Challenges of Trustable AI and Added-Value on Health
B. Séroussi et al. (Eds.)

doi:10.3233/SHTI220392

When Context Matters for Credible Measurement of Drug-Drug Interactions Based on Real-World Data

Romain LELONG[a,b], Badisse DAHAMNA[a,b], Hélène BERTHELOT[a], Willy DUVILLE[a], Catherine LETORD[a,b], Julien GROSJEAN[a,b] and Catherine DUCLOS[a,1]

[a] *Université Sorbonne Paris Nord, Laboratoire d'Informatique Médicale et d'Ingénierie des connaissances en e-Santé, LIMICS, Sorbonne Université, INSERM, F-93000, Bobigny, France*

[b] *Department of Digital Health, Rouen University Hospital, Rouen, France*

Abstract. The frequency of potential drug-drug interactions (DDI) in published studies on real world data considerably varies due to the methodological framework. Contextualization of DDI has a proven effect in limiting false positives. In this paper, we experimented with the application of various DDIs contexts elements to see their impact on the frequency of potential DDIs measured on the same set of prescription data collected in EDSaN, the clinical data warehouse of Rouen University Hospital. Depending on the context applied, the frequency of daily prescriptions with potential DDI ranged from 0.89% to 3.90%. Substance-level analysis accounted for 48% of false positives because it did not account for some drug-related attributes. Consideration of the patient's context could eliminate up to an additional 29% of false positives.

Keywords. drug-drug interaction, prescription, data warehouse, methodology

1. Introduction

Observational studies are becoming more feasible with the computerization of health data. Many studies concerning the SARS-COV2 have used electronic medical records that have improved our knowledge on this new disease. However, the credibility of some of these studies has been questioned as some have been retracted after being published in major journals (1).

Numerous studies have reported the frequency of drug-drug interactions (DDI) among patients, with surprisingly wide-ranging values, from a few tenths to a few tens (2–4). This discrepancy has a multifactorial explanation: origin of data (prescription, reimbursement), perimeter of both data and subjects (inpatient, outpatient, admissions, elderly), definition of the DDIs (referential, DDI checkers, severity), definition of exposure (a posteriori reconstitution of the daily prescription, definition of drug co-occurrence), drug-level used to perform the analysis (clinical drug, active ingredient, ATC class).

[1]Corresponding Author, Catherine Duclos, LIMICS, Université Sorbonne Paris Nord, 74 rue Marcel Cachin, Bobigny, France; E-mail: catherine.duclos@inserm.fr

For a good detection of potential DDIs, a more contextualized definition of DDIs is also important and limits false positives (5). The context can be divided into drug-related factors (e.g. dosage, route of administration, formulation) or patient-related factors (e.g. comorbidities, elimination phenotypes) (6) but experiments of contextualized detection have been only performed on a few DDIs.

In this paper, we use a unique prescription dataset from the Rouen University Hospital data warehouse (7) to test the impact of different contextual items on the DDI frequency measurement.

2. Material and Methods

2.1. Identification of the manufactured pharmaceutical products potentially eligible for a DDI.

An initial list of Proprietary Medicinal Products (PMP) marketed in 2017 was compiled with the available data in the Répertoire des Spécialités Pharmaceutiques (http://agence-prd.ansm.sante.fr/php/ecodex/). These PMP were identified by their specific French code name "Code Identifiant de Spécialité" (CIS, Proprietary Medicinal Product identifier). The French Thesaurus of DDIs (8) was the reference material for contra-indicated DDI. These DDIs were manually analyzed by two pharmacists to identify the context attributes that might narrow the scope of a DDI to a subset of either substances, or PMPs or patients. The PMPs description was enriched with the attributes of interest through the information contained in their Summary of Product Characteristics. The initial list of PMPs was then reduced to those containing the substances referred in DDIs (without further filtering). For each DDI, the list of eligible PMPs was filtered by the context attributes applicable for this DDI. Finally, a combinatorial calculation was performed to create all PMPs pairs whose substance component belongs to either the object or the precipitant of the DDI. This list constituted the List 1 of all theoretical PMPs pairs potentially involved in a DDI, without any filter. This first list was then reduced according to the different applicable filters and an additional filter of no interaction between the substance and itself was applied on the PMPs pairs. This final list was considered the gold standard list of PMPs pairs.

2.2. Data extraction process

Medications electronically prescribed for patients hospitalized in 2017 in Rouen University Hospital were extracted from EDSaN data warehouse in accordance with current regulations on health data privacy (anonymous, partial, aggregated data with a minimum threshold of ten). For reasons of parsimony, only daily prescription lines containing a PMP likely to be involved in a DDI were included in the study. As drugs were identified by their French code name "Unité Commune de Dispensation" (UCD, common dispensation unit), a mapping between the CIS and the UCD was performed using the multilingual terminology server HeTOP (9) which integrated the UCD repository provide by the French Agency of Digital Health (https://esanté.gouv.fr/) (10). The metadata extracted were: the anonymous patient identifier, the anonymous hospital stay identifier, the anonymous daily prescription identifier and the drugs identified by

their UCD. A DDI was only considered if the two drugs involved coexisted in the same daily prescription (DP).

2.3. Analysis

The number of DPs was calculated on the whole 2017 prescriptions and was used as the denominator of the frequency indicators. For each DP, all drugs pairs were generated and compared to the list 1 of PMPs pairs. Only the DPs containing at least one PMPs pair involved in a DDI were retained and their number was calculated. The number of DPs with DDIs was then recalculated by applying the filters corresponding to each studied context to the prescription dataset. These numbers are the numerators of the frequency indicators. The percentage of false positives was defined as the number of falsely detected PMPs pairs out of the whole detected PMPs pairs.

3. Results

A total of 256 contraindicated DDIs were studied. A DDI could occur between two classes of substances (e.g. *irreversible monoamine oxidase inhibitors and monoamine oxidase-metabolized triptans*), a class and a substance (e.g. *statins and fusidic acid*), a class with itself (e.g. *fibrates and other fibrates*), or between two substances (*e.g. gemfibrozil and dasabubir*). Hierarchical relationships existed between some substances and classes (e.g. *rasagiline and selegiline are members of MAOI-B class*). Substances were either active or inactive components of PMPs (*e.g. sorbitol, alcohol*).

Among the 11,221 PMPs marketed in 2017, 5,032 PMPs had potential involvement in a DDI; 194,866 theoretical PMPs pairs involved in a DDI were formed by combinatorial association of PMPs belonging to either the object or the precipitant of the DDI (list 1 of PMPs pairs). For example the 479 PMPs related to *statins* could theoretically interact with the 20 PMPs related to *fucidic acid* and led to 7,664 PMP pairs. Of these 194,866 PMPs pairs, 92,691 could be excluded from the list 1 because they did not fit the contextual description expected in the DDI definition such as (i) ineligible dosage (*e.g. acetylsalicylate dosage < 500mg*) (ii) ineligible route (*e.g. nasal*) (iii) bioavailability issue (*e.g. drug without systemic effect*) (iv) substance restriction (*e.g. warfarin is the only substance concerned by a DDI on anticoagulants*) (v) or ineligible indication (*e.g. beta blockers that don't have heart failure as an indication*). In the preceding example, only 4 PMPs related to *fucidic acid* had systemic effect, so only 1,916 PMP pairs were retained for the gold standard for the DDI between *statins* and *fucidic acid*. Of the remaining 102,175 PMPs pairs (gold standard), 14,140 could be further filtered using patient data such as history (e.g. *history of gastrointestinal ulcer*), or biology (e.g. *hypokalemia*).

Of the 5,032 expected CIS, 4,840 were mapped to an UCD using HeTOP. The lack of mapping was due to a lack of coverage of the repository provided by the French regulatory authority.

The dataset extracted from EDSaN contained 916,584 DPs for 2017. Within these prescriptions, only 1,963 of the UCDs were of interest and only 333 of these were co-occurring as a pair of DDI. In the end, only 990 different PMPs pairs from the list 1 were identified.

Depending on the different context filters to be applied, the frequency of DPs with a DDI varied as presented in Table 1. Without any filter, the percentage of DPs with a

potential DDI was 3.9%. When drug context restrictions were applied, the percentage decreased to 2.1%, and with the assumption of a required but unmet patient context, the percentage dropped to 0.89%.

Substance-level analysis accounted for 48% of falsely detected PMP pairs that could be corrected by filtering by drug attributes. Consideration of the patient's context could eliminate up to an additional 29% of false positives. A DP containing initially a potential DDI was detected for 3,068 patients and only for 60% of them when the drug related filters were applied.

Among the 916,584 DPs, 35,798 contained at least a potential DDI pair from the list 1. After applying the successive filters, up to 77% of them could be eliminated.

Table 1. Evolution in DDI frequency taking contextual elements into account and percentage of DP considered falsely detected

Applied Filter	Percentage of DP with a DDI	% of DP eliminated because falsely detected
Without any filter	3.90%	-
Suppress PMPS with a substance interacting with itself	3.26%	16%
Restrict to substances subsets of certain DDIs	2.86%	10%
Restrict to eligible dose forms	2.67%	5%
Restrict to eligible indications	2.15%	14%
Restrict to eligible dosage	2.10%	1%
Restrict to systemic bioavailability	2.10%	0%
Apply patient related filters	0.89%	up to 31%

4. Discussion and Conclusion

In the reported experience, we showed that, with the same dataset, the measurement of the frequency of potential DDIs can vary with a fourfold, depending on the application of contexts items described in the DDI thesaurus.

The right definition of what drugs should be included in a DDI is a first statement. These drugs cannot be solely defined by their substance or ATC class because it is sometimes too broad when forms or dosage matter. This would lead to an overestimation of the frequency of DDIs. The generic drug definition (substance + dosage +form) is sometimes not suitable when excipient or indication matter. This would lead to an underestimation of the frequency of DDIs. PMP seems to be the right level of analysis, but its scope is national which makes international comparisons difficult. The second statement is the importance of patient context in the analysis of DDIs. As we did not extract these patients content, we made some hypothesis about their existence. First we assumed that PMPs were used according to their regulatory authorization (for the indication) and were administrated. This may also have overestimated the frequency of potential DDIs. Second we made the hypothesis they were present. But in real world, we would have to deal with what explicitly exists or not and what is not explicitly stated. Assuming that something that is not explicitly stated is exists would lead to either an overestimation or an underestimation of the frequency of DDIs. Our experiment has some limitations. Prescription data were limited to the drugs prescribed and no other attributes were available (such as the administered dose, the method of administration...). It does not reflect the real exposure

of the patient and may result in an overestimate. Only drugs prescribed on the same day were considered, which may have underestimated the frequency of potential DDIs, because some drugs such as monoamine oxidase inhibitors can interact for up to 15 days after discontinuation. After filters were applied, the remaining DDIs could be considered as true positives, but the link to adverse events should be researched to be affirmative. To avoid contesting the national referential of DDIs (11), information on evidence and incidence should be provided (12) .

This study confirms the importance of context in limiting a large proportion of false positives in DDI detection (5). This gives useful guidance to conduct studies that attempt to determine the frequency of DDI on real-world data or for critical appraisal of such studies. This methodology could be reused to produce indicators on prescription containing contra-indicated DDI and to help pharmacists to improve their quality process.

Acknowledgments

This study was partially granted by (a) QLAP (Quantification des perofmances des logiciels d'aide à la prescription pour la détection des intéractions médicamentueses) ANSM – Appel à projet 2016 – Projet 7, (b) ReMIAMes (Ressources et méthodes libres pour la détection des interactions médicamenteuses dans les entrepôts de données de santé) ANR-19-CE19-0025-01

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