A cooperation project between hospital pharmacists and general practitioners about drug interactions in clinical practice

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ABSTRACT

Objectives (1) To evaluate drug–drug interactions (DDIs) in general practitioners' (GPs) prescriptions; (2) to implement a cooperation project between pharmacists and GPs to improve DDI management and patient care.

Methods In 2013, pharmacists from the Community Drug Assistance ASL TO1 launched a cooperation project involving 48 GPs. As a first step, GPs were asked to select, from a list, drug associations for which they recommended analysis of occurrence in their prescriptions. The pharmacists (1) analysed GPs' prescriptions dated 2012–2014, according to the list of DDIs selected (n=9); (2) evaluated solutions for DDI management, using the Micromedex DDI checker database and literature analysis; they then (3) disseminated DDI-related information to GPs through training meetings and (4) assessed the efficacy of these actions through a questionnaire submitted to the GPs in 2013.

Results (1) Prescriptions analysis: a reduction in the number of DDIs was observed (–14% in 2013 vs 2012, –9% in 2014 vs 2012); in some cases these reductions were statistically significant (calcium carbonate + proton pump inhibitors (PPIs) –50%, p<0.0041, amoxicillin+lansoprazole –42%, p<0.0088). (2) Questionnaire: this was completed by 75% of GPs. The literature analysis was considered interesting by 94% of GPs; solutions were adopted by 89% of GPs and 34% of GPs affirmed that clinical improvements after application of the measures were observed in their patients, even if they could not provide quantitative data for this outcome.

Conclusion The cooperation project between pharmacists and GPs was effective because it established a professional exchange between the two health professionals. The pharmacist gave support to GPs, which benefited the patients, who gained clinical improvements and improved satisfaction with their medical care, as declared by the GPs in answers to the questionnaire.

INTRODUCTION

Drug–drug interactions (DDIs) frequently occur,¹ and may generate adverse drug reactions (ADRs),^{2–5} as numerous studies have clearly shown.^{1 3 6 7} One of the main causes is polypharmacy,^{2 3 6–10} especially in elderly patients, who often present multimorbidity with complex clinical conditions.^{2 3 6 9} Older patients frequently receive prescriptions for drugs from a number of different specialists, to treat specific disease symptoms.^{2 3 10} Not all DDIs give rise to dangerous ADRs.^{1–3} The majority of ADRs are preventable,^{4 5} and thus a careful review should

be made whenever new drugs are added to poly-medication prescribed to vulnerable subjects.¹

One way to improve drug management would be to provide education and information to health professionals,^{8 11} and thus the intervention of the pharmacist might be strategic.^{1 8 11} Moreover, intraprofessional cooperation could be particularly useful to general practitioners (GPs), who are at the front line of patient care, following the patient's entire clinical history.²

The Italian National Health System (INHS) is made up of different layers. It guarantees equal rights to all citizens, and gives them access to general care by assigning a GP to each patient. Among the different health facilities, local health authorities (LHAs; Assistenza Sanitaria Locale (ASL) in Italian)¹² play a major role, regulating the functioning of health services in the community. For example, the Community Drug Assistance (CDA; Servizio Farmaceutico Territoriale in Italian) service has several responsibilities towards GPs: these include monitoring GPs' prescriptions, providing pharmaceutical training and updating information, as well as analysing prescriptions given in hospital discharge letters. The health professionals designated to undertake these tasks in the CDA are pharmacists.

Pharmacists working in the Italian CDA have postgraduate training in hospital pharmacy. Their education includes 5 years for the pharmacy degree, and a further 4 years' specialisation in hospital pharmacy. Some 450 000 prescriptions are written monthly within the area of the CDA Regione Piemonte - TO1 LHA; of these, 30% originate from hospital therapeutic advice in patient discharge letters.

The addition, by specialists, of new drugs without a critical revision of the patient's entire treatment schedule generates drug redundancy, drug duplications and in many cases, DDIs are present in GPs' prescriptions.⁷ Analysis of GPs' prescriptions plays a very important role in dealing with this phenomenon.^{3 13}

The objectives of this study were: (1) to clarify the impact of DDIs induced by hospitals' therapeutic advice, by analysing GP prescriptions; (2) to establish intraprofessional cooperation between pharmacists and GPs, to enhance awareness of the importance of DDI management in a patient-centred therapeutic approach. One underlying motivation was that a reduction in the number of hospital second admissions due to ADRs in polymedicated patients would provide valuable savings in LHA budgets.

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Figure 1 Evolution of DDI project and description of the steps.

METHODS

The study was conducted in four steps, analysing GPs' prescriptions between 2012 and 2015, as shown in figure 1. The principal tools were (1) screening reimbursed prescriptions issued in 2012, 2013 and 2014 (concerning drugs refunded by the INHS¹²) and (2) administering a questionnaire to GPs.

The four steps of the cooperation project are described in detail below

Step 1

DDIs were detected in patient discharge letters, using *Micro-medex*¹⁴, a database that can be used to consult the summary of product characteristics (SPC) and highlight DDIs in treatments; its sources are current evidence from the literature. The criteria used to identify DDIs were: polypharmacy (exposure to at least five therapeutic classes)³; treatments given to elderly patients; drugs with particular clinical relevance and/or particular specialised use; DDIs for which feasible therapeutic alternatives were available (ie, the possibility of prescribing a different active ingredient, without therapeutic complications, in the place of another); DDIs that were adjustable, while avoiding changes in treatment (ie, possible administration at different times). Some 'minor' DDIs were also highlighted. A list of DDIs (DDI dossier, see online supplementary table) found in discharge letters was created.

Step 2

The head of the CDA contacted three group-leader GPs from three districts: D1, D2 and D3; these group leaders took part, with their colleagues, in work teams, in all involving 46 GPs and two doctors on call. The 46 GPs were responsible for a population of 49 898.

The LHA ASL TO1 area includes six districts with a total of 478 077 inhabitants. The female gender is predominant; there is a high percentage of elderly people (25.7% over 65). (Online supplementary figure 2) provides a more detailed overview of the LHA, particularly for D1, D2 and D3).

During two meetings organised with GPs, a list of drug combinations potentially generating ADRs was agreed, selected on the basis of their frequency in GPs' prescriptions, and monitoring was planned (table 1) for their prescription: verapamil+simvastatin (V+S), potassium chloride+potassium canrenoate (P+PC), calcium carbonate+proton pump inhibitors/PPIs (CC+PPIs), levothyroxine+PPIs (L+PPIs), fluconazole+PPIs (F+PPIs), amoxicillin+lansoprazole (A+L), verapamil+simvastatin+ezetimibe (V+S+E), amoxicillin+clavulanic acid+lansoprazole (A+CA+L) and calcium carbonate+vitamin D+PPIs (CC+VD+PPIs). We left GPs free to choose DDIs that they considered more interesting for their prescriptive activity, using in this way a transversal approach, to make them feel more involved in the project and facilitate cooperation.

From scientific documentation obtained using *Micromedex*, the pharmacists undertook a literature review to determine the clinically evident consequences of the selected DDIs, and the most significant articles were selected for an educational/informative programme targeting GPs. A report based on this literature survey, with practical solutions for DDI management, was produced by the pharmacists and given to the GPs.

Step 3

DDIs were subdivided into two categories: those concerning treatments for chronic disease (V+S, P+PC, CC+PPIs, L+PPIs, V+S+E, CC+VD+PPIs) and those occurring in occasional

Table 1 Drug–drug interactions (DDIs) identified and number of patients with multiple DDIs in 2012, 2013 and 2014 prescriptions, with their relative p values

DDIs	2012 (n)	2013 (n)	2014 (n)	2013 versus 2012 (%)	2014 versus 2012 (%)	2014 versus 2013 (%)	p Value 2013 versus 2012	p Value 2014 versus 2012	p Value 2014 versus 2013
Number of DDIs identified in the 2012, 2013 and 2014 prescription analysis									
V+S	17	12	11	–29	–35	–8	0.7091	0.4489	0.8351
P+PC	19	19	24	0	26	26	0.7436	0.2854	0.6451
CC+PPIs	76	38	39	–50	–49	3	0.0052	0.0030	0.9084
L+PPIs	461	447	515	–3	12	15	0.0251	0.0001	0.0879
F+PPIs	38	38	38	0	0	0	0.5600	0.7272	0.8170
A+L	120	73	67	–39	–44	–8	0.0165	0.0011	0.4342
V+S+E	3	3	5	0	67	67	1.0000	0.4895	0.7269
A+CA+L	305	256	258	–16	–15	1	0.7758	0.3701	0.5878
CC+VD+PPIs	431	376	375	–13	–13	0	0.8008	0.5040	0.3634
Total	1470	1262	1332	–14	–9	6			
Number of patients with multiple DDIs	130	13	16				0.0001	0.0001	0.7125

* DDIs: verapamil+simvastatin (V+S), potassium chloride+potassium canrenoate (P+PC), calcium carbonate+proton-pump inhibitors/PPIs (CC+PPIs), levothyroxine+PPIs (L+PPIs), fluconazole+PPIs (F+PPIs), amoxicillin+lansoprazole (A+L), verapamil+simvastatin+ezetimibe (V+S+E), amoxicillin+clavulanic acid+lansoprazole (A+CA+L), calcium carbonate+vitamin D+PPIs (CC+VD+PPIs).

treatments (F+PPIs, A+L, A+CA+L). Inclusion criteria for the selection of patients with possible DDIs in their treatments took into account the time lapse between prescriptions, from which it was possible to identify concurrent administration—that is, associations between pairs of drugs. For occasional treatments, only those of ≤ 30 days were considered, under the assumption that treatments of longer duration were reserved for patients with more severe diseases. Standard doses for each drug were assumed, as recommended for the most common uses in the SPC. To calculate the treatment period, the prescription delivery date was taken as the date of the start of the patient's exposure to the drug.⁵ It was also assumed that the patient completed the treatment, in calculating the drug exposure period.⁶ Prescription data were collected as contracted by the LHA 'ASL TO1' to record the prescriptions dispensed monthly by pharmacies in the LHA area. Prescriptions were extracted from the administrative prescription database, in which drugs are named together with their Anatomical Therapeutic Chemical Classification Code. Patients with prescriptions at longer time lapses (>30 days, or not concurrent administration) and those aged under 18 were excluded. The 2012 prescriptions analysis was part of this step. This was important to verify GPs' prescribing skill before inviting them to enter the cooperation programme. Reports with findings were sent by email to GPs and a summary of results was presented to GPs in October 2013. The presence of multiple DDIs was detected by prescription cross-checking.

Step 4

The final step was to produce the questionnaire, used to evaluate the efficacy and feasibility of the cooperation project between pharmacists and GPs. Questions (yes/no and multiple choice questions) addressed: GPs' prescribing skill and their usual approach to DDI management; efficacy of the meetings and of the report drawn up by pharmacists, including DDI literature analysis and report on evidence-based practical solutions, to improve GPs' expertise in DDI management; any clinical improvements among patients, patients' appreciation of the solutions applied, use of blood or diagnostic tests, possible ADR developed by patients treated with interacting drugs. The printed questionnaire was submitted at a meeting, and sent by email. Reports with the results obtained were sent to all participants by email in December 2013.

In 2015, a prescription analysis for 2013 and 2014 was carried out. Descriptive statistics were used to illustrate the results of the prescription analysis. Fisher's test was used in the DDI and questionnaire analysis, using the GraphPad software package. Values with a p value <0.05 were considered significant.

RESULTS

Prescription analysis

During the study period, of the total GPs' prescriptions taken from the administrative prescription database, 2% contained DDIs (in 2012, 12 024/515 840; in 2013, 12 815/557 796; in 2014, 13 422/563 730), which involved 4% of patients (in 2012, 1340/34 225; in 2013, 1249/35 290; in 2014, 1316/35 169). Between 2012 and 2014, the percentage of GPs' prescriptions taken from the database (9%), and the percentage of prescriptions containing DDIs (12%) both increased.

Patients receiving prescriptions with DDIs were mostly women, with a mean of 78% (in 2012, 1045/1340; in 2013, 982/1249; in 2014, 1021/1316).

The patients were subdivided (see online supplementary figure 3) into 17 age groups (range 18–102 years). Most patients were

aged 68–82 years (43%). This group was predominant in patient numbers, prescription numbers and DDI numbers, throughout 2012–2014.

Table 1 describes the distribution of DDIs identified by prescription analysis in 2012, 2013 and 2014, together with p values. In 2013 and 2014 there was a decrease in the percentage of prescriptions with DDIs (-14% in 2013 and -9% in 2014) compared with 2012. DDIs were found most frequently in prescriptions for L+PPIs, CC+VD+PPIs, A+CA+L, A+L and CC+PPIs. Statistically significant reductions were achieved for the DDI associated with CC+PPIs ($p=0.0052$ in 2013 vs 2012; $p=0.0030$ in the 2014 vs 2012), and with A+L ($p=0.0165$ and 0.0011 in 2013 vs 2012 and 2014 vs 2012, respectively). For the DDI associated with L+PPIs, a statistically significant decrease was only seen in 2013 versus 2012, ($p=0.0251$). In 2014 vs 2012 ($p=0.0001$) the lack of decrease might be attributed to the statistically significant increase in the total number of DDIs in 2014 (515) versus 2012 (461), which was very different from our predictions. Some unknown factor might have led an increase in the number of DDI prescriptions. Other interesting reductions in DDIs were found for A+CA+L and CC+VD+PPIs.

These analyses of GPs' prescriptions showed that some patients had double or triple DDIs (table 1). Moreover, a DDI that was not included in the list of drug associations monitored (see table 2) was discovered: levothyroxine+calcium carbonate association (L+CC).

Questionnaire

The list of questions and their answers is given in table 3.

Seventy-five per cent of GPs completed the questionnaire, and of these, 97% stated that they had found DDIs in their prescribing activity.

Information technology was the tool most widely used to identify them (38%), followed by SPC (29%), literature (21%) and databases (9%). Other tools (1.5%) were not specified.

According to GPs' answers, the documentation provided was found to be a useful tool (94%), and was used by 89% of GPs. These answers were supported by the clinical improvements observed by the GPs. In particular, GPs stated that they had applied the solutions proposed mostly for the following DDIs: L+PPIs (20%), A+CA+L (18%), CC+PPIs and A+L (13%). Most replies were in line with the prescription analysis outcomes.

Clinical improvements after application of solutions were seen in 34% of patients, and were monitored through blood tests, where possible (V+S, CC+PPIs, L+PPIs, V+S+E, CC+VD+PPIs), by 30% of GPs. Moreover, 14% of GPs stated that patients were satisfied, though 80% of GPs had no patient feedback.

It was not easy to determine why solutions were sometimes not applied (ie, clinical reasons, patient compliance, patient management), because 59% of GPs did not answer that question. The non-application where known was due to practical difficulty (27%), incomplete information (3%) or mistrust (3%). For 8% of GPs there were other reasons, which some explained by the presence of a specialist prescription, as in another study,⁸ leading to the impossibility of changing treatment; these GPs added that no patients had had ADRs. Lastly, 1/36 GPs reported ADRs related to the DDIs.

The difference in replies between GPs working in different districts (D1 and D3) was also verified. The p values showed that there was no statistically significant difference between the two groups, indicating that the GPs' prescribing skill was

Table 2 DDIs selected by GPs, with the relative description from the *Micromedex* database and from articles

DDIs	DDI description	Therapeutic alternatives/DDI management suggestion
Verapamil + simvastatin (+/-ezetimibe) [V+S, V+S+E]	According to <i>Micromedex</i> , this interaction is classified as 'major' (another Italian interaction checker gives it as a 'Clinically relevant interaction to manage by modifying the dosage'). ²⁰ The concurrent use of verapamil and simvastatin may result in increased exposure to simvastatin and an increased risk of myopathy and rhabdomyolysis. ^{14,20–23} The concomitant use of a CYP3A4 inhibitor, like verapamil, leads to an increase in the simvastatin plasmatic levels. ^{21–23} This may cause muscle diseases, such as rhabdomyolysis. Further, an association of statins and ezetimibe might lead to muscular disease. ²⁴	To prevent ADRs, the dose of simvastatin should be reduced by 50–80%, ²¹ or alternatively simvastatin may be replaced by pravastatin, which is not metabolised by CYP3A4. ^{21–23}
Potassium chloride + potassium canrenoate [P+PC]	According to <i>Micromedex</i> , this interaction is classified as 'major' (another Italian interaction checker classifies it as a 'Clinically relevant interaction'). ²⁰ The concurrent use of potassium-sparing diuretics with potassium supplements can substantially increase the risk of hyperkalaemia, especially in the presence of renal dysfunction, and also that of cardiac arrhythmia.	The combination of potassium supplements with potassium-sparing diuretics should be avoided, because it provokes decreased renal clearance. Joint use requires strict monitoring. ^{14,20}
Calcium carbonate (+/-vitamin D) + rabeprazole/ pantoprazole/ lansoprazole* [CC+PPIs, CC+VD+PPIs]	Although this DDI is not found in <i>Micromedex</i> (another Italian interaction checker gives it as an 'Uncertain and/or variable interaction'), ²⁰ literature sources attest that an acid gastric environment is important to adsorb calcium. Altered calcium absorption may lead to increased levels of circulating parathyroid hormone, associated with low calcium levels, increasing the risk of fractures. The normal production of gastric acid favours calcium ionisation and thus its adsorption. ^{20,25}	Monitoring of calcium levels could be useful when calcium carbonate administration is associated with PPIs.
Levothyroxine + pantoprazole/ omeprazole* [L+PPIs]	According to <i>Micromedex</i> , this interaction is classified as 'moderate' (another Italian interaction checker gives it as an 'Uncertain and/or variable interaction'). ²⁰ The concurrent use of levothyroxine and PPIs may result in increased levels of TSH. ^{14,15,20,26,27} Levothyroxine absorption is maximum when the stomach is empty, which reflects the importance of gastric acidity. ^{15,26,27} Levothyroxine must be administered on an empty stomach. ^{15,26} Patients with altered gastric acid production, such as those suffering from <i>H. pylori</i> infection or atrophic gastritis, who might, for example, have hypochlorhydria, have an increased thyroxine requirement. ^{15,26,27}	Monitoring of TSH levels could be useful when levothyroxine administration is associated with PPIs.
Fluconazole+ esomeprazole* [F+PPIs]	According to <i>Micromedex</i> , this interaction is classified as 'moderate' (another Italian interaction checker gives it as an 'Uncertain and/or variable interaction'). ²⁰ The concurrent use of esomeprazole/omeprazole and fluconazole may result in increased esomeprazole/omeprazole plasma concentrations. Moreover, the concurrent use of fluconazole and selected CYP2C19 substrates (moderate), such as pantoprazole, lansoprazole or rabeprazole, may result in increased plasma concentrations of CYP2C19 substrate. ¹⁴ Omeprazole, like esomeprazole, is metabolised by CYP2C19 and CYP3A4. Fluconazole is a strong CYP2C19 inhibitor, and a weak CYP3A4 inhibitor. When fluconazole is administered, omeprazole metabolism decreases, and its plasma concentration increases. ²⁸ The metabolic capacity of esomeprazole is similar to that of omeprazole. ²⁹	None found.
Amoxicillin (+/-clavulanic acid)+ lansoprazole [A+L, A+CA+L]	Although this DDI is not found in <i>Micromedex</i> (another Italian interaction checker gives it as an 'Uncertain and/or variable interaction'), ²⁰ literature sources attest that the combined use of lansoprazole and amoxicillin may provoke glossitis, which has been reported in some patients. ^{20,30}	Even though the clinical relevance of this interaction has not been established, and thus no recommendations have been made, ²⁰ lansoprazole appears, to our knowledge, to be the only PPI which generates a DDI in association with amoxicillin. For this reason, another PPI could be used in place of lansoprazole with amoxicillin, to avoid the DDI. Finally, we observed that a study attests to there being no interference between esomeprazole and amoxicillin. ³¹

Legend of DDIs grouped by potential risk as determined from the *Micromedex* database: (1) contraindicated, (2) major, (3) moderate, (4) minor.

*These DDIs regard all the PPIs normally. In table 2 just some PPIs were listed, because these drug associations were found in therapy advice in discharge letters.

ADR, adverse drug reaction; ATC, Anatomical Therapeutic Chemical classification system; DDIs, drug–drug interactions; GPs, general practitioners; PPIs, proton pump inhibitors; TSH, thyroid-stimulating hormone.

Anatomical Therapeutic Chemical Classification Code: amoxicillin (J01CA04), amoxicillin-clavulanic acid (J01CR02), calcium carbonate (A12AA04), calcium carbonate+vitamin D (A12AX), potassium canrenoate (C03DA02), esomeprazole (A02BC05), fluconazole (J02AC01), lansoprazole (A02BC03), levothyroxine (H03AA01), omeprazole (A02BC01), pantoprazole (A02BC02), potassium chloride (B05XA01), rabeprazole (A02BC04), simvastatin (C10AA01), simvastatin+ezetimibe (C10BA02), verapamil (C08DA01).

comparable. The D2 GPs were not considered in this comparison, owing to poor participation.

DISCUSSION

The study showed that administrative prescription databases are an important source for studying DDIs in general practice. In all districts of the LHA studied, women were more subject to DDIs, which can be explained by the gender distribution among the population. This confirms reports that, because women receive more prescriptions than men,^{5–7,13} they are more exposed to DDIs, polypharmacy^{5,6,10} and ADRs.² An additional reason might be the presence of a selection bias, because women are more prone to undertake medical examination and clinical

monitoring; thus increasing the chance of receiving prescription drugs.

Most of the patients exposed to DDIs were elderly. The age group most exposed to DDIs was 68–82 years, in line with both expectations and previous studies.^{3,5,6} Elderly people often present several comorbidities, and thus commonly receive a greater number of prescriptions; polypharmacy is emerging as a determinant for frailty. The high proportion of DDIs in women and the elderly is also explained by the higher life expectancy for women than men in Italy.¹²

The number of DDIs decreased after the start of the cooperation project (2013), although the number of prescriptions, including those for drugs under monitoring, increased during

Table 3 List of questions and the results of the questionnaire, with their relative p values

Question	Districts (Ds) 1, 2, 3	D1	D2	D3	Fisher's test (D1 and D3)
Number of GPs who completed the questionnaire	36	12	5	19	0.5555
1. Have you ever found any DDI while prescribing?					
0=no	1	0	1	0	
1=yes	35	12	4	19	
2. If yes, please specify the tool used					
1= IT (information technology - prescription programme)	25	10	3	12	0.4009
2 = database	6	0	0	6	0.0736
3 = summary of product characteristics	19	4	2	13	0.2313
4 = scientific article/literature	14	7	3	4	0.0798
5 = other (specify)	1	0	1	0	1.0000
NA = no reply	1	0	1	0	1.0000
3. Did you find the literature provided during the meeting of 12 June 2013 to be useful?					
0=no	0	0	0	0	
1=yes	34	12	5	17	
NA = no reply	2	0	0	2	
4. Have you adopted the solutions proposed and identified in the literature in your prescribing?					
0=no	3	2	0	1	
1=yes	32	9	5	18	
NA = no reply	1	1	0	0	
5. For which DDI(s) could you adopt the solution proposed?					
V+S = verapamil+simvastatin	8	3	1	4	1.0000
P+PC = potassium chloride+potassium canrenoate	3	2	0	1	0.5518
CC+PPIs = calcium carbonate+rabeprazole/pantoprazole/lansoprazole	11	4	0	7	1.0000
L+PPIs= levothyroxine + pantoprazole/omeprazole	17	4	2	11	0.3883
F+PPIs = fluconazole+esomeprazole	8	4	2	2	0.1881
A+L = amoxicillin+lansoprazole	11	2	1	8	0.3044
V+S+E = verapamil+simvastatin+ezetimibe	3	1	1	1	1.0000
A+CA+L = amoxicillin+clavulanic acid+lansoprazole	15	6	1	8	0.7611
CC+VD+PPIs = calcium carbonate+vitamin D+rabeprazole/pantoprazole/lansoprazole	3	0	0	3	0.2886
NA = no reply	3	2	0	1	0.5518
6. Did you identify any ADRs among the patients who received DDI prescriptions?					
0=no	35	12	5	18	
1=yes	1	0	0	1	
7. Did you see a clinical improvement in the patients for whom you adopted the proposed solution?					
0=no	21	4	2	15	
1=yes	12	6	3	3	
NA = no reply	3	2	0	1	
8. Have these patients been satisfied with their treatment?					
0=no	1	0	0	1	

Continued

Table 3 Continued

Question	Districts (Ds) 1, 2, 3	D1	D2	D3	Fisher's test (D1 and D3)
1=yes	5	2	3	0	
2=don't know	29	10	2	17	
AA = any answer	1	0	0	1	
9. Did you use any blood tests or laboratory or diagnostic tests to verify clinical improvement?					
0=no	24	7	2	15	
1=yes	11	5	3	3	
NA = no reply	1	0	0	1	
10. If you did not apply the solution proposed, why did you not do so?					
1 = practical difficulty (ie, clinical reasons, patient compliance, patient management)	10	7	1	2	
2 = incomplete information	1	0	0	1	
3 = mistrust	1	1	0	0	
4 = solution considered inefficacious	0	0	0	0	
5 = other (specify)	3	2	0	1	
NA = no reply	22	3	4	15	

ADR, adverse drug reaction; DDI, drug–drug interaction.

the period. This phenomenon is not new to us; every year we observe a physiological increase in the number of prescriptions of around 3%, due to progressive ageing of the population.

It might be thought that the decrease in DDIs from 2012 to 2013 and from 2012 to 2014 was related to the cooperation project. In almost all the interventions declared by GPs (question 5 in table 3), except for F+PPIs, there was a decrease in DDIs: in some cases this was statistically significant (CC+PPIs, A+L, L+PPIs, the last of these only in 2013, and for multiple DDIs), and in others, the decrease was not statistically significant, but was important (A+CA+L, and CC+VD+PPIs).

Another goal of the project was to make GPs aware of the importance of improving their prescribing skill, either by enhancing interventions to educate patients, or by planning laboratory or other tests and dose adjustment, all activities being part of positive clinical behaviour.⁴ These actions, in particular education on drug use, appeared to satisfy patients and in some cases to lead to clinical improvement. Further, this explains why there was not a significant reduction in DDIs in 2012 versus 2013 or versus 2014; it was found that to stop prescribing two drugs with an association was not always the best way to manage a DDI.

The project also showed GPs how common DDIs were in their prescriptions. Further, an unexpected DDI, not included in the study goals, was found: LL+CC. According to *Micromedex*, this is classified as a 'moderate' DDI. Calcium may form an insoluble chelate with levothyroxine, with consequent partial reduction of its efficacy. Administration of the two drugs should thus be separated by at least 4 hours. If there is concomitant use, periodic checks on the thyroid gland function are recommended.^{15–18}

In this context, GPs must be informed about DDIs to ensure proper continuity of care from hospital to community. The most important new element that the project introduced was to link GPs' prescription data to their answers to the questionnaire, which thus became the main tool whereby pharmacists could inform GPs and correctly interpret GPs' prescription data. This approach showed the project to be of use in informing GPs about clinically relevant/non-relevant DDIs, combining general training about DDIs with more specific training focused on clinically relevant DDIs. It was of interest to note that the meetings and literature provided to GPs (in particular, the practical solutions) were a useful tool that helped them to manage DDIs^{2,3,8,9}; because GPs were provided with material about the DDIs they had selected, it attracted their attention more than a simple DDI alert would have done.⁴

The study pointed out the importance of training to achieve results and improve clinical practice, but also showed that training must be maintained over time; the best results were those of 2013. The data for 2014 were less positive, although nevertheless encouraging, suggesting that GPs' knowledge about DDIs became established, but also showing the importance of continual education to maintain and improve clinical objectives.

It appears that an approach like the project presented here is, in general, useful for improving patient care, and cooperation between physicians and pharmacists,¹¹ although the management of National Health Systems differs from one country to another. For example, similar projects, involving patient education, would be applicable in several National Health Systems, both in countries with a similar number of physicians per population—for example, Italy, Sweden, and Germany, and in countries where this ratio is lower (ie, France, Spain and the United Kingdom), but in which there are more pharmacists per head of population (eg, France and Spain).¹² This approach could outline a model for integration among different health professionals, in

which the expertise of each could implement and enrich others, thanks to multidisciplinary cooperation.

Limitations

The major limitation of our work was the absence of a control group which would have allowed us to make a comparison.

A second limitation of this study is that the possibility cannot be excluded that other external factors, independent of the cooperation project, might have influenced the decrease in DDI prescriptions. Moreover, DDI prescription analysis was not followed by analysis of clinical outcomes in the population studied,^{4 5 19} and did not monitor adherence to treatment.^{6 10} On the other hand, the DDIs we analysed were 'potential DDIs' and only a minority of them will cause ADRs.

A third limitation is that the number of DDIs analysed was low, because (1) only DDIs prescribed in discharge letters and their impact on GPs prescriptions were considered, and not all PPIs that might potentially interact with levothyroxine, calcium carbonate and fluconazole; (2) only prescriptions of reimbursed drugs were investigated, excluding others, such as over-the-counter medicines. This limitation also applies to other Italian and international studies.^{3 5–7 10 19}

Another limitation concerns ADR reporting. One ADR was reported by a GP in the questionnaire, but no suspected DDI ADR report was made during the cooperation project period. To verify the number of total ADRs, a search was made for ADR reports concerning the drugs under scrutiny, both as suspected, and as concomitant, from 1 January 2012 to 30 March 2015 in the Italian *National Pharmacovigilance Network*. Of 33 reports identified, none concerned the DDIs studied here, which suggests that reporting of suspected ADRs is not widespread among GPs.

CONCLUSIONS

The prescription analysis showed that DDIs are widespread in GPs' prescriptions, which could be dangerous. The cooperation project between pharmacists and GPs was effective because it established a professional exchange between the stakeholders. The pharmacist gave support to GPs, for the benefit of patients, who gained clinical improvements and improved satisfaction with their medical care. Collaboration between pharmacists and GPs is valuable and should be encouraged.^{2 8 11}

The meetings held were found to be extremely important, because GPs, as shown by their questionnaire answers, recognised the efficacy of the education programme thanks to direct contact with the pharmacist.^{9 11}

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Key Messages

What is already known on this subject

- ▶ Drug–drug interactions (DDIs) are a crucial problem, particularly for polymedicated patients with chronic diseases, such as the elderly.
- ▶ Fostering cooperation among health professionals can lead to improvements in DDI management.
- ▶ Medication review among community-dwelling older patients is of utmost importance; unfortunately, prescriptions are more frequently analysed for DDIs in hospital.

What this study adds

- ▶ Two different, but simultaneous, approaches were used to analyse DDI management in the community: a general practitioners' prescription analysis, and a questionnaire to collect information on GPs' prescribing skill.
- ▶ The link between hospital practice and its effect on the local community is shown. The article predicts an attitude towards DDIs in general practice.
- ▶ Monitoring therapeutic advice on hospital discharge, and the impact of that advice on GPs' prescriptions, is examined.

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