Analysis of contradictions and prevalence of adverse drug interactions

Doctoral (PhD) thesis

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Abbreviations and acronyms

ADR	adverse drug reaction
DDI	drug–drug interaction
FDA	U.S. Food and Drug Administration
MAO	monoamine oxidase
NSAID	nonsteroidal anti-inflammatory drug
ORCA	operational classification of drug interactions
SmPC	summary of product characteristics
SSRI	selective serotonin reuptake inhibitor
WHO	World Health Organization

I. Introduction

"There are some patients that we cannot help; there are none whom we cannot harm."
/Arthur L. Bloomfield, 1888-1962/

The seminal 1999 study "To Err is Human" [1] raised public awareness to the high rate of medical errors that occur in hospitals. According to another analysis from 2016, more than 250 000 people die in the United States every year from medical errors, making them the third leading cause of death after cardiovascular disease and cancer [2]. Although the methodology and findings of both studies have been highly criticized, there is an undeniable need for the systemic improvement of patient safety. Since medication errors are the leading cause of avoidable harm in healthcare, in 2017 the WHO launched a global initiative to reduce severe medication-associated harm by 50% over the next 5 years [3]. According to the European Commission, adverse drug reactions (ADRs) can be responsible for 2.5-8.4 million hospital admissions annually, corresponding to 100 800-197 000 deaths in the EU [4]. The same study estimates the total societal cost of ADRs to be around €79 billion.

Although drug interactions only account for a small proportion of ADRs, they place a significant burden on the healthcare system. A recent meta-analysis of 13 studies found that drug-drug interactions (DDIs) are responsible for approximately 1.1% of hospital admissions and 22.2% of all ADRs leading to admission are caused by DDIs [5]. Due to population aging and increasing polypharmacy, these ratios are expected to increase.

The growing number and availability of electronic patient databases prompted numerous recent publications which describe drug interactions on a regional or even a national level. With the analysis of prescription drug claims and drug utilization databases, valuable information on the population-specific pattern and importance of DDIs can be obtained.

In Hungary, Nyaka et al. published similar data, based on the analysis of 1.2 million prescriptions. The rate of clinically significant interactions was found to be approximately 3% [6]. One of the key challenges when evaluating the clinical significance of DDIs is the lack of reliable data on the percentage of potential interactions resulting in an actual ADR. Increasing digitization of healthcare provides real world data to be utilized in clinical research and drug therapy optimization. Owing to this innovative approach, a lot of new information about DDIs has become available; which could not have been obtained using traditional approaches like clinical trials or spontaneous reporting.

An interaction occurs when the effects of one drug are changed by the presence of another drug, herbal medicine, food, drink or other environmental chemical agent [7]. Thus, we can state that interactions don't exclusively develop between pharmaceuticals. The increasing number of patients taking "supplementary products" (dietary supplements, natural remedies, herbs, functional food etc.) together with prescribed medicines has become a new challenge for health care systems. The widespread and usually uncontrolled use of supplementary products may compromise the safety and/or effectiveness of the therapy. The FDA estimates that over 50 000 adverse events are related to dietary supplements per year [8]. Furthermore, each year 23 000 emergency department visits in the US are attributed to ADRs related to these products [9]. Interactions between drugs and supplementary products develop with the same mechanisms as drug-drug interactions. The clinical importance of some drug-drug interactions is controversial, and in case of interactions involving herbal products it is downright divisive. In addition to limited availability of clinical data, realistic appraisal of clinical relevance is complicated by factors like variability of product composition, unclear nomenclature and the ingredient responsible for the interaction being undefined.

Since most adverse consequences of DDIs are preventable, minimizing the risks associated with them should be an essential part of clinical routine, especially in case of vulnerable populations (e.g. elderly or patients with reduced hepatic or renal function). Due to the complexity of interactions and enormous number of available products, computerized solutions have become the basis of preventive interaction screening. Automated interaction screening is widely implemented with the hope of increasing patient safety, however, issues related to inappropriate alerting, such as unclear clinical significance, database inconsistencies and alert fatigue are significant barriers to its effectiveness. To make interaction screening more meaningful to healthcare professionals, an overhaul of the classification systems and alert messages is needed. In the present situation diagnosing the problems and mapping the ambiguities can be the first step forward.

II. Aims

This thesis is based on four research projects focusing on different aspects of potential drug interactions.

II. 1. Comparative evaluation of drug interaction screening programs

Interaction databases provide healthcare professional with convenient and compact synthesis of current knowledge worldwide. However, different screening programs commonly contain inconsistent information and are not equally reliable. The goal of this study was to establish a set of criteria involving practical aspects as well and to assess four Hungarian and two English-language databases.

II. 2. Prevalence of critical drug interactions in Hungarian outpatients

Real-world data is playing an increasing role in improving patient safety through aiding optimized clinical decision making. Through the analysis of prescription drug claims and drug utilization databases, real-world information on critical DDIs can be obtained. Several similar studies have been performed recently, however, no countrywide data on DDIs in the Hungarian population has been published as of yet. The aim of this study was to establish a list of critical potential DDIs and estimate their prevalence in the Hungarian outpatient population.

II. 3. Identification and evaluation of drug-supplement interactions in Hungarian hospital patients

Unsafe use of supplements is considered an unrecognized global public health problem similar to polypharmacy [10, 11]. In this pilot study we wanted to assess the potential impact supplements have on prescribed drug therapy. The aims of our study were (1) to establish the prevalence of supplement use among Hungarian hospital patients, (2) to identify potential drug-drug, drug-supplement and supplement-supplement interactions, and (3) to assess the efficiency of computerized interaction screening.

II. 4. Evidence-based analysis of herb-drug interactions

Transparent and clinically utilizable classification of drug interactions can only be established through structured, evidence-based assessment of underlying data and clinical relevance. In the field of drug-drug interactions, multiple efforts have been made recently to address these challenges. However, such systematic analysis has not been realized in the field of herb-drug interactions. The aim of the study is to present a structured analysis of evidence on two common pharmacodynamic herb-drug interactions: *Ginkgo biloba* + antithrombotics and *Hypericum perforatum* + antidepressants.

III. Methods

III. 1. Comparative evaluation of drug interaction screening programs

Databases studied

Our analysis included two Hungarian drug information websites commonly used by healthcare practitioners (Pharmindex Online, Dr.Info), two English-language databases (Lexi-Interact, Medscape Drug Interaction Checker) and the interaction screening modules of two popular Hungarian pharmacy software applications (Medivus, Gyógyír.Win). Search results in databases were compared to information in the summaries of product characteristics (SmPCs) of medicines and warnings in the patient information leaflet or at the manufacturers' website in case of supplementary products.

Comparison based on interacting pairs

For a detailed comparison of database content, 40 drug-drug and 8 drug-supplement pairs were selected with potentially serious interactions based on the literature. 1-4 products were assigned for each active ingredient resulting in a total of 273 combinations analysed. Interaction search results were assessed by the following criteria: (1) severity and (2) documentation rating, (3) information on frequency, (4) potential consequence, (5) mechanism, (6) patient management (e.g. non-interacting alternative), (7) type of interaction alert (single ingredient or group-based), (8) references and (9) further information (e.g. predisposing factors).

Comparison based on case studies

To model the complex nature of real-life scenarios, we set up 8 case studies. These hypothetical medication regimens helped us analyse how the individual databases work. Each case included on average 5 products.

III. 2. Prevalence of critical drug interactions in Hungarian outpatients

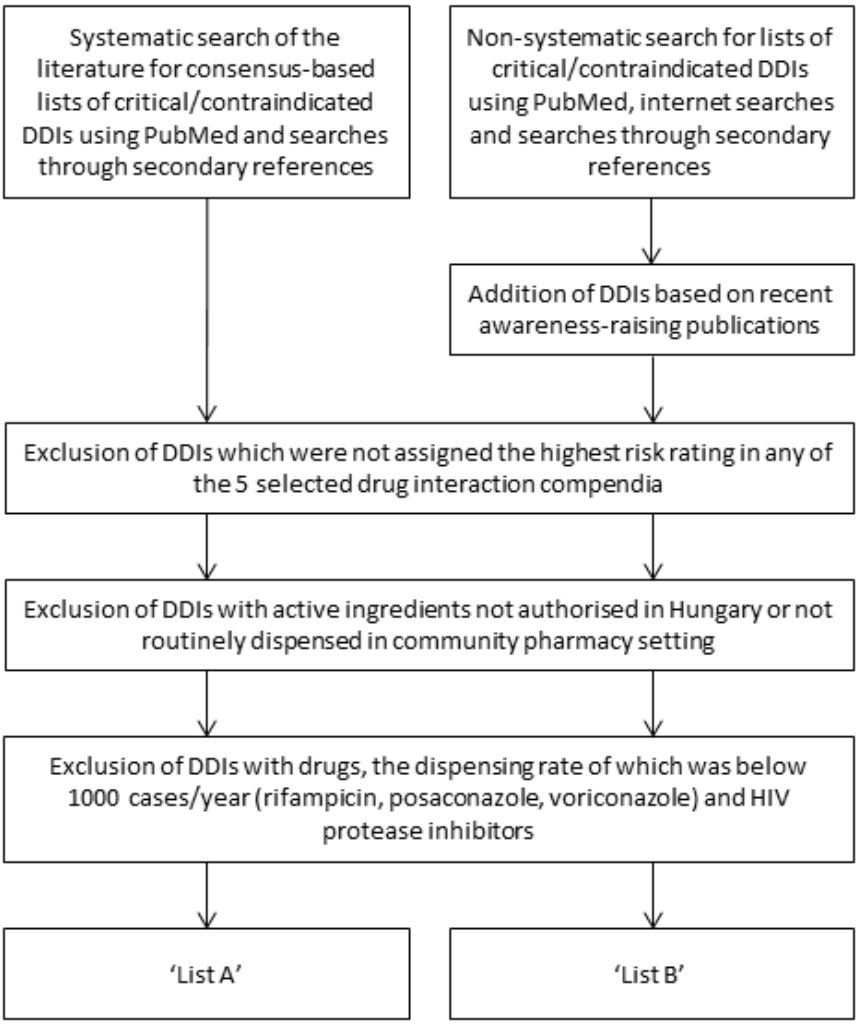
Selection of DDIs for analysis

There is no conclusive and generally accepted repository of high-risk DDIs. Present study focused on DDIs which are (1) of high clinical importance thus being most likely to cause significant harm if not detected, (2) well-supported by available evidence and (3) affect drugs which are routinely dispensed in the community pharmacy setting. The process of selection of DDIs for the analysis is illustrated on **Figure 1**.

Analysis of risk ratings of the selected DDIs

The selected drug pairs were analysed in 5 drug interaction compendia: Lexicomp Drug Interactions, Medscape Drug Interaction Checker, Drugs.com, Janusmed Interactions (previously known as SFINX – Swedish Finnish Interaction X-referencing) and the Operational Classification of Drug Interactions (ORCA) based on the book 'Top 100 Drug Interactions 2018 – A guide to patient management' by PD Hansten and JR Horn [12].

Figure 1. The process of selecting DDIs for analysis



Data sources

A retrospective analysis of prescriptions filled between 2013 and 2016 was performed. The source of drug utilization data was the IQVIA's national prescription fill database. The number of interacting drug pairs dispensed at the same time to the same patient was established.

III. 3. Identification and evaluation of drug-supplement interactions in Hungarian hospital patients

Study population

With the approval of the Regional Research Ethics Committee, a cross-sectional point-of-care survey was carried out among 200 patients treated at the First Department of Internal Medicine, Clinical Centre, University of Pécs. Patients who were waiting at outpatient care centres or were present in hospital rooms were requested to participate on randomly selected days between November 2011 and May 2012.

Data collection and analysis

Data was collected through personal interviews carried out by trained pharmacists and a review of the medical records. Information was obtained on prescribed medicines and supplementary products taken during the 2 weeks prior to the study and their procurement sources.

We examined the correlation between supplement use and gender, age (under 60 years vs. older), patient setting (outpatient vs. inpatient) and place of treatment (different specialties). Chi-square test was used to evaluate differences in supplement use across subgroups. Two-sample *t*-test and ANOVA test were used for comparison of the average number of supplements in different subgroups.

Interaction analysis

Potential interactions were assessed in two English-language (Lexi-Interact, Medscape Drug Interaction Checker) and one Hungarian database (Mediris). We selected the 50 most frequent interactions in our sample, and then analysed the overlap between the results in different databases. After summarizing interaction data from all 3 databases, the prevalence of potentially severe interactions was determined. If risk ratings were different the more serious one was taken into account.

III. 4. Evidence-based analysis of herb-drug interactions

The assessment criteria described in drug-drug interaction literature [13-15] served as the basis of our set of criteria, compiled in a way that addresses the characteristics of supplementary products as well. The selected herb-drug interactions were assessed by the following criteria: (1) potential consequence, (2) type of available evidence, (3) what form/extract of the herb were the original publications based on, (4) amount of the compound responsible for the interaction in commercially available products, (5) time-dependence, (6) extrapolatability to pharmacologically similar substances, (7) general importance of the interaction and practical considerations. The Drug Interaction Probability Scale [16] was used to assess causation for the events described in published case reports.

IV. Results

IV. 1. Comparative evaluation of drug interaction screening programs

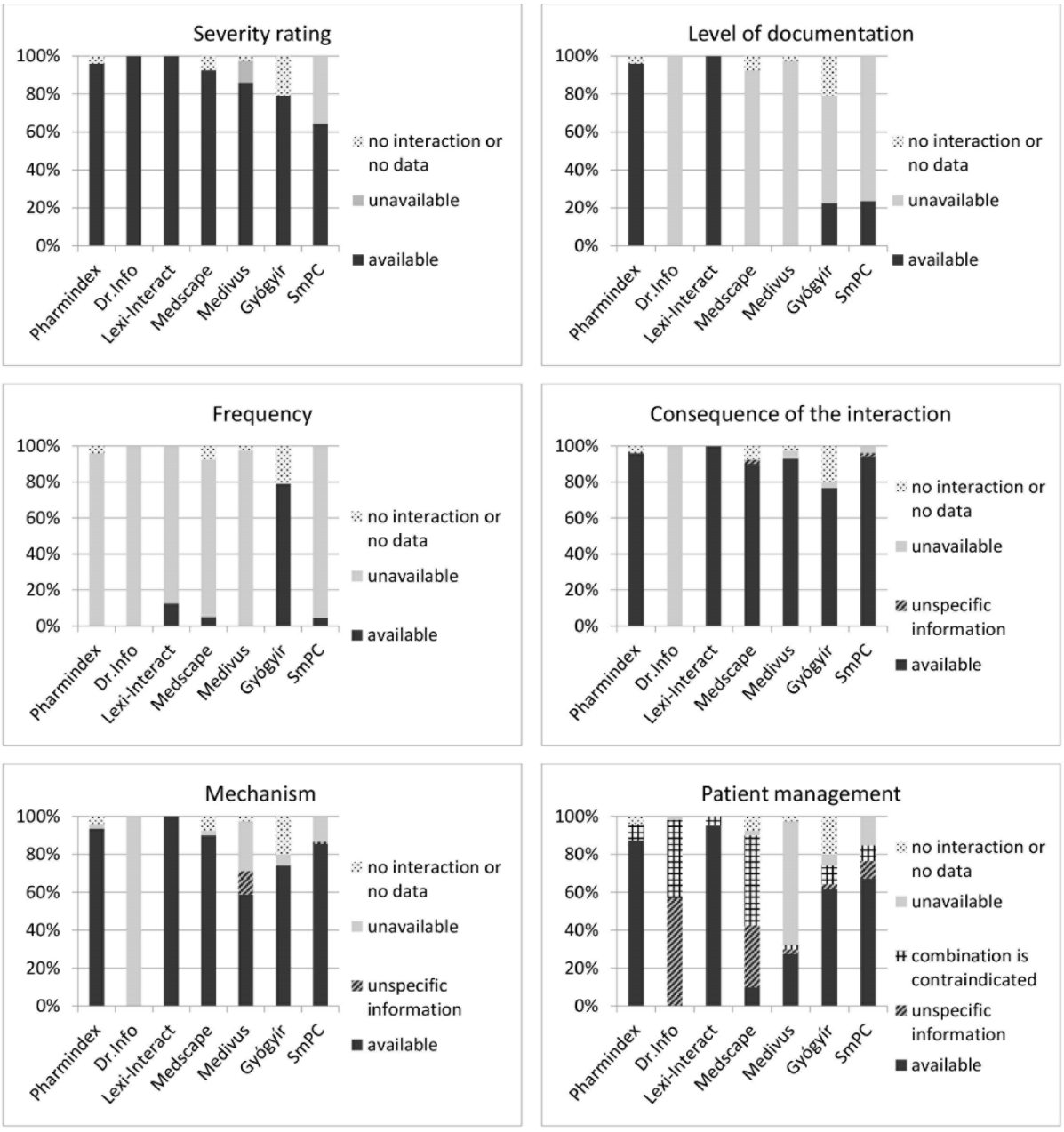
Comparison based on interacting pairs

Databases display warnings in the majority of DDI cases, however much of the time these warnings are of little use, since they lack sufficient information on how to prevent adverse outcomes (e.g. guidance on dose adjustment or patient monitoring). **Figure 2** summarizes the information displayed in the 6 databases and the summaries of product characteristics.

With 55% of the studied drug pairs, the information provided on the mechanism was different between the databases, while the rate at which DDIs differed on possible outcome and patient

management was 25% respectively. When examining different products containing the same active ingredient, the information displayed varied in 0-66,7% of cases. Compared to drug-drug interactions, drug-supplement interactions were less likely to be found in Hungarian databases, up to 80% of searches for supplementary product interactions did not produce satisfactory results.

Figure 2. Availability of different categories of information (% of all DDI pairs)



SmPC – summaries of product characteristics

Comparison based on case studies

The interaction outcomes differed in 2 databases between when the active ingredients were selected separately or as a combination during search. Lower risk due to topical use was only

indicated by 3 of the databases. As all of the databases handled interactions on the level of pairs, none of them was able to alert users about increased risks because of multiple interactions with the same mechanism. Differences between the displayed interactions of warfarin and rivaroxaban indicate inhomogeneous construction of group-based interactions, while the unavailability of rivaroxaban interactions in certain databases suggests a lack of update with data regarding newer drugs.

IV. 2. Prevalence of critical drug interactions in Hungarian outpatients

List of critical DDIs

After excluding interactions with drugs not marketed in Hungarian community pharmacies (e.g. irinotecan, pethidine), drugs with low dispensing rates (rifampicin, posaconazole, voriconazole) and HIV protease inhibitors, our analysis covered 39 DDIs. The final version of 'List A' included a total of 19 DDIs representing 140 ATC pairs, while 'List B' stood for 20 interactions described by 123 ATC pairs.

Total number of prescriptions

The total number of prescriptions filled varied between 173 924 449 and 176 368 468 per year between 2013 and 2016.

Cases of co-dispensing medications with critical drug-drug interactions

The prevalence of the selected potential DDIs ranged from 0.00 to 61.68 per 100 000 prescriptions per year on 'List A' and 0.00-355.89 on 'List B'. The total prevalence of DDIs on 'List A' varied between 172-186 thousand cases per year, the co-dispensing of coumarin anticoagulants with NSAIDs and MAO-inhibitors with amphetamine derivatives being the most and least frequent DDIs, respectively. The aggregate prevalence of DDIs on 'List B' was one order of magnitude higher with 1.60-1.66 million cases per year. The number of cases decreased throughout the study period with 11 DDIs and increased with 7. In case of the remaining 21 interacting pairs there was no discernible tendency.

IV. 3. Identification and evaluation of drug-supplement interactions in Hungarian hospital patients

Supplementary product use

Out of the 200 surveyed patients, 171 (85.5%) took supplementary products during the two weeks prior to the interview. Vitamins and minerals (n=115), herbal products (n=98) and over-the-counter medicines (n=55) were the most popular types of products. 36% of inpatients using supplements continued taking at least one of the supplements during their hospital stay. 2 out of 5 supplementary products were purchased outside a regulated pharmacy environment. A higher percentage of women used supplementary products than men (90% vs 79%; p=0.027); and the average number of supplements used was significantly higher (p=0.047) among women (2.68) than men (2.11). There was no significant difference in supplement use between patients

under 60 years and older (p=0.887), inpatients and outpatients (p=0.407), or patients of various wards (p=0.303). There was a marked difference between data obtained from patient interviews and the medical records. 88% of supplementary products were not listed in the medical documentation.

Interactions

Based on summarized interaction data from all 3 databases, potentially severe drug-supplement interactions were detected with 89 patients (45.2% of supplement users). However, the majority of interactions were not included in one or the other of the three databases (see **Figure 3**). In addition to that, the risk ratings of the same interactions varied greatly between the databases (see **Table I**). Discrepancies were especially characteristic to drug-supplement interactions.

Figure 3. The overlap between the 50 most common interactions by category

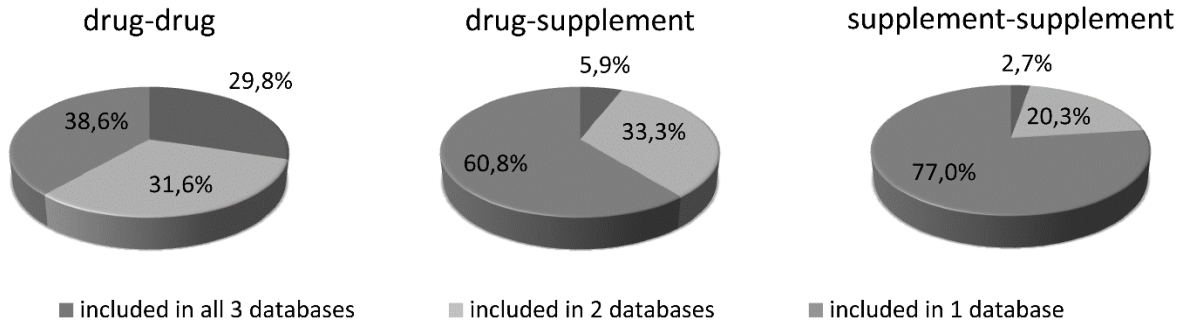


Table I. Comparison of risk rating for the most common interactions

Comparison of risk rating in Medscape and Lexi-Interact	**Drug-drug** (n=24)	**Drug-supplement** (n=18)	**Supplement-supplement** (n=17)
Identical	79.2%	33.3%	41.2%
Different	20.8%	66.7%	58.8%
Kappa coefficient*	0.37	0.04	0.21

*Kappa coefficient is a measure of inter-rater agreement. A kappa of 1 indicates perfect agreement, whereas a kappa of 0 indicates incidental agreement.

IV. 4. Evidence-based analysis of herb-drug interactions

Interaction between Ginkgo biloba and antithrombotics

There is a contradiction between case reports supporting the interaction and randomized controlled clinical trials providing negative evidence, however both types of studies have significant limitations. Interpretation of data is complicated by the lack of phytochemical characterization of the ginkgo products in the majority of case reports. It is worth mentioning that the most extensively cited early study confirming the antiplatelet effect of ginkgo used a concentrated ginkgolid mixture which is different in composition from the nowadays predominant EGb 761 extract. There is no conclusive evidence for a higher risk of bleeding

when ginkgo and antithrombotics are combined, compared to the monotherapy with these drugs. Despite being one of the best-studied herb-drug interactions, recommendations on its management are hardly unanimous among different databases, SmPCs and product information leaflets.

Interaction between St. John's wort (Hypericum perforatum) and antidepressants

Combined use of St. John's wort with other serotonergic substances increases the risk of serotonin syndrome through pharmacodynamic mechanism. Out of the 12 case reports suggesting an interaction, 10 cases involve a selective serotonin reuptake inhibitor (paroxetine, sertraline, fluoxetine or citalopram), one report is related to nefazodone and buspiron respectively. Similarly to the previous example, most case reports contain incomplete information; thus, they only scored 1–4 out of a maximum of 10 points on the Drug Interaction Probability Scale. Unspecific symptoms and unclear anamnesis made it impossible to establish a causal relationship. No more than 4 out of 12 case reports contained any information on the type of the St. John's wort product used, and precise composition was only described in one of the cases. Contrary to its pharmacokinetic interactions based on metabolic enzyme induction, pharmacodynamic interactions of St. John's wort are not related to one specific component. This interaction is based on a mechanism which plays an important role in the antidepressant effects of the herb; therefore, the interacting potential cannot be separated from the therapeutic action in this case. Unlike ginkgo, multiple different preparations of St. John's wort are used for medical purposes, produced by various extraction methods from the dried flowering aerial parts. One of the popular traditional uses in Hungary consists of making an infusion of the herb. Aqueous extracts prepared by this method contain hypericins in amounts comparable to the recommended antidepressant dose, therefore their interacting potential is not negligible. On the other hand, infusions contain only trace amounts of hyperforin due to the lipophilic properties of the ingredient, hence are unlikely to be associated with pharmacokinetic interactions.

V. Conclusion

V. 1. Comparative evaluation of drug interaction screening programs

Databases display warnings in case of the majority of DDIs, but content of these warnings is frequently incomplete. While the potential outcome and mechanism are generally described, guidance on patient management is less frequently provided. Information on dose- and time-dependence is seldom included. Potentially serious drug-supplement interactions are less often indicated compared to interactions between drugs. Conflicting information from different sources might confuse users and hinder the development of consistent, evidence-based practice. Although SmPCs are the legally accepted sources of information about medicines, including drug interactions, their advice is sometimes unclear or unhelpful; and information asymmetry

between the involved products is common. Our results indicate that because of the significant discrepancies, relevant interactions may go undetected, if only one database is used. The number of inappropriate alerts could easily be reduced by introducing several simple filters: separating drugs with a topical effect and omitting interaction alerts about the components of combination products.

V. 2. Prevalence of critical drug interactions in Hungarian outpatients

The goal of preventive interaction screening is to ensure that no patient receives a potentially dangerous combination without previous evaluation and ongoing control of risks. Our motivation to perform this study was to obtain real-world data laying the groundwork for the much-needed development of routine interaction screening and DDI-related clinical decision support. The main question we wanted to answer was whether a preselected group of critical DDIs poses a significant danger to the Hungarian ambulatory population. There were 1.8 million cases of co-dispensing each year, where prescribers' and community pharmacists' role in recognizing and managing potentially serious interactions was or would have been critical. Reaching a consensus on an elementary set of interactions would be a great leap forward in improving patient safety.

V. 3. Identification and evaluation of drug-supplement interactions in Hungarian hospital patients

The simultaneous use of prescribed medicines and supplementary products was prevalent in both inpatients and outpatients. As supplement use is not routinely included in their medical records, interviewing patients was clearly necessary to obtain information on this matter. Several respondents did not tell their doctor about their consumption of supplements on purpose, which is something that warrants serious consideration. The data we presented suggests that a full medication history should specifically address supplements and use of these products should be documented. One of the main flaws of screening supplements for interactions is the lack of a comprehensive and verified database of these products; whereas being familiar with the ingredients would be essential for the assessment of risks. Professional opinions diverge about the importance of some DDIs. This is reflected by the way in which information about these interactions varies from database to database. The confusion surrounding drug-supplement interactions is even more substantial.

V. 4. Evidence-based analysis of herb-drug interactions

The harmful consequences of herb-drug interactions can and should be prevented, however, screening and management of potential interactions is a challenging task for healthcare professionals. Evidence-based management of herb-drug interactions requires complex clinical, pharmacological and pharmacognostical expertise. Furthermore, the well-known pitfalls of interaction screening are complicated by additional factors, like the lack of

standardised nomenclature of herbal ingredients and considerable product variability. Because of the latter, it is critical not to automatically extrapolate the interacting properties of a given component to all products containing the herb.

V. Summary and novel findings

Comparative evaluation of drug interaction screening programs

- While interaction databases inform users on the majority of potentially serious drug-drug interactions, guidance on patient management was only given in 4 of the 7 sources in more than half of the cases.
- With 55% of the studied drug pairs, the information provided on the mechanism was different between the databases, while the rate at which DDIs differed on possible outcome and patient management was 25% respectively.
- When examining different products containing the same active ingredient, displayed information varied in as much as 67% of cases.
- Irrelevant alerts could easily be reduced by introduction of several simple filters: separating products with topical effects and omitting interactions between the ingredients of combination medicines.
- Up to 80% of searches for supplementary product interactions did not produce satisfactory results, indicating that databases are less reliable in this field.

Prevalence of critical drug interactions in Hungarian outpatients

- Since there is no conclusive and generally accepted repository of high-risk drug-drug interactions, published consensus-based lists can be considered as a starting point.
- After excluding drugs with low dispensing rates, the analysis covered DDIs, the risk ratings of which were inconsistent among different drug interaction compendia.
- Based on the analysis of pharmacy dispensing data between 2013 and 2016, there are 1.8 million cases of co-dispensing each year, where prescribers' and community pharmacists' role in recognizing and managing potentially serious interactions is critical.
- The prevalence of the selected potential DDIs ranged from 0.00 to 355.89 per 100 000 prescriptions per year.
- The number of co-dispensing cases decreased throughout the study period with 11 DDIs and increased with 7. In case of the remaining 21 interacting pairs there was no discernible tendency.

Identification and evaluation of drug-supplement interactions in Hungarian hospital patients

- Out of 200 surveyed patients of internal medicine, 85.5% took at least one supplementary product (including OTC medicines) during the two weeks prior to the interview.
- Women were more likely to take supplements than men. There was no significant difference in supplement use between patients under or over 60 years, between inpatients and outpatients and among patients in various wards.
- There was a marked difference between data obtained from patient interviews and the medical records, 88% of supplementary products was not mentioned in the latter source.
- 39.4% of supplementary products were purchased outside a regulated pharmacy environment.
- Potentially severe drug-supplement interactions were detected with 89 patients (45.2% of supplement users); however, the majority of interactions were not included in one or the other of the three databases. In addition to that the risk ratings of the same interactions varied greatly between databases.

Evidence-based analysis of herb-drug interactions

- Based on previous literature on drug-drug interactions, we developed a set of criteria for the assessment of herb-drug interaction which addresses the characteristics of supplementary products as well. Evidence on interactions of two commonly used herbs was assessed by these criteria: *Ginkgo biloba* + antithrombotics and *Hypericum perforatum* + antidepressants.
- When compared to interactions between drugs, the assessment of drug-supplement interactions requires the consideration of additional factors. Herbal products vary in composition; therefore, it is paramount to specify where our evidence comes from (species, part of plant, type of extract) and the concentration of the interacting component in the available products. However, no information on supplementary product composition was available in 64% and 67% of the analysed case reports involving ginkgo and St. John's wort, respectively.
- Case reports usually lack the level of detail required to be viewed as conclusive evidence. This is why they scored a maximum of 4 out of 10 on the Drug Interaction Probability Scale.
- Even in the case of the best-studied herb-drug interactions there is considerable disagreement on their significance, and what attention they require from practicing professionals.

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