Contradictions in the interpretation of drug/supplement interactions and difficulties of their management in everyday clinical practice

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BACKGROUND, METHODS

The growing use of supplementary products (herbal remedies, food supplements, OTC medicines etc.) poses an unignorable and poorly explored risk to hospital patients. These products may affect the safety and efficacy of the medical treatment therefore require increased awareness from healthcare professionals. In our previous study [1] we found that 171 (85,5%) of 200 interviewed hospital patients took at least one supplementary product in the two weeks preceding the study.

200 interviewed hospital patients
average age of 56.7 years,
male to female ratio 2:3,
36 smokers and 139 nonsmokers

→ average number of prescribed medicines: **7.8**
average number of supplementary products
- according to patient interviews: **2.4**
- according to medical records: **0.3**

→ **types of supplementary products**: vitamins and minerals (115 patients), herbs or herbal products (98), non-vitamin non-herbal OTC (55), homeopathy (5), other(41)

→ **databases used for drug interaction screening:**
- Mediris (HC Pointer Ltd.)
- Medscape Drug Interaction Checker (Web MD Llc.)
- Lexi-Interact (Lexi-Comp Inc.)

FACTORS TO CONSIDER WHEN EVALUATING POSSIBLE DRUG-SUPPLEMENT INTERACTIONS

1. UNDERLYING EVIDENCE
- type of the evidence (clinical trials, case reports, in vitro studies, theoretical based on known pharmacological effects , etc.)
- which form of a given interacting substance has been reported on (species, plant-part, type of extract, etc.) → does the interaction apply to a larger group of substances?

2. MECHANISM OF INTERACTION

3. INCIDENCE
- frequency of the given combination
- percentage of patients with clinical symptoms

pharmacological properties of the drug and the supplement
(pharmacokinetics, therapeutic index, consequences of decreased or increased drug response, etc.)

route of administration
(e.g. interactions affecting absorption apply only to oral forms)

time period of application
(e.g. CYP 450 enzyme induction needs longer time to develop than inhibition)

(co-)morbidity, special conditions
(e.g. perioperative period)

dose
(e. g. low dose multivitamins seem not to influence the medical therapy – except of vitamin K + coumarin anticoagulants)

→ 4. CLINICAL RELEVANCE ←

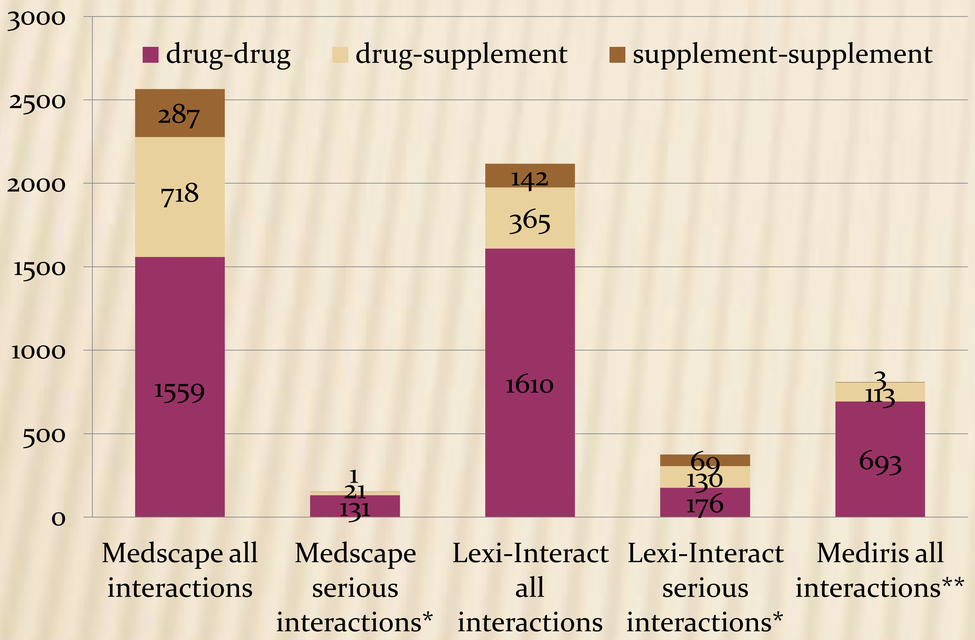
liver and kidney function
(metabolic and elimination capacity)

amount of the interacting component in the product
(e. g. St John's wort extracts with low hyperforin content do not alter the pharmacokinetics of oral contraceptives)

additional medication
(possibility of multiple interactions with the same mechanism)

other patient related risk-modifying factors
(age, sex, genetics, etc.)

RESULTS



*found interactions in the two most severe risk categories
**Mediris database contains only interactions which are considered serious

Figure 1. Number of interactions found in the three databases

228 possibly serious drug-supplement interactions identified → **70 clinically relevant** drug-supplement interactions, 14 of them were included in all 3 databases, 44 in 2 and 12 in only one

71 possibly serious supplement-supplement interactions identified → **2 clinically relevant** supplement-supplement interactions, 1 of them was included in all 3 databases, the other one in only one

We faced the following **difficulties in the course of interaction screening**:

- There are significant differences between the databases, as to which interactions are included and how their severity is rated. These differences are greater with drug-supplement interactions (see Tables 1 and 2).
- Using only one database, relevant interactions may remain unexplored.
- The overwhelmingly high number of interaction alerts makes the use of databases tedious and impractical.
- There are ingredients that cannot be found in one or the other of the databases.

	drug-drug	drug-supplement	supplement-supplement
included in all 3 databases	29.8%	8.9%	2.7%
included in 2 databases	31.6%	33.3%	20.3%
included in 1 database	38. %	60.8%	77.0%

Table 1. The overlap between the 50 most common interactions by category

	drug-drug	drug-supplement	supplement-supplement
risk rating is identical	79.2%	33.3%	41.2%
risk rating is different	20.8%	66.7%	58.8%

Table 2. Differences and similarities of risk rating of the interactions which are included both in Medscape and Lexi-Interact databases

CONCLUSION

Computer programs used for preventive interaction screening should fulfill the following criteria to work properly:
- clear ingredient nomenclature and the option to search synonyms
- standardized classification of supplements – similarly to the ATC classification of medicines
- interaction screening should be based on a verified and comprehensive database

The influence of supplementary products on medical treatment cannot be overlooked. The method of interaction analysis used in this study is too time-consuming for everyday practice. The search for interactions is only effective if the database used for it meets the specifications listed above. Supplement use should be controlled by clinical pharmacists and included in patient documentation.

[1] A. Végh, E. Lankó, A. Fittler, L. Botz. *Identification and prevention of deleterious effects of supplementary health products on medical therapy – A challenge for clinical pharmacists*. abstract in EJHP 2012; 19(2), p. 95.

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