Creation of a list of modifiable and clinically important drug-drug interactions (DDIs) in elderly poly-treated patients: the experience of the Emilia Romagna Region

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Background. Elderly patients represent a population highly susceptible of inappropriate prescriptions and poly-pharmacy, which may cause potential drug–drug interactions (DDIs) and relevant hospital admission. Although a lot of lists of DDIs have been already created, they are not easily measurable in the setting of outpatients claim databases.
Aim. To compile a list of potential DDIs suitable for appropriateness of prescription in elderly patients.
Methods. As part of a regional pharmacovigilance project, the list was developed by a panel of pharmacists, pharmacologists and pharmacovigilance experts of 7 Local Health Authorities (Emilia Romagna Region, 3.4 million inhabitants). Biomedical literature (Pubmed database) was first perused to identify already published lists of DDIs. This initial list was refined by checking Micromedex, summary of product characteristics and published case reports. Drugs not actually marketed in Italy or not reimbursed by the Italian Health Service (e.g., benzodiazepines) were discarded. The following criteria were also considered: (a) clinically important DDIs (i.e., potentially causing life-threatening clinical events); (b) modifiable DDIs (i.e., existence of therapeutic alternatives); (c) measurable through prescription databases; (d) including at least one chronic agent. Underlying mechanisms, clinical consequences and suggestions for proper management were also provided. DDIs requiring only clinical monitoring or dose adjustment (i.e., absence of real therapeutic alternatives) were also excluded. Finally, agreed DDIs were used to search prescription databases, focusing on elderly patients (≥65 years) with poly-pharmacy (at least 5 chronic drugs).
Results. The final list included 53 potential DDIs. Vitamin K antagonists and antihypertensive drugs (e.g., diuretics and ACE inhibitors) were most frequently represented as chronic therapy (in 9 and 7 potential DDIs, respectively), followed by antidepressants (especially selective serotonin reuptake inhibitors), statins and antidiabetics (5, 5 and 4, respectively). Anti-infectives (especially macrolides, fluoroquinolones and cotrimoxazole) were identified in 17 DDIs as precipitant drugs (i.e., acute administration causing interaction with chronic medication). Antidepressants (concomitant selective serotonin reuptake inhibitors and non-selective monoamine reuptake inhibitors), NSAIDs (for instance, 'triple whammy', i.e., ACE inhibitors+diuretics+NSAIDS), macrolides and PPIs (with clopidogrel) were deemed as emerging DDIs requiring *ad hoc* focus. In the majority of DDIs, instead of indicating specific alternatives, it was proposed to reconsider the need for therapy initiation as proper clinical management (e.g., antidepressants and PPIs). Pharmacokinetic features (e.g., Cytochrome P450 inhibition) were mostly highlighted as underlying mechanisms.
Conclusion. During the first year of the project, the expert panel scrutinized the available evidence and highlighted a number of potential DDIs, which are being investigated in prescription databases to estimate their prevalence in the Emilia Romagna Region. This will allow to assess the actual clinical relevance in general practice. Active pharmacovigilance interventions are also planned as educational tools to inform general practitioners and reduce the burden of potential DDIs, thus supporting appropriate prescriptions.