THE PREVALENCE OF POTENTIAL DRUG-DRUG INTERACTIONS IN THE THERAPY OF ROMANIAN COMMUNITY PHARMACY'S PATIENTS

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Abstract

Drug-drug interactions (DDIs) are a concern for patients and providers, as multiple medication use is becoming more common to manage complex diseases. However, a high prevalence of potential drug-drug interactions (pDDIs) can lead to a higher probability to develop an adverse drug reaction (ADR) or suboptimal therapeutic effects. The objective of our study was to measure the frequency, nature and severity of the potential DDIs in prescriptions from a Romanian community pharmacy. We analysed 308 prescriptions (all reimbursed prescriptions from one month) of 243 patients for the detection of the pDDIs. Our study showed that potential drug-drug interactions are highly prevalent (34.42% of prescriptions with at least one DDI) in patients' therapy and the modernization of prescribing and dispensing medicines is necessary.

Rezumat

În terapia modernă polimedicația este o necesitate în cazul pacienților cu mai multe afecțiuni, dar aceasta poate determina o incidență crescută a interacțiunilor medicamentoase și a reacțiilor adverse la medicamente sau reducerea efectului terapeutic ale acestora. Obiectivul studiului de față a fost determinarea frecvenței, naturii și severității interacțiunilor medicamentoase potențiale identificate în prescripțiile din farmacia comunitară din România. Au fost analizate 308 rețete compensate provenite de la 243 de pacienți dintr-o farmacie, pe parcursul unei luni. Rezultatele studiului arată o prevalență ridicată a interacțiunilor medicamentoase potențiale în terapia pacienților, subliniindu-se astfel nevoia existenței sistemelor computerizate de semnalare a interacțiunilor medicamentoase, atât la nivelul prescrierii de către medic, cât și la nivelul eliberării medicamentului de către farmacist.

Keywords: drug-drug interactions, adverse drug reactions, community pharmacy.

Introduction

Adverse drug reactions (ADRs) represent a major health issue worldwide, as their consequences are often serious - accounting for up to 18% of hospital admissions and being the sixth leading cause of mortality [1,11,15,16]. An observational study conducted in an internal medicine ward in Romania showed that ADRs represent 6% of the total number of admission causes. The same study showed that 25.9% of all validated ADRs (detected at the admission or during hospitalization) are consequences of drug-drug interactions (DDIs) [9].

DDIs are an important cause of ADRs and may lead to an increased risk of hospitalization (2.8% of hospital admissions) and higher healthcare costs [12,18,19].

DDIs are a concern for patients and providers, as multiple medication use is becoming more common to manage complex diseases. Polypharmacy is the most important risk factor for DDIs [7,10]. The prescription of more drugs for one patient is a common and necessary practice for the patients, but physicians should keep in mind that the incidence of potential DDIs approaches 40% for patients taking 5 drugs, and exceeds 80% for patients taking 7 or more medications [10]. In addition to polypharmacy, age is also a key risk factor for DDIs along with acute medical condition, female sex, prescriptions from multiple physicians and drugs with narrow therapeutic range [3,4,22].

Studies on the subject of potential DDIs (pDDIs) in out-patients therapy were conducted in different countries, but to our knowledge, not in Romania. Regarding the elderly, *Björkman et al* found in their study made on 6 European countries pharmacies, 0.83 potential DDIs/person and 46% of the patients had at least one potential DDI [5], while in Mexico the percentage of elderly patients with at least one DDI was almost double (80%)[8]. In Switzerland the percentage of potential DDIs in general population prescriptions was 23% according to *Dallenbach et al* [7] and in Dutch pharmacies was found that only 6% of the prescriptions presented at least one potential DDI [6].

Because of the differences among the healthcare systems, results from one country prevalence studies cannot be extrapolated to other countries. Drugs that are approved to be marketed and reimbursed in some countries, and also the prescribing policies, may be very different in others. The aging of the population and the increasing complexity of the patients' medication regimens, as well as the fragmented healthcare system in Romania, with multiple prescribers for one patient and no electronic charts, are important elements that might lead to DDIs [14,21].

The objective of our study was to measure the frequency, nature and severity of the potential DDIs in prescriptions from a Romanian community pharmacy.

Materials and Methods

The retrospective study was conducted on the one month (30 days) period reimbursed prescriptions (January 2010) from a community pharmacy from Romania.

We analysed 308 prescriptions for 243 patients for pDDIs using Thomson Micromedex program [13]. If a patient presented to the pharmacy with more than one prescription, all prescriptions were analysed in order to detect the pDDIs between drugs on different prescriptions, if the drugs were meant to be taken in the same period of time.

We define a potential DDI as being a pair of drugs that interact in such a manner that the effectiveness or toxicity of one or two drugs might be altered.

Potential DDIs were classified according to Micromedex program as *contraindicated associations* (the drugs are contraindicated for concurrent use), *major* DDI (the interaction may be life-threatening and/or require medical intervention to minimize or prevent serious adverse effects), *moderate* DDI (the interaction may result in exacerbation of patients' condition and/or require a modification in therapy) and *minor* (the interaction would have limited clinical effects). The most severe category is the *contraindicated association*.

Data including age, sex, medication, detected pDDIs and degree of severity were analysed using descriptive statistics.

Results and Discussion

Patients' characteristics and prescribed drugs

Two hundred and forty-three patients presented to a community pharmacy in January 2010 with 308 reimbursed prescriptions issued by a general practitioner or by the specialist. The number of medicines prescribed was 931 (3.83 drugs/patient) out of which 913 were purchased (18 drugs not taken by 15 patients): cardiovascular drugs represent the great majority of prescribed drugs (64.03%). Patients' characteristics and prescribed drugs are presented in Table I.

Table I

Characteristics of the patients and prescribed drugs.

Characteristics		
Age-years (n=243)	Mean (95% CI)	60.78 (57.74-63.82)
Gender-no. (%) (n=243)	Male	99 (40.74)
	Female	144 (59.26)
Medicines prescribed (n=931) ATC* group-no. (%)	Cardiovascular system **(C)**	596 (64.03)
	Nervous system **(N)**	65 (6.99)
	Alimentary tract and metabolism **(A)**	60 (6.43)
	Antiinfectives for systemic use **(J)**	57 (6.13)
	Musculoskeletal system **(M)**	54 (5.81)
	Respiratory system **(R)**	50 (5.38)
	Genitourinary system and sex hormones **(G)**	21 (2.26)
	Blood and blood forming organs **(B)**	16 (1.73)
	Other groups	11 (1.20)

Anatomical Therapeutic Chemical **(ATC) group [12] , **CI**-confidence interval*

Potential DDIs

In the 243 patients included in the study with 308 prescriptions, we identified 252 pDDIs (1.04 pDDIs /patient). Our study confirmed our supposition that pDDIs have a high prevalence in patients' therapy, 117 (48.15%) patients being at risk of developing negative consequences of a DDI (an ADR or the loss of the therapeutic effect). The numbers are lower than the ones found in Mexico outpatients (80%) but higher than in a study performed in hospitalized patients in Switzerland (30% at hospital entry) [23] and higher than in geriatric outpatients from the Netherlands (25%) [22]. Regarding the prevalence of prescriptions containing a pDDI, in our study 106 (34.42%) of the total number of prescriptions contain at least one pDDI. To this number we should also add the 29 cases of patients having a second (or third) prescription and presenting pDDIs between drugs from different prescriptions being administered in the same period of time (56 pDDIs). We should also mention that the total number of prescriptions (308) includes the one-drug prescriptions as well. In Thai out-patients the prevalence of prescriptions containing at least one pDDI was 20.06%, but in Dutch community pharmacies it was found that only 6% of the prescriptions presented at least one potential DDI [6].

As for the number of pDDIs per patient our result (1.04 pDDIs/patient) is comparable to the highest values from a study performed on the elderly from six European countries. In the Republic of Ireland and Germany the results were close to ours (1.05 and 1.04 respectively) but in countries like Portugal and Northern Ireland (0.62 and 0.67 respectively) the number of pDDIs per patient was significantly lower [5].

The majority of pDDIs were between the medicines on the same prescription - 196 pDDIs (77.78%) in 106 prescriptions and in 29 patients we found 56 pDDIs (22.22%) between drugs on different prescriptions but to be taken during the same period of time. The association of angiotensin converting enzyme (ACE) inhibitors with thiazide diuretics was the most prevalent pDDI (found in 54 patients), followed by the combination beta-adrenergic blockers and dihydropyridine calcium channel blockers (in 31 patients) and ACE inhibitors again combined with non-steroidal anti-inflammatory drugs (NSAIDs) in 15 patients. These results can be explained by the fact that the cardiovascular drugs constitute the great majority of the prescribed drugs (64.03%), similar with another study results [17]. All these three combinations are of "moderate" severity and could have led to postural hypotension (first dose), hypotension and/or bradycardia and decreased antihypertensive effects respectively. The most prevalent "major" pDDIs were the associations of calcium channel blockers with statins (13

patients) which may lead to myopathy or rabdomyolysis and Ginko biloba extract combined with NSAIDs (in 5 patients), with an increased risk of bleeding.

We did not found "contraindicated associations" and the number of "major" pDDIs was 50 (19.84%); the majority of pDDIs were "moderate" - 192 (76.19%) and "minor" - 10 (3.97%) pDDIs. In Table II are listed the most prevalent pDDIs and their severity category.

Table II

The most prevalent pDDIs

Drug combinations	Number of potential DDIs (n=252), (%)	Severity	Potential effect of the DDI
ACE inhibitors + thiazide diuretics	54 (21.43)	moderate	May result in postural hypotension (first dose)
Beta-adrenergic blockers + dihydropyridine calcium channel blockers	31 (12.31)	moderate	May result in hypotension and/or bradycardia
ACE inhibitors + NSAIDs	15 (5.95)	moderate	Decreased antihypertensive effects
Calcium channel blockers + statins	13 (5.16)	major	Increased exposure to statins and increased risk of myopathy or rabdomyolysis
Beta-adrenergic blockers + NSAIDs	11 (4.36)	moderate	Decreased antihypertensive effects
Beta-adrenergic blockers + digoxin	10 (3.97)	moderate	May result in digitalis toxicity (nausea, vomiting, arrhythmias) and/or AV block
Beta-adrenergic blockers + antidiabetic agents	8 (3.17)	moderate	May result in hypoglycaemia, hyperglycaemia or hypertension
Dihydropyridine calcium channel blockers + NSAIDs	7 (2.78)	minor	Increased risk of gastro-intestinal haemorrhage
Thiazide diuretics + NSAIDs	6 (2.38)	moderate	Decreased antihypertensive and diuretic effects
Beta-adrenergic blockers + alpha blockers	6 (2.38)	moderate	May result in postural hypotension (first dose)
Ginko biloba extract + NSAIDs	5 (1.98)	major	Increased risk of bleeding
Other potential DDIs	86 (34.13)		

In clinical practice certain associations can be prescribed often because it is considered that the benefit outweighs the risk (*eg.* ACE inhibitors + thiazide diuretics). In this cases careful monitoring and counselling of the patients are necessary in order to avoid the occurrence of adverse drug interactions.

We did not investigate if any of the pDDIs detected materialized in negative clinical consequences, but it is important to remember that a high prevalence of pDDIs leads to a higher probability to develop an ADR or

suboptimal therapeutic effects, and further more, they can seriously affect the patients' safety and increase the healthcare costs.

Differences among the countries are likely to reflect different therapy traditions as well as different policies regarding the use and implementation of clinical guidelines. However, health professionals from countries like the Netherlands and Portugal are being helped in their prescribing activity by well-organized health systems, where different support strategies for risk management are available (electronic prescription entry, computerized medication records). Systematic screening for DDIs can be fastidious and time-consuming in the rapidly growing field of therapeutics.

A limitation of our study is the fact that the prescriptions studied were only the reimbursed ones and besides those, the patients might also have been on other medications (non-reimbursed medications, *"over the counter drugs"*). If to the considered medication, the patient would have taken a low dose of aspirin for example, the number of pDDIs would be a lot greater.

Conclusions

A 2007 World Health Organization report referring to the cases of drug-drug interactions from the Vigibase (the international ADR database) stated that co-medication of contraindicated drugs is a longstanding international problem [20].

Our study showed that potential drug-drug interactions are highly prevalent in patients' therapy. The use of modern computerized programs in the prescription practice and in pharmacies is necessary in order to prevent ADRs and other negative consequences of drug interactions. Further research could look in to which of the pDDIs have clinical consequences.

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