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Assessment of the clinical relevance of pharmacists' interventions performed during medication review in a rheumatology ward

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ABSTRACT

Background: Pharmacists contribute to reduce the number of medication errors during medication review. Nevertheless, few French studies report the potential clinical impact of pharmacists' interventions performed after detecting drug-related problems. The objective was to evaluate the clinical relevance of pharmacists' interventions in a rheumatology ward from medical and pharmaceutical perspectives.

Method: The analysis was conducted on pharmacists' interventions performed between January 1 and December 31, 2015 in a French teaching hospital. Similar pharmacists' interventions were grouped in one item and they were analysed according to 11 drug categories. The clinical significance of pharmacists' interventions was considered independently by a pharmacist and a rheumatologist using a validated French scale that categorises drug-related problems from minor to catastrophic. The agreement between the two professionals was analysed using the weighted kappa coefficient.

Results: Of 1313 prescriptions reviewed, 461 pharmacists' interventions (171 items) were formulated for drug-related problems with an acceptance rate of 67.2%. Of the 418 interventions selected for clinical significance analysis, 235 interventions (56.2%) for the physician and 400 interventions (95.7%) for the pharmacist were at least significant. The two professionals evaluated equally the clinical relevance of 90 items (50.6%). The categories with the most similarities were the analgesics/anti-inflammatory drugs (78.1%), the antidiabetics (75.0%) and the anticoagulants (71.4%). The agreement was estimated by a weighted kappa coefficient of 0.29.

Conclusion: This work highlights the positive clinical relevance of pharmacists' interventions in rheumatology and the importance of medico-pharmaceutical collaboration to prevent medication errors.

1. Introduction

In the hospital environment, patient medication management is a complex process. At each stage, there is a high iatrogenic risk [1]. A National survey on serious adverse events in hospitals in France demonstrated that medications are the second cause of serious adverse drug events (ADE) [2]. Among these ADE caused by medications, 15,000 to 60,000 could be avoided each year. The analysis of these adverse events shows that medication errors occur mostly at drug prescription stage [3–5], in 35% of cases. Through their activity of medication review, clinical pharmacists participate in controlling medication iatrogenesis. Considering to the Pharmaceutical Care Network Europe (PCNE), medication review is a 'structured evaluation of a patient's medicines with the aim of optimising medicines use and improving health outcomes', leading to the detection of 'drug-related problems and recommending interventions' [6]. Several international studies have demonstrated that medication review, along with the inclusion of a clinical pharmacist in the medical department, contributed to decrease medication errors (ME) [7–9], as well as in the length of hospital stay [10,11], and mortality [12]. Clinical pharmacists can have a direct action through recommendations formulated during medication review to physicians. These pharmacists' interventions (PIs) are

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defined as 'any action initiated by a pharmacist directly resulting in a change in the patient's management or therapy' [13]. PIs include identification, prevention and resolution of drug-related problems (DRP) concerning prescriptions. Each PI may have an effect on patient management if it is accepted by the physician. Measurement of the potential clinical impact of PI is a notion that is still rarely examined in France [14,15]. Moreover, this measurement could be difficult since there is no consensus on which scale to use. Scales have been widely used: Hatoum et al. [16], Bayliff et al. [17], Overhage et al. [18], but they have not been adopted in current French practice. A recent French scale was validated in the study of Doerper et al. [19] to evaluate the severity of the potential harm of ME reported by medication reconciliation. This scale makes it possible to evaluate the clinical significance of detecting DRP at different stages and notably, at the prescription stage. Others scoring methods for assessing the potential impact of medication review have been described in the literature [20–22]. To our knowledge, there is no French study concerning the potential clinical impact of PIs in rheumatology.

2. Aim of the study

The objective of the study was to evaluate the clinical relevance of PIs performed during medication review in a rheumatology ward from medical and pharmaceutical perspectives.

3. Ethics approval

This was a retrospective study using only routine care data and anonymized data. Therefore, no ethical approval was deemed required.

4. Method

The study was conducted in a rheumatology department with 31 beds of a French University Hospital. Computerized prescriptions (CristalNet® software) are reviewed by senior pharmacists or resident pharmacists on a daily basis for input prescriptions following the French Society of Clinical Pharmacy (SFPC) methodology [23]. Resident pharmacists are trained, validated and supervised by a senior pharmacist experienced. Medication review is based on medication history, medical information (clinical, biological and pathophysiological data) and therapeutic objectives (type 2B according to the PCNE [6] or level 2 according to the SFPC [24]). PIs are performed by pharmacists or resident pharmacists and classified according to the SFPC recommendations [25]: identification of the DRP (10 items), pharmacist's intervention (7 items) and acceptance by the prescriber (Table 1). Physician acceptance of the PI was assessed according to the prescription modification. Then PI are recorded by pharmacists in ACT-IP®, an online database (developed by the SFPC) allowing PIs documentation and analysis [26].

Table 1
DRP and pharmacists' intervention considering the classification of the French Society of Clinical Pharmacy (SFPC).

Drug-related problems
1. Non conformity to guidelines or contra-indication
2. Untreated indication
3. Subtherapeutic dosage
4. Supratherapeutic dosage
5. Drug without indication
6. Drug interaction
7. Adverse drug reaction
8. Improper administration
9. Failure to receive drung
10. Drug monitoring
Pharmacist's interventions
1. Addition of a new drug
2. Drug discontinuation
3. Drug switch
4. Change of administration route
5. Drug monitoring
6. Administration mode optimisation
7. Dose adjustment

All PIs carried out from 1 January 2015 to 21 December 2015 were included in this study. They were analysed retrospectively to evaluate their clinical impact. After extraction of the ACT-IP® data, they were processed with the Excel® software.

PIs were excluded for the clinical impact evaluation in case of not interpretable data, prescription of medicines not available in the hospital or insufficient clinical relevance estimated by the pharmacist.

The selected PIs were gathered in 11 categories: anticoagulants, gastrointestinal drugs, analgesics/anti-inflammatory drugs, anti-infective drugs, psychotropic drugs, antidiabetic drugs, absorption-modifying drugs, injectable electrolytes and parenteral nutrition, cardiovascular drugs, immunosuppressive drugs and biologics and finally a group of miscellaneous drugs. Within each category, the PIs related to the same situation were grouped under the same item.

The potential clinical impact rating scale used [19] has 5 levels: minor, significant, major, critical and catastrophic. It is similar to the National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) scale used for categorizing ME [27]. The study scale was validated initially in a French study to evaluate the severity of the potential harm of ME reported by medication reconciliation. This scale was selected because of the equivalence of the ME consequences (sub- or supra-therapeutic dosage, untreated indications…) found by the reconciliation with those found by the medication review. A senior pharmacist who participated in medication review and a senior practitioner in rheumatology independently evaluated all included PIs. They considered the maximum severity that could occur if the DRP would not have been identified by pharmacist medication review. At the evaluation time, the 2 practitioners were aware on the DRP description, the drug(s) concerned, the patient's clinical, biological and pathophysiological data at the time of PI.

The similarity between the physician's evaluation and that of the pharmacist was estimated based on the number of items evaluated in an identical manner. The agreement between the 2 evaluators was estimated by the kappa coefficient of concordance (linear weighting) and for which the value close to 1 corresponds with the highest degree of concordance [28]. A threshold above 0.6 was used to identify a satisfactory level of concordance. Statistical analysis was performed using MedCalc® software.

5. Results

In one year, 1313 prescriptions were analysed, representing 373 patients with a male/female ratio of 0.6. The mean age of the patients was 65 years [10–95] and the main reasons for hospitalization were chronic inflammatory rheumatism and bone diseases. The mean number of drugs initially prescribed was 8. A total of 461 PIs were formulated, which represented 35% of the prescriptions analysed. Among these PIs, 310 were accepted by the clinicians (67.2%). The DRP detected were mainly problems concerning improper route of administration (31.7%), overdosage (24.5%) and unjustified drugs (17.6%). The details of DRP detected are recorded in Fig. 1.

A total of 43 PIs were excluded, leaving 418 PIs (90.7% of the PIs carried out) for the clinical significance evaluation. Those PI were considered as clinically non relevant (i.e., incomplete drug prescription and non-optimal dosage regimen without consequences for the patient), not interpretable (missing evaluation information) or related to medicines not available in the hospital. The details of the selection of PIs are presented in Fig. 2. They were grouped into 171 items (examples of items are provided in Table 2).

The rating of PIs clinical relevance according to the physician and the pharmacist is presented in Table 3. For the physician, 235 PIs (56.2%) had at least one significant impact versus 400 PIs (95.7%) for

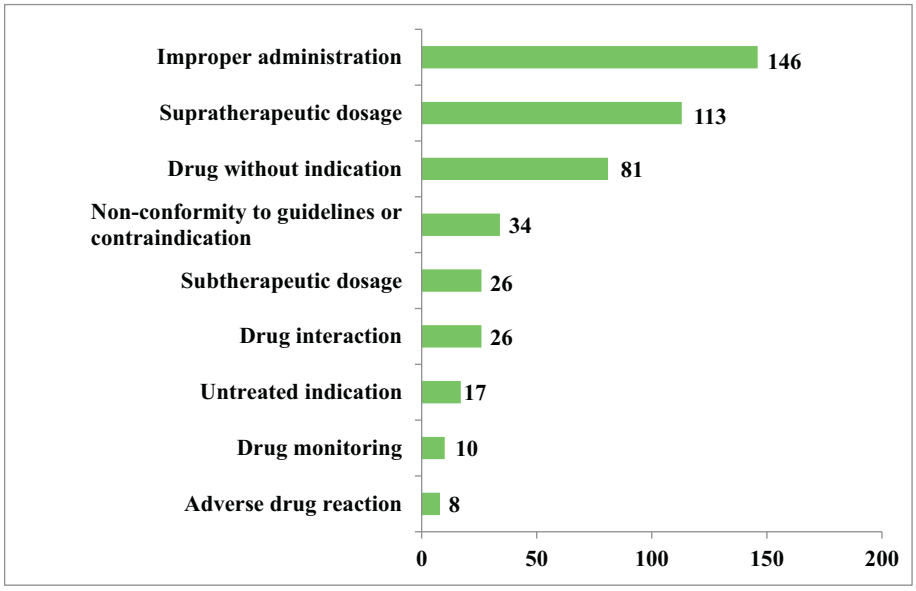

Fig. 1. Drug-related problems identified during the medication review (in 2015, for the 1313 prescriptions analysed).

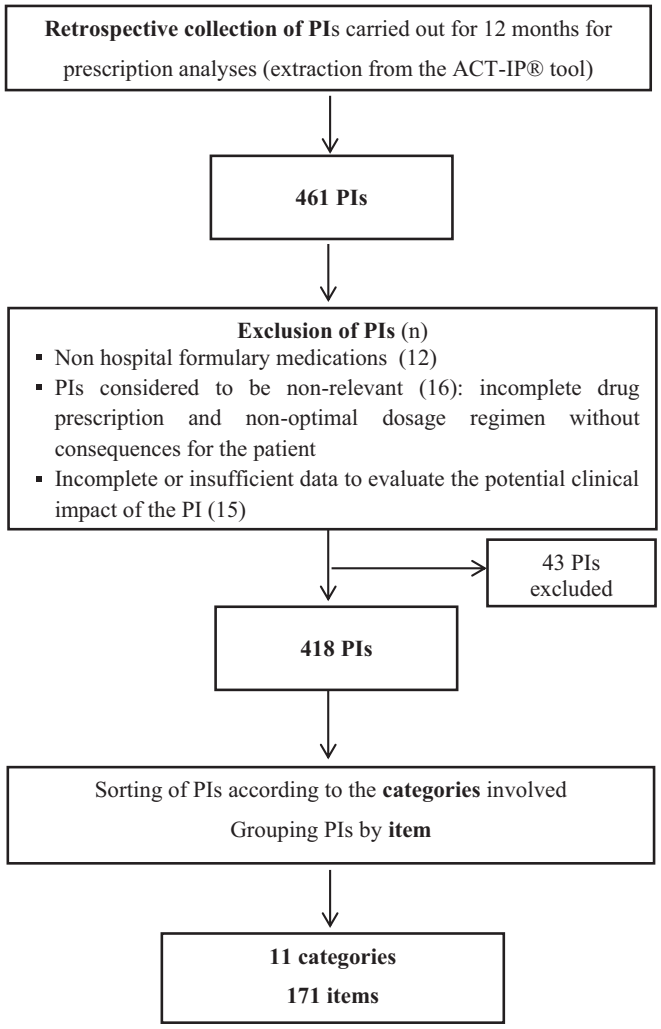

Fig. 2. Results of the selection of PIs to be analysed.

the pharmacist. One PI out of ten was major for the physician versus more than one PI out of five for the pharmacist. The physician considered that one PI (0.2%) had a critical impact for the patient (major impact for the pharmacist). This PI concerned a supra-therapeutic dosage for a cardiovascular drug: amlodipine for which 10 tablets were prescribed in error. No PI was evaluated as having a catastrophic clinical impact for the patient. For the physician, no PI in the anti-infective, psychotropic, absorption-modifying, antidiabetic and miscellaneous drug categories had a major impact. For the pharmacist, only the PIs in the absorption-modifying drug category had no major impact. The rates of similarity between the physician and the pharmacist, according to the categories and PIs items are presented in Table 4. The physician and the pharmacist evaluated the potential clinical impact of 90 PI items in the same manner (i.e., 52.6% of the PI items). The rating of PIs items according to the professional and the clinical impact level is presented in Table 5. The agreement between the physician and the pharmacist was estimated by a weighted kappa coefficient of 0.29 (95% CI 0.19–0.39).

6. Discussion

To our knowledge, this is the first study to evaluate the clinical relevance of PIs carried out during medication review in rheumatology. The study shows a high level of PIs (35%) in comparison to the data in the literature where it varies between 1% and 37% in France [26,29]. A previous study conducted in rheumatology [30] showed a lower rate of PIs (12.5%). This difference may be explained by a strong pharmaceutical presence in the department for the previous study which allows the pharmacist to intervene before the prescription. In our study, the main problems noted were an improper administration (31.7%), overdosages (24.5%) and unjustified drugs (17.6%). These results are consistent with the data in the literature [30–32].

The 67.2% acceptance rate of PIs by physicians was close to the rates found in the literature, which vary from 39% to 100% [26,29].

6.1. Clinical relevance of pharmacists' interventions

Globally, the majority of PIs were considered to have at least a significant impact (95.7% for the pharmacist and 56.2% for the physician). More specifically, for the pharmacist, more than one PI out of five was major versus one PI out of ten for the physician. This means that it could have a temporary clinical consequence for the patient. Major PIs were especially those related to anticoagulants and injectable drugs (electrolytes and parenteral nutrition). The physician evaluated

Table 2
Number and examples of PI items used in the clinical relevance study and grouped by category.

Category = N number of PIs carried out per category	Examples of items (n number of PIs carried out per items)
Injectable electrolytes and parenteral nutrition = 5	- Medication prescribed without justified indication: injectable potassium with kaliemia at 4.4 mmol/l (1) - Intravenous/oral conversion: injectable potassium and moderate hypokalaemia (1)
Antidiabetic drugs = 9	- Supra-therapeutic dosage: full dose of sitagliptine in a patient with renal failure (1) - Supra-therapeutic dosage: 2 brands of metformin (2 different formulations) (1) - Supra-therapeutic dosage: 2 doses of insulin in the morning (included and not included in the protocol) (1)
Anti-infective drugs = 14	- Ceftriaxone: incomplete prescription without the solute, volume in dilution, duration of the perfusion (6) - Prescription of amoxicillin although there is a resistance to ampicillin on the antimicrobial susceptibility testing (1) - Duration of gentamicin antibiotic therapy not specified (1)
Absorption-modifying drugs = 16	- Administration plan not optimal: calcium administration time not adjusted in relation to the other medicines (6)
Anticoagulants = 19	- INR below 2: Sub-therapeutic dosage of fluindione (5) - INR above 3: Supra-therapeutic dosage of fluindione (4) - Recommendation not to combine rivaroxaban and carbamazepine (1)
Cardiovascular drugs = 20	- Metoprolol/simvastatin: prescription not adapted to the breakability of the tablet (2) - Rilmenidine: inappropriate medicine in elderly patients (admitted for fall-related syndrome) (4) - Supra-therapeutic dosage: 2 prescriptions of lysine acetylsalicylate (1)
Immunosuppressive drugs and biologics = 34	- Contraindication: Ciclosporin and colchicine (1) - Abatacept: usually SC route (pen) and prescription in vial for IV injection in the hospital (2) - Prescription of methotrexate every day in the software (2)
Miscellaneous drugs = 52	- Risedronate: Problem with administration modalities (2) - Supra-therapeutic dosage: Allopurinol not adapted to renal function (2) - Contraindication: levodopa and metochlopramide (2)
Psychotropic drugs = 55	- Benzodiazepine overdosage in patients over 65 years of age (18) - Supra-therapeutic hydroxyzine dosage in elderly patients (2)
Gastrointestinal drugs = 84	- No indication found in the medical record for proton pump inhibitors (41) - Phloroglucinol/trimebutine/metoclopramide/domperidone/loperamide: prescription to be suspended due to non-administration for several days (8)
Analgesics and Anti-inflammatory drugs = 110	- IV/PO conversion (ketoprofen/acetaminophen/tramadol) (14) - Morphine: Problem with the choice of extended- and immediate release doses (sub-therapeutic) and inter-doses too low in relation to the baseline dose (12) - Supra-therapeutic dosage of acetaminophen: 4 g systematically in a patient over 75 years of age (11)

PIs related to the same situation were grouped under the same situation, i.e. 171 items.

43.8% of PIs as having a minor impact while the pharmacist estimated them at 4.3%. However, the physician did not consider them useless (data not shown) and wanted them to be reported. The formulation of these PIs provides the opportunity to remind senior physicians and residents of good prescription practices.

Comparison with results in the literature is difficult because the methodologies used are varied (number and professions of evaluators, scales used, drug categories and types of PIs analysed, etc.). Nevertheless, in studies, most PIs were considered to have at least a significant impact [14,15,21,22,33]. For example, the expert group (2 geriatricians and 2 pharmacists) in the study by Ziane et al. considered that 55.2% of the PIs were at least significant [15]. The evaluation by Cortejoso et al. showed that 75.3% of the PIs were associated with errors categorized as significant [21].

In our study, a difference in the evaluation of the potential clinical impact was noted between the physician and the pharmacist. In

Table 3
Clinical relevance of PIs in terms of the category according to the physician and the pharmacist n (%).

	Minor		Significant		Major		Critical	
	Pharmacist	Physician	Pharmacist	Physician	Pharmacist	Physician	Pharmacist	Physician
Totals	18 (4.3)	183 (43.8)	308 (73.7)	191 (45.7)	92 (22.0)	43 (10.3)	0 (0)	1 (5.0)
Analgesics and Anti-inflammatory drugs	3 (2.7)	32 (29.1)	65 (59.1)	51 (46.4)	42 (38.2)	27 (24.5)	0 (0)	0 (0)
Antidiabetic drugs	0 (0)	0 (0)	7 (77.8)	9 (100)	2 (22.2)	0 (0)	0 (0)	0 (0)
Anticoagulants	1 (5.3)	1 (5.3)	5 (26.3)	9 (47.4)	13 (68.4)	9 (47.4)	0 (0)	0 (0)
Absorption-modifying drugs	0 (0)	2 (12.5)	16 (100)	14 (87.5)	0 (0)	0 (0)	0 (0)	0 (0)
Injectable electrolytes and parenteral nutrition	0 (0)	0 (0)	3 (60.0)	3 (60.0)	2 (40.0)	2 (40.0)	0 (0)	0 (0)
Psychotropic drugs	4 (7.3)	13 (23.6)	49 (89.1)	42 (76.4)	2 (3.6)	0 (0)	0 (0)	0 (0)
Anti-infective drugs	1 (7.1)	3 (21.4)	11 (78.6)	11 (78.6)	2 (14.3)	0 (0)	0 (0)	0 (0)
Immunosuppressive drugs and biologics	0 (0)	20 (58.9)	13 (38.2)	11 (32.4)	21 (61.8)	3 (8.8)	0 (0)	0 (0)
Gastrointestinal drugs	6 (7.1)	80 (95.2)	77 (91.7)	3 (3.6)	1 (1.2)	1 (1.2)	0 (0)	0 (0)
Miscellaneous drugs	3 (5.8)	25 (48.1)	45 (86.5)	27 (51.9)	4 (7.7)	0 (0)	0 (0)	0 (0)
Cardiovascular drugs	0 (0)	7 (35.0)	17 (85.0)	11 (55.0)	3 (15.0)	1 (5.0)	0 (0)	1 (5.0)

No IP was classified as catastrophic by the physician and the pharmacist.

Table 4
Similarity of the clinical relevance of PIs for the physician and the pharmacists according to the category.

Categories	Number of items with a similar impact for the physician/pharmacist (%)
Analgesics and Anti-inflammatory drugs	5 (78.1)
Antidiabetic drugs	6 (75.0)
Anticoagulants	5 (71.4)
Absorption-modifying drugs	4 (66.6)
Injectable electrolytes and parenteral nutrition	3 (60.0)
Psychotropic drugs	16 (59.3)
Anti-infective drugs	5 (55.6)
Immunosuppressive drugs and biologics	7 (46.7)
Gastrointestinal drugs	6 (33.3)
Miscellaneous drugs	10 (32.3)
Cardiovascular drugs	3 (23.1)

Table 5
Clinical relevance of the 171 items for the physician and the pharmacist according to the clinical imtpact level.

		Physician				
Pharmacist	Clinical impact level	Minor	Significant	Major	Critical	Total
	Minor	15	1	0	0	16
	Significant	56	63	5	0	124
	Major	2	17	11	1	31
	Critical	0	0	0	0	0
	Total	73	81	16	1	171

The weighted κ was calculated from the data in this table.

general, the physician evaluated more moderately the clinical relevance of PIs than the pharmacist. This difference in risk assessment was noted in previous studies [20,34]. This variation may be explained by a different perception of iatrogenic risk for the patient by the two professionals.

The highest difference of perception was observed in the gastrointestinal, immunosuppressive and biologics categories, the clinical significance of PIs was clearly higher for the pharmacist than for the physician. In the gastrointestinal category, 95.2% of the PIs were categorized as minor for the physician while these PIs were considered as significant (91.7%) by the pharmacist. This difference was potentially explained by pharmacists' high sensitivity to the misuse of proton pump inhibitors PPI (i.e., unjustified indication, negative benefit-risk ratio). For the other categories, the divergence may be explained by the common use of these classes of medicines in rheumatology. Moreover, pharmacists can overestimate the impact of PIs related to medications that are at risk and/or costly (for example methotrexate, biologics).

The absence of divergence was observed for anticoagulants, absorption-modifying drugs and injectable drugs. These drug categories are mostly classes considered to present a risk for the patient with potential adverse events after overdosage, for example. Overall, even though 52.6% of the PI items were evaluated in the same manner by the pharmacist and the physician, the judgment agreement remained low (weighted kappa of 0.29). However, the judgment difference between the physician and the pharmacist was rarely important when they judged a PI differently. Such results had already been noted in the study by Bosma et al. where the weighted kappa coefficient was 0.3 [20].

6.2. Strengths and limits of the study

The clinical relevance assessment method seems to be a strong point of the study. In fact, few studies showed an independent evaluation of the potential clinical impact of PIs by physicians and pharmacists [20,33]. To our knowledge, no French study compared the evaluation of the clinical significance of PIs by a physician and a pharmacist. In many studies, the evaluation was carried out by a group of medical and/or pharmaceutical healthcare professionals who collectively analysed the potential clinical impact of PIs [14,15,17,18,21,22,33–35]. In this study, independent evaluation by two evaluators provided the opportunity to compare the medical and pharmaceutical opinions on PIs carried out during medication review in rheumatology.

However, the selection of PIs for evaluation was subjective and the reasons for exclusion of PIs are open to discussion. This selection was based on our professional experience, which was the case for other authors before us [16], simplified for evaluators the rating step. PIs concerning medications not listed in the hospital drug formulary were excluded because they constituted a drug management problem at the hospital without major risk generally. The inclusion of these PIs in the studies was frequently the cause of high rates of PIs without any clinical impact [15]. However, the presence of drugs not listed in the formulary can cause DRP: dosage error, non-equivalent substitution, absence of treatment, etc. [14].

Another limit to this study is related to the subjectivity of the evaluation. The affiliation of both evaluators with the study establishment may cause a bias in the rating of PIs. The pharmacist evaluator was one of the pharmacists involving in the medication review and the physician evaluator was part of the study ward. However, both evaluators are hospital practitioners with extensive knowledge of the rheumatology context. It may be considered that in light of their knowledge of the context, their opinion is pertinent.

Finally, it was a monocentric and retrospective study, the results of which were based on rheumatology practices. The results cannot be extrapolated to other types of therapeutic management.

7. Conclusion

The study shows that the pharmacist detected a high number of DRP with significant clinical relevance during medication review in rheumatology. The multidisciplinary evaluation of the PIs impact highlights the strong collaboration between pharmacists and physicians in rheumatology. This evaluation of the significance of medication review on the patient's clinical status is required to emphasize the importance of medication review and to increase the awareness of senior physicians on the risk related to prescriptions. In addition, the difference in physicians and pharmacists' points of view allows to compare opinions and improves both medical and pharmaceutical practices. This collaboration between physicians and pharmacists makes the pharmacists' intervention more effective, improves the quality of patient care and decreases the iatrogenic risk.

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None.

Conflicts of interest

The authors declare that they have no conflicts of interest with regard to this work.

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