reviews indicate that Computerized Physician Order Entry (CPOE) that provide contextual help at the point of prescription, help in the prevention of prescribing errors and drug adverse events [11-13]. When CPOE are implemented, the clinical workflow can be affected, and generate diverse responses among the physicians using them. When asked about the potential help of CPOE in the prescription process, more than half of the practitioners agreed that they are useful [9, 14], however some studies report that doctors ignore such alerts in 57 to 95% of the time [15, 16]. One of the most important reasons for this high rate of alert overriding is evident in the literature, and is, without a doubt, due to the high rate of false positives (clinically inadequate alerts) which give rise to “alerts fatigue.” This high number of incorrect alerts predisposes physicians to underestimate the CPOE as useful tools in their practice. Among the causes of the high rate of manual override of the alerts we found [8, 17]:

- Problems related with the design of the knowledge database of such systems that generate a high rate of false positives.
- Issues related to the utility of the alerts interface.
- The lack of permanent inspection of the interaction between the system and the users, in order to create cycles of continuous improvement.

The Hospital Italiano de Buenos Aires has implemented a CPOE, in the context of an electronic medical record [18], that includes an alert system for drug-drug interactions. This work is motivated by the fact that we have not evaluated the rate of overriding alerts by our physicians and on the problem described in the literature about these clinical decision support systems. The objective of our present work is to describe the analysis of the knowledge database of our drug-drug interaction alert system. This analysis includes annotation and purging of the knowledge database according to clinical significance, and proposes changes in its classification of recommendations and alerts visualization.

Selected for best paper award.
Table 1 - Description of fields contained in individual monographs of each DDI of the knowledge database

<table>
<thead>
<tr>
<th>Drug-Drug Interaction Monographs</th>
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</thead>
<tbody>
<tr>
<td><strong>Title</strong></td>
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<tr>
<td><strong>Summary</strong></td>
</tr>
<tr>
<td><strong>Recommendations</strong></td>
</tr>
<tr>
<td><strong>Related drugs</strong></td>
</tr>
<tr>
<td><strong>Routes of administration</strong></td>
</tr>
<tr>
<td><strong>Mechanism of interaction</strong></td>
</tr>
</tbody>
</table>
| **Significance** | Code assigned to each interaction. It is based on three parameters: potential damage to the patient, frequency and predictability of occurrence, and quality of the documentation that sustains the interaction. They are classified into four levels:  
**Level 1:** High significance, interaction with great potential to cause damage to the patient, predictable, and frequent, and that it is well documented  
**Level 2:** Moderate significance, potentially damaging interaction, less predictable, less frequent, or with incomplete documentation  
**Level 3:** Minimal significance, interaction with low potential for damage to the patient, of variable predictability, of infrequent appearance, or that is based on little documentation  
**Level 4:** Without clinical significance, even though this type of interaction can occur, the documentation is based on theoretical considerations or is not clinically significant. Also adverse effects can not be predicted |
| **References** | Includes the bibliographic references of published works sustaining the presented information |

**Methods**

The knowledge database of the alert system was created using different sources, including clinical pharmacology textbooks, monographs on products, consultation with specialist in our institution, specific literature searching and a publication on pharmacological interactions named “Evaluation of Drug Interactions (EDI)” [19] maintained by First DataBank Inc. [20]. To build the knowledge database, the information contained in Table 1 was applied.

The EDI is organized in 18 chapters, according to drug groups (antihypertensive drugs, narcotics, etc.) and according to its index around 43,000 potential DDI exist. These DDI are generated from the related drugs included in each of the monographs in the EDI [20]. Our knowledge database was created mainly using this index as a guideline. Due to the smaller number of individual drug monographs of a drug-drug or drug-family interaction in comparison with the potential DDI contained in the index (1,201 vs. 43,000), the first step (done by a clinical pharmacologist), was annotating and purging each potential pair according to other sources. In addition, rounds with experienced professionals with the drug in question were also conducted. The objective was that only those interactions with a clear bibliographical and clinical background would remain in the knowledge database. Once the purging was completed, each DDI was analyzed, and a new classification of alerts was defined according to the recommendations for an action contained in the monograph. Finally all interactions were categorized either as active or passive, depending on whether they would manifest themselves actively, interrupting the prescriptive workflow or not.

**Results**

The first step was the purging of the unsubstantiated interactions based on the EDI index. Each of the 1,201 monographs in the EDI were individually analyzed, particularly the section named “Related drugs”, where the 43,000 DDI included in the EDI index originated from. As a result of this analysis by a clinical pharmacologist, consultations with other sources, and revision rounds with specialists with daily experience in the use of the drugs, 39,191 DDI were discarded from the knowledge database (originally created from the EDI index as a guideline), and only 2,608 DDI were kept, each related to an individual DDI monograph. Therefore, our knowledge database was formed now with 3,809 DDI (Figure 1).

After this purging, the entries were reclassified according to their clinical significance:

- **Level 1:** 600 (High significance, interaction with great potential to cause damage to the patient, predictable, and frequent, and that it is well documented)
- **Level 2:** 1494 (Moderate significance, potentially damaging interaction, less predictable, less frequent, or with incomplete documentation)
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- **Level 3:** 1653 (Minimal significance, interaction with low potential for damage to the patient, of variable predictability, of infrequent appearance, or that is based on little documentation)
- **Level 4:** 62 (Without clinical significance, even though this type of interaction can occur, the documentation is based on theoretical considerations or is not clinically significant. Also adverse effects cannot be predicted)

In addition, during the revision process, each DDI was analyzed in detail from its recommendations given to the prescribing physician. Based on this analysis, a five-domain taxonomy was created. All the recommendations contained in the alert system were then grouped according to this taxonomy (Figure 2).

**Figure 1 - Purging of the knowledge database**

**Recommendations taxonomy**

**Avoid joint use**

This domain refers to those interactions that do not provide other options to the physician but to avoid both drugs in combination. This domain is the most important of all because it does not provide alternatives to the prescription. The physician must therefore justify his/her action if he/she decides to proceed and prescribe both drugs simultaneously.

**Monitoring Required**

This domain includes two sub-domains: clinical monitoring and monitoring by complementary tests. Clinical Monitoring includes all recommendations related to signs or symptoms that physician should inquire about during consultation and follow up with the patient to verify the effectiveness of the drug, control adverse events, or check for drug toxicity.

Some examples include:
- Clinical monitoring of desired effects:
  - Neuromuscular blockage
  - Heart frequency
  - Blood pressure

- Clinical monitoring of adverse effects:
  - Hyperglycemia
  - Gastric ulcers
  - Skin rashes

- Clinical monitoring to detect toxicity:
  - Neurotoxicity
  - Mielotoxicity
  - Cardiotoxicity

Clinical Monitoring with Complementary Tests includes laboratory tests and other studies in this category:
- Monitoring with laboratory tests:
  - Liver function tests
  - Complete Blood Count (CBC)
  - Drugs blood level
- Monitoring with other studies:
  - Electrocardiogram (EKG)
  - Electromyogram (EMG)
  - Central venous pressure

**Evaluate alternative drugs**

This domain includes a recommendation to search for other drugs as possible substitutions for one of the interacting pair; it also includes a support system that would provide substitution alternatives, assuring identical or similar therapeutic efficacy as the drug being replaced, and also make sure that an alternative drug will not interact with the second drug in the pair. Some examples of alternative options are:

- Acetyl salicylic acid: Acetaminophen
- Cimetidine: Famotidine/Nizatidine
- Guanetidine: Methildopa
- Erythromycin: Azitromicine

**Modify administration**

This recommendation does not avoid the joint administration of both drugs; however, it suggests the mode of administration, for instance:
- Space the administration of both drugs as far apart as possible in time
- Modify the dosage of one or both drugs
- Select alternative routes for administering one or both drugs
- Choose alternative pharmaceutical formats

**Inform the patient**

Faced with the decision to administrate an interacting pair of drugs, physicians can inform the patient about signs of alarm and other additional recommendations in order to minimize possible consequences of the interaction. Among others, they are:
- Signs of alarm related to hepatotoxicity
- Potential decrease in the contraceptive effect (evaluate alternative contraceptive methods)
• Modifications in the diet
• Signs of alarm of myolysis

**Table 2 - Re-categorization of the DDI in actives (Significance level 1 + avoid joint use domain) or passives (Significance level 2, 3 y 4 + other domains)**

<table>
<thead>
<tr>
<th>Significance</th>
<th>Avoid joint use Domain</th>
<th>Other domains</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 1</td>
<td>39</td>
<td>561</td>
</tr>
<tr>
<td>Level 2</td>
<td>80</td>
<td>1414</td>
</tr>
<tr>
<td>Level 3</td>
<td>14</td>
<td>1639</td>
</tr>
<tr>
<td>Level 4</td>
<td>1</td>
<td>61</td>
</tr>
</tbody>
</table>

**Actives = 695**  
**Passives = 3114**

**Discussion**

The knowledge database of the support systems for decision making in the field of pharmacological prescription is generally commercially acquired, or is developed based on periodical publications. Such knowledge databases are frequently quite inclusive, putting more emphasis on the domain coverage than in the clinical relevance or the severity of adverse effects that interactions may provoke [22]. Due to this limitation, and based on the information supplied by different studies [23, 24] in which problems with the EDI are presented, we decided to undergo an analysis and subsequent purging of the knowledge database of our alert system (the EDI being an important source as guideline of our alert system as indicated above).

Clear recommendations are available as to what characteristics pharmacological alerts must meet [17, 21, 25]. Therefore, the objective of the redesign of the knowledge database of our alert system was undertaken to improve the acceptance of these alerts by physicians, and minimize interruptions in the prescribing process, only leaving the most serious DDI in this group. Already there are reports that confirm that the redesign of this knowledge bases (only leaving a reduced and very specific set of alerts) has increased acceptance by physicians in general [26] and reduces the number of manual overrides of the alerts [27]. We also believe that the creation of taxonomy of recommendations related to DDI allows the physician to accept such recommendations more readily, without having his/her actions being considered as ignored alerts.

Before we implement the changes in the knowledge base of our alert system, we will conduct a study to evaluate the usability of new alerts with a group of physicians from our institution. Based on the results of this evaluation, future implementation will be decided.

**References**


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