

Impact of pharmacist-led interventions in identifying and resolving drug related problems and potentially inappropriate prescriptions among rural patients: A pilot study

Salvador Gutiérrez-Igual^{a,b,c,*}, Rut Lucas-Domínguez^{d,e,f,*}, José Sendra-Lillo^{a,b}, Alberto Martí-Rodrigo^{a,b}, Isabel Romero Crespo^{a,b}, M. Carmen Montesinos^{b,c,g}

^a *Muy Ilustre Colegio Oficial de Farmacéuticos de Valencia (MICOF), Valencia, Spain*

^b *Chair for the Rational Use of Medicines, MICOF-University of Valencia, Valencia, Spain*

^c *Department of Pharmacology, Faculty of Pharmacy and Food Sciences, University of Valencia, Valencia, Spain*

^d *Department of History of Science and Information Science, Faculty of Medicine and Dentistry, University of Valencia, Valencia, Spain*

^e *UISYS, Joint Research Unit. University of Valencia, Valencia, Spain. Associated Unit Research Institute for Higher Education and Science (INAECU) (UAM-UC3M), Spain*

^f *CIBERONC, Valencia, Spain*

^g *Interuniversity Research Institute for Molecular Recognition and Technological Development (IDM), University of Valencia, Polytechnic University of Valencia, Valencia, Spain*

ARTICLE INFO

Keywords:

Medication review
Clinical pharmacy services
Drug-related problems
Potentially inappropriate prescriptions
Rural health

ABSTRACT

Background: Drug-related problems are a major problem that can lead to increased morbidity, mortality, and healthcare costs due to heightened medical visits, hospital readmissions, or emergency room visits. In rural areas, new tools for clinical pharmacy services, such as medication review, could decrease this problem.

Objective: To analyze the prevalence of clinically relevant drug-related problems (DRPs) and potentially inappropriate prescriptions (PIPs) identified by new medication review software (Revisem®) in rural pharmacies. The effectiveness of resolving DRPs and PIPs in patients who received pharmacist-led intervention (PLI) was also evaluated.

Methods: A prospective, multicenter, observational pilot study in 17 rural pharmacies from the Valencian region (Spain) was conducted over a period of 6 months. Revisem®, a type 1 medication review software, was developed and implemented to detect and resolve drug-related issues (DRPs and PIPs). The clinical history of 135 polymedicated patients was recorded, as well as the PLI conducted after the identification of incidences. The mean number of DRPs and PIPs before and after PLI were analyzed and compared.

Findings: A total of 1545 drug-related issues were detected in 135 patients (86 women). 1166 were DRPs and 379 were PIPs. Interactions were the most common incidence (43.7 %), with furosemide and omeprazole being the drugs with the highest number of significant interactions. In the before-after intervention study, the mean number of incidents detected per patient by Revisem® decreased from 9.7 ± 6.9 to 8.8 ± 6.9 ($p < 0.05$) after PLI. Written reports were the most frequent means of communication between pharmacists and physicians (45.0 %). The acceptance rate of pharmacists' suggestions was 45.2 %.

Conclusion: The impact of pharmacist-led interventions in rural pharmacies allowed the detection of a high number of drug-related issues and significantly reduced the number of DRPs and PIPs, preventing negative health outcomes.

1. Introduction

Pharmaceutical Care Network Europe (PCNE) defined “Medication Review (MR)” in 2018 as a structured assessment of patients’

medications with the aim of optimizing medication use and improving health outcomes. This entails detecting drug-related problems (DRPs) and recommending interventions.¹

The detection of potential or unsolved DRPs can lead to unnecessary

* Corresponding authors.

E-mail addresses: salvador.gutierrez@micof.es (S. Gutiérrez-Igual), rut.lucas@uv.es (R. Lucas-Domínguez).

<https://doi.org/10.1016/j.rcsop.2024.100536>

Received 5 August 2024; Received in revised form 17 October 2024; Accepted 21 October 2024

Available online 24 October 2024

2667-2766/© 2024 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

visits to health care centers, hospital admissions, and long-term care that could be avoided with early detection.^{2,3} Although most DRPs are classified as preventable, many of them, if not identified and prevented in time, can be fatal. In hospital settings, from 1.3 % to 41.3 % of admissions are related to the incidence of DRPs.^{4–7} In the United States, they are one of the main causes of death after hospital admission (3–6 %), while in nearby countries such as Portugal, approximately 43,000 patients per year are admitted due to a DRPs.¹ In Spain, several DRPs prevalence studies have been undertaken, with prevalence rates ranging from 45.1 % to 79.1 %, depending on the population studied.^{8–10} At the provincial level, a study performed at the Hospital Universitario Doctor Peset in Valencia identified a total of 895 DRPs in 153 polymedicated elderly patients, 83.9 % of which were preventable.¹¹

In socioeconomic terms, DRPs are extremely costly for both, patients and healthcare systems. A study in the USA found that the economic burden due to drug-related morbidity and mortality amounted to \$177.4 billion per year.^{5,6} Considering the current demographic trend in Europe, the percentage of the population aged 65 years or older could reach 28 % by 2060. This progressive tendency of our aging population would lead to a rise in the prevalence of chronic diseases and comorbidities, which would imply more complex pharmacotherapeutic treatments, a higher incidence of DRPs, and a progressive increase in the associated medical costs.¹¹

Previous studies have evaluated the positive impact of pharmacist-led intervention (PLI) in preventing and resolving DRPs and optimizing patients' pharmacotherapy by detecting and resolving potentially inappropriate prescriptions (PIPs).^{12,13} It is a well-documented fact that patients in rural areas have limited access to healthcare services, in addition to the well-known digital gap, compared to urban areas.¹⁴ Therefore, rural pharmacies face increasing challenges in implementing significant changes in healthcare practice due to scarce resources and depopulation. In this context, an increasing number of articles have been published in recent years assessing the impact of PLI in rural areas, with positive and promising outcomes on the healthcare of the patients involved.^{15–19}

In Spain, the territorial area covered by rural community pharmacies is exceptionally extensive. There are more than 4400 pharmacies in small rural municipalities (20 % of the total number of pharmacies in Spain), serving around 5.6 million people living in these areas (almost 10 % of the Spanish population). In other words, 90 % of the inhabitants of small rural areas have a rural pharmacy in their municipality.²⁰

The implementation of innovative technologies that facilitate the quick identification of DRPs and PIPs, as well as the protocolization of PLI, seems to be a useful tool in community pharmacies and hospitals.²¹ Research in this area has shown that the development and implementation of technological tools in the health care setting through clinical pharmacy services (CPS) has a positive impact on patients' health, both in community and in specialized care settings.^{22,23}

The Official College of Pharmacists of Valencia named MICOV has developed a type 1 medication review software (Revisem®) designed to be integrated into the daily healthcare practice of community pharmacies and to facilitate the detection of DRPs and PIPs. An observational study was conducted to evaluate the improvement in healthcare achieved from the use of Revisem®, with the following objectives: (1) To analyze the prevalence of DRPs and PIPs in patients living in rural communities in the province of Valencia, Spain, and to determine the clinical relevance of the most prevalent ones. (2) To quantify and describe the PLI conducted by rural community pharmacists and their acceptance by physicians. (3) To evaluate the impact of PLI on the resolution of DRPs and PIPs detected in polymedicated elderly patients, in terms of optimization and appropriateness of pharmacotherapy.

2. Methods

2.1. Study settings and participants

A prospective, multicenter, observational pilot study (InPRESC) was developed in 17 community pharmacies of Valencia (Spain) located in rural municipalities under 5000 inhabitants. The term "rural municipality" was obtained from Law 45/2007, of December 13, 2007, for the sustainable development of the rural environment.²⁴ The 17 rural municipalities included in the study were representative of all Health Departments in the non-metropolitan area of the province of Valencia: Sagunto (1), Valencia-Arnau Vilanova-Llíria (2), Requena (2), Manises (1), Xàtiva-Ontinyent (5), La Ribera (1) and Gandia (5). The population density of the 17 rural municipalities over 54 years of age was 6592 in 2023.²⁵ The study was conducted based on the STROBE guidelines.

The study design comprises two phases:

- Cross-sectional observational phase: The objective of this phase was to determine the prevalence of DRPs and PIPs. To this end, an observational analysis was conducted. DRPs and PIPs identified through the use of Revisem® medication review software were recorded. This phase did not include any direct intervention and was limited to the identification and quantification of incidents.
- Before-after pharmacist-led intervention phase: Subsequently, the study evaluated the impact of PLI on the resolution of detected DRPs and PIPs. For this purpose, a before-after intervention study was designed by evaluating the physician's acceptance of pharmaceutical interventions. The effect of the intervention was measured by comparing the number of DRPs and PIPs before and after PLI.

The duration of the study was 6 months, from August 1st, 2023, to January 31st, 2024. The sample size was calculated considering the number of polymedicated inhabitants aged 55 years or older in the participating rural municipalities, with an expected incidence rate of 90 %, a confidence level of 95 %, and a precision of 5 %. The required number of patients was 135, applying a 5 % loss rate.

2.2. Medication review as a clinical pharmacy service

The 17 participating pharmacists were previously trained and qualified to provide the CPS of medication review through a mandatory course organized by MICOV in two consecutive phases: first, an initial theoretical training, which covered the community pharmacy CPS, the MR service specifications, and the standard operating procedures necessary to implement it; followed by a second practical session, in which they were instructed in the correct use of Revisem® software using case studies on detection, reporting and resolution of DRPs and PIPs. Once their competency had been assessed, they started recording medication reviews of all patients included in the study. The Revisem® software tool allows the detection of the DRPs, and PIPs proposed by the PCNE V9.0 for type 1 MR, namely: contraindications; precautions for use; inappropriate dosage, inappropriate timing of administration and/or dosing intervals; duplicity; drug interactions; inappropriate route of administration and/or dosage form; and potentially inappropriate prescriptions or PIPs (STOPP and START criteria).¹

Age (≥ 55 years) and polymedicated patients (≥ 5 chronic treatments) were established as the inclusion criteria for the selection of candidate patients who attended the participating pharmacies. In addition, priority for medication review was given to those patients with more than 3 underlying chronic pathologies or with renal and/or hepatic failure. The exclusion criteria were patients under chronic treatment with medication dispensed in hospitals and patients whose clinical history was incomplete or did not follow the established procedures. When analyzing the results of pharmacist-led intervention, patients who did not receive an answer from the physician were excluded from reducing potential bias in the results.

The guidelines for patient selection and the protocolized method followed for all rural pharmacies in the pilot study are shown in Fig. 1.

2.3. Data collection

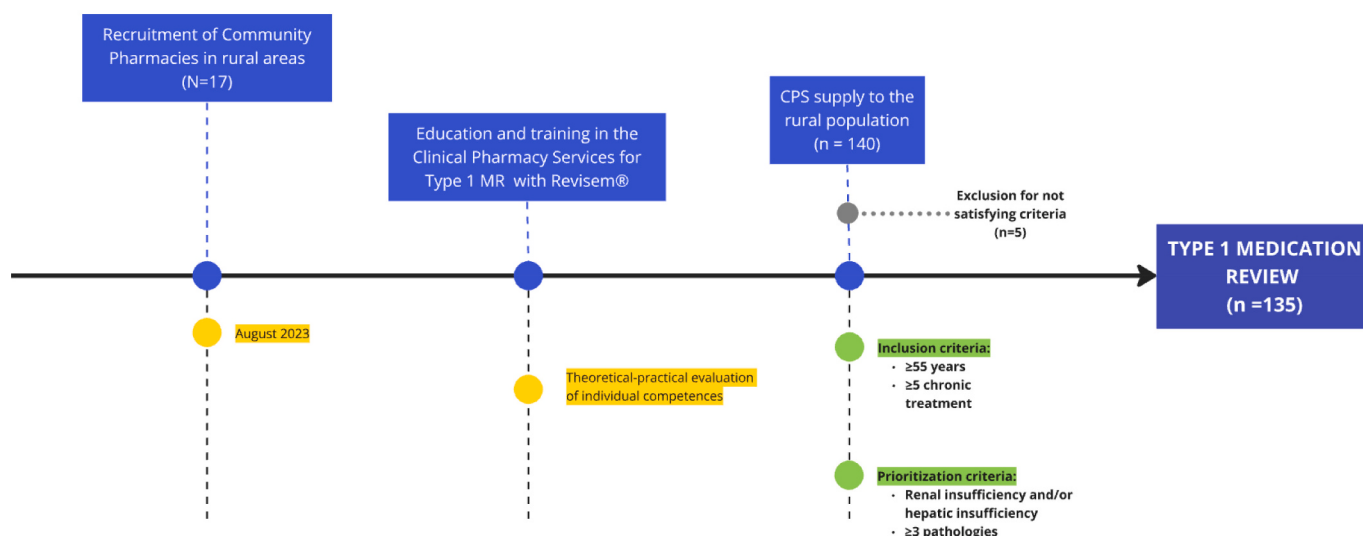
Patients' data, recorded by pharmacists participating in the study, were collected in a systematized and protocolized mode using Revisem® digital software. The main variables of analysis were sex, age, total number of initial and final medications, total number of initial and final DRPs and PIPs, number of DRPs and PIPs detected by typology according to PCNE criteria,¹ number of PLI executed, number of medications involved in the events detected, and number of changes or modifications to the medical prescription made after reporting any patient incident.

All quantitative variables were managed to assess the prevalence of the different DRPs, and PIPs identified in the study population, regardless of whether the pharmacist performed PLI or not. In addition, patients with PLI underwent progress follow-up to assess the changes achieved after communication with the physician, whether written or verbal through the patient or verbal through the pharmacist. Data from the last patients were analyzed as a before-after study of PLI.

2.4. Pharmacist-led intervention

After reviewing the medication of the patients included in the study through Revisem®, pharmacists proposed an intervention in that clinically relevant DRPs and/or PIPs identified. To do this, they documented:

(a)



(b)

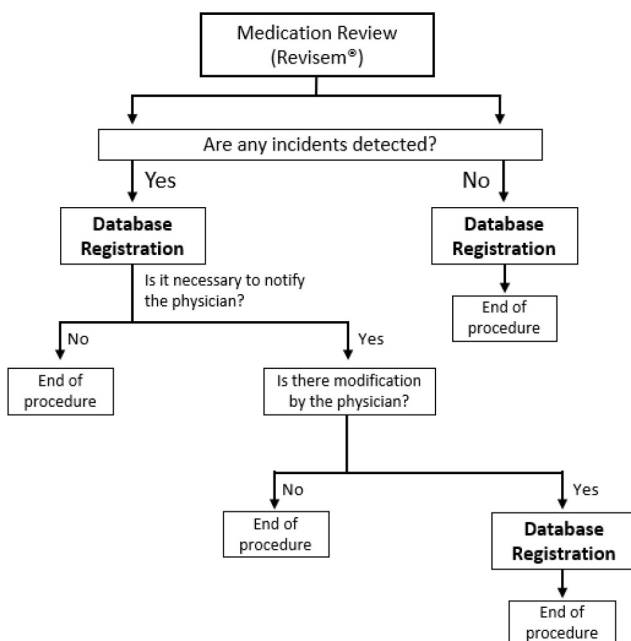


Fig. 1. (a) Flow diagram of the evolution of the study with the inclusion and exclusion criteria used in the methodological development to obtain the total sample of patients required. (b) The protocolized methodological procedure used to record the data obtained after the type 1 medication review with Revisem®.

the health problem identified through a patient interview; the drug involved by its Anatomical Therapeutic Chemical Classification (ATC); if it was the first time being detected; and the proposal they considered ideal to resolve the drug-related issue, whether it was a dose modification, drug discontinuation, substitution, change in duration, the start of a new drug, or other.

After the PLI, Revisem® automatically generated a report with the information collected by the pharmacist, specifying the type of DRPs and/or PIPs identified, the health problem and medication involved, and the optimal proposal according to the pharmacist's professional criteria to solve the drug-related issue. The patient communicated the report to the primary care physician or specialist, and any intervention accepted by the physician was recorded on the Revisem® digital software, along with the final resolution of the incidence and/or changes made.

If the physician did not accept the intervention, it was recorded as 'not accepted' and the DRPs/PIPs were considered not solved. Finally, the patient's final medication review report was signed and closed with the result of the intervention.

In patients where no response was obtained during the subsequent visits, the options 'no answer by physician' and 'don't know' were selected in the section corresponding to the resolution of the notified incidence.

2.5. Assessment of pharmacist-led intervention

To assess the effectiveness of the results obtained after the PLI and the physician's response, the total number of initial DRPs, PIPs, and involved drugs was compared with the final total number of each of these for every patient who underwent intervention. Considering that the final number of medications could vary either positively (START criterion) or negatively (STOPP criterion), both criteria were analyzed as categorical variables to assess whether there was any change in the final treatment or not after the intervention and communication to the physician.

2.6. Statistical analysis

Descriptive statistics were performed for all variables associated with the number of DRPs and PIPs of patients included in the study. Categorical variables were described using absolute frequencies and percentages, while the mean and standard deviation were used for continuous variables. Analysis between quantitative grouped variables with more than two variances was performed using an ANOVA test. Differences between before and after pharmacist-led interventions were assessed using Chi-Squared, Fisher's exact test, and *t*-test. All statistical analyses were performed using the IBM SPSS Statistics V25 computer package. (INC. Chicago, IL, USA).

3. Results

3.1. Cross-sectional observational phase

3.1.1. Patients and drug-related issues prevalence

Pharmacists reviewed the medication of 135 patients using the Revisem® digital software during the 6-month pilot study. The mean age per patient was 76.1 ± 9.9 years old, in treatment with an average of 10.1 ± 4.3 medications. 63.7 % of patients were female ($n = 86$). All patients included were 55 years or older and on chronic treatment with 5 or more drugs.

During this period, 1545 drug-related issues were identified in 135 patients, of which 1166 (75.5 %) were DRPs and 379 (24.5 %) were PIPs. The mean number of total incidences was 11.4 ± 8.0 per patient. The overall mean for each of the identified DRPs, as well as the analysis of each type of DRPs and PIPs according to the demographic and pharmacological variables analyzed, is shown in Table 1. Further details can be found in the supplementary material (Supplementary Figs. 1 and 2).

The most common health problems detected in the sample of the rural population under study were arterial hypertension (8.2 %; $n = 68$), hypercholesterolemia (6.0 %; $n = 50$) and type 2 diabetes mellitus (5.7 %; $n = 47$). The most frequent therapeutic groups, classified according to the ATC4, were A02BC proton pump inhibitors (8.0 %; $n = 99$), N05BA benzodiazepine derivatives (5.9 %; $n = 73$), and C10AA HMG CoA reductase inhibitors (5.4 %; $n = 67$). Finally, the three most prescribed drugs were A02BC01-Omeprazole (5.3 %; $n = 66$), C10AA05-Atorvastatin (2.7 %; $n = 33$), and N02BE01-Paracetamol (2.7 %; $n = 33$). The remaining position of each subdivision is shown in Supplementary Table 1.

3.1.2. Interactions classification

Interactions were the most common identified DRPs, accounting for 43.7 % ($n = 674$) of the total number of incidences ($n = 1545$), affecting 109 (80.7 %) of the 135 patients analyzed. Of the initial total, 563 interactions were analyzed. The rest of them corresponded to 21 patients who either discontinued their participation in the project or whose complete data could not be accessed.

In terms of the clinical relevance of these interactions, 32.3 % ($n = 182$) were classified as "Theoretical interaction, inferred by pharmacological and/or physiological considerations", while those of greater clinical relevance, such as those classified as "Important interaction and widely studied in clinical practice", represent 2.8 % ($n = 16$). The predominant clinical effect is the potentiation of the toxicity of one of the interacting drugs (41.2 %; $n = 232$).

The analysis of the data generated by Revisem® showed that in 4.4 % of the identified drug interactions ($n = 25$), co-administration of specific drugs should be avoided due to the significant risk of adverse effects. A prominent example of this problem is the interaction between benzodiazepine derivatives, such as diazepam, and omeprazole, where it is advisable to avoid their combination due to the possible increase in benzodiazepine plasma levels with the consequent risk of toxicity. It should be noted that this interaction accounts for 44.0 % of all interactions with this alert consideration.

Among the detected interactions, the ATC therapeutic groups corresponding to proton pump inhibitors (PPIs) (ATC A02BC) and the sulfonamides, high-ceiling diuretics, plain (ATC C03CA, corresponding to bumetanide, furosemide and torsemide), are responsible for the highest number of total detected interactions (31.6 %; $n = 178$). Within each of the ATC groups mentioned, drugs with the highest percentage of interactions are ATC A02BC01 (omeprazole) and C03CA01 (furosemide). Particularly noteworthy are the interactions of omeprazole with furosemide or quetiapine with diazepam due to their high frequency or therapeutic relevance. For more information, see Table 2 in the Supplementary Appendix (Supplementary Table 2).

3.2. Before-after pharmacist-led intervention phase

3.2.1. Before-after analysis of DRPs and PIPs

A total of 82 PLI were proposed by the pharmacists during the medication review for 53 patients (39.3 %), of which 73 cases received a response, and 33 out of the 73 (45.2 %) were fully accepted by the physicians. The number of total incidences identified in patients who received PLI was reduced from the initial 515 to 471, an 8.5 % reduction, after intervention and communication to the physician. Fig. 2 shows the significant ($p < 0.05$) percentage reduction in incidences by age group in patients who underwent PLI. In the before-after intervention study, the analysis of the differences between the number of initial and final incidences showed a significant reduction ($p < 0.05$) for each of the demographic and pharmacotherapeutic variables of the participating patients. The analysis of the total number of events for each type of pharmacotherapy variable before and after the intervention is shown in Table 2.

Of the 53 patients with proposed intervention, the mean number of final incidences decreased significantly from 9.7 ± 6.9 to 8.8 ± 6.9 ($p <$

Table 1
(a) Prevalence of drug-related problems (DRPs) and (b) potentially inappropriate prescriptions (PIPs) detected by Revisem® related to demographic and pharmacological variables in inhabitants of rural areas in the province of Valencia.

	(a)	n	DRP type																			
	N (%)		Interactions					Precaution of use					Duplicity					Contraindication				
			Total	%	Mean	SD	p-value	Total	%	Mean	SD	p-value	Total	%	Mean	SD	p-value	Total	%	Mean	SD	p-value
Sex																						
	135	1166	674	57,8 %				430	36,9 %				41	3,5 %				21	1,8 %			
Male	49	455	277	41,1 %	5,65	5,55	0,001	159	37,0 %	3,25	2,79	0,001	12	29,3 %	0,24	0,52	0,002	7	33,3 %	0,14	0,41	0,018
Female	86			59,9 %				271	63,0 %					29	70,7 %					14	66,7 %	
	(63,7)	711	397	%	4,62	4,34		%	3,15	2,55		%	0,34	0,70		%	0,16	0,40				
N. Inhabitants																						
151–250	42	325	200	29,7 %	4,76	4,87	0,006	110	25,6 %	2,62	2,12	0,001	4	9,8 %	0,10	0,30	0,027	11	52,4 %	0,26	0,54	0,098
251–350	33			16,0 %				86	20,0 %	2,61	2,34		7	17,1 %	0,21	0,48		1	4,8 %	0,03	0,17	
	(24,4)	202	108	%	3,27	3,69		%				0	0,0 %	0,00	0,00		1	4,8 %	0,50	0,71		
351–450	2 (1,5)	16	8	1,2 %	4,00	2,83		7	1,6 %	3,50	2,12		0	0,0 %	0,00	0,00		0	0,0 %	0,00	0,00	
451–550	8 (5,9)	38	19	2,8 %	2,38	1,69		17	4,0 %	2,13	1,55		2	4,9 %	0,25	0,71		0	0,0 %	0,00	0,00	
651–750	3 (2,2)	27	12	1,8 %	4,00	1,00		15	3,5 %	5,00	2,00		0	0,0 %	0,00	0,00		0	0,0 %	0,00	0,00	
751–850	3 (2,2)	12	5	0,7 %	1,67	2,08		7	1,6 %	2,33	2,52		0	0,0 %	0,00	0,00		0	0,0 %	0,00	0,00	
>850	44			47,8 %				43,7 %					68,3 %					38,1 %				
	(32,6)	546	322	%	4,89	3,87		188	%	1,84	1,28		28	%	0,48	0,68		8	%	0,09	0,20	
Age grouped																						
<55	6 (4,4)	35	19	2,8 %	3,17	2,04		12	2,8 %	2,00	1,67		2	4,9 %	0,33	0,52		2	9,5 %	0,33	0,52	
55–59	3 (2,2)	20	11	1,6 %	3,67	4,73		9	2,1 %	3,00	3,61		0	0,0 %	0,00	0,00		0	0,0 %	0,00	0,00	
60–64														12,2								
	6 (4,4)	92	54	8,0 %	9,00	5,66		33	7,7 %	5,50	3,51		5	%	0,83	0,98		0	0,0 %	0,00	0,00	
65–69	11 (8,1)	44	20	3,0 %	1,82	2,14		21	4,9 %	1,91	1,58		1	2,4 %	0,09	0,30		2	9,5 %	0,18	0,40	
70–74	15			16,5 %				54	12,6 %	3,60	2,47	0,136	4	9,8 %	0,27	0,59	0,612	2	9,5 %	0,13	0,35	0,914
	(11,1)	171	111	%	7,40	5,95	%				14		%	0,35	0,66	6		%	0,15	0,36		
75–79	40			32,6 %				138	32,1 %	3,45	2,70			24,4								
	(29,6)	378	220	%	5,50	4,85		%					%	0,33	0,76		8	38,1 %	0,27	0,58		
80–84	30			19,3 %				82	19,1 %	2,73	2,13		10	%								
	(22,2)	230	130	%	4,33	4,08		%					%	0,33	0,76		8	%	0,27	0,58		
85–89	20			14,7 %				78	18,1 %	3,90	3,16		5	%	0,25	0,55		1	4,8 %	0,05	0,22	
	(14,8)	183	99	%	4,95	5,41		%					%	0,25	0,55		1	4,8 %	0,05	0,22		
90–94	4 (3,0)	13	10	1,5 %	2,50	2,65		3	0,7 %	0,75	0,96		0	0,0 %	0,00	0,00		0	0,0 %	0,00	0,00	
Number of drugs																						
<5	11 (8,6)	15	7	1,0 %	0,64	0,67		7	1,6 %	0,64	1,03		0	0,0 %	0,00	0,00		1	4,8 %	0,09	0,30	
5–8	44			15,9 %				77	17,9 %	1,75	1,64		2	29,3 %	0,05	0,21		4	19,0 %	0,09	0,36	
	(32,6)	190	107	%	2,43	1,85		%					4,9 %	0,05	0,21		4	%	0,09	0,36		
9–12	45			32,5 %				148	34,4 %	3,29	1,93	0,001	12	%	0,27	0,54	0,001	9	42,9 %	0,20	0,46	0,854
	(33,3)	388	219	%	4,87	3,95	%				%		0,27	0,54	%	0,20		0,46	%	0,20	0,46	
13–16	22			26,4 %				111	25,8 %	5,05	2,28		9	22,0 %	0,41	0,67		5	23,8 %	0,23	0,43	
	(16,3)	303	178	%	8,09	4,83		%					%	0,41	0,67		5	%	0,23	0,43		
17–21				24,2 %				87	20,2 %	6,69	3,25		18	43,9 %	1,38	0,96		2	%	0,15	0,38	
	13 (9,6)	270	163	%	12,54	5,29		%					%	1,38	0,96		2	9,5 %	0,15	0,38		
Health Departments																						
Gandía	25	162	96	14,2 %	3,84	3,84		61	14,2 %	2,44	2,12		4	9,8 %	0,16	0,47		1	4,8 %	0,04	0,20	
	(18,5)			%				%					%					%				
La Ribera	3 (2,2)	27	12	1,8 %	4,00	1,00	0,006	15	3,5 %	5,00	2,00	0,007	0	0,0 %	0,00	0,00	0,444	0	0,0 %	0,00	0,00	0,136
Manises	6 (4,4)	34	22	3,3 %	3,67	2,16		10	2,3 %	1,67	1,51		1	2,4 %	0,17	0,41		1	4,8 %	0,17	0,41	
Requena	8 (5,9)	23	13	1,9 %	1,63	1,60		9	2,1 %	1,13	1,81		1	2,4 %	0,13	0,35		0	0,0 %	0,00	0,00	
Sagunto	6 (4,4)	21	10	1,5 %	1,67	1,21		9	2,1 %	1,50	1,22		2	4,9 %	0,33	0,82		0	0,0 %	0,00	0,00	

(continued on next page)

Table 1 (continued)

	(a)		DRP type																				
	N (%)	n	Interactions					Precaution of use					Duplicity					Contraindication					
			Total	%	Mean	SD	p-value	Total	%	Mean	SD	p-value	Total	%	Mean	SD	p-value	Total	%	Mean	SD	p-value	
Valencia-Arnau Vilanova Llíria	9 (6,7)	54	24	3,6 %	2,67	2,29		29	6,7 %	3,22	3,19		1	2,4 %	0,11	0,33		0	0,0 %	0,00	0,00		
Xàtiva-Ontinyent	78 (57,8)	845	497	73,7 %	6,37	5,43		297	69,1 %	3,81	2,71		32	78,0 %	0,41	0,73		19	90,5 %	0,24	0,49		
	(b)		PIP type																				
	N (%)	n	STOPP criteria					START criteria															
			Total	%	Mean	SD	p-value	Total	%	Mean	SD	p-value	Total	%	Mean	SD	p-value						
Sex		135	379	294	77,6 %			85	22,4 %														
Male	49 (36,3)	121	92	31,3 %	1,88	1,81		29	34,1 %				29	34,1 %				0,59		0,76		0,350	
Female	86 (63,7)	258	202	68,7 %	2,35	1,83	0,150	56	65,9 %				56	65,9 %				0,65		1,04			
N. Inhabitants																							
151–250	42 (31,1)	90	68	23,1 %	1,62	1,31		22	25,9 %				22	25,9 %				0,52		0,67			
251–350	33 (24,4)	83	72	24,5 %	2,18	1,83		11	12,9 %				11	12,9 %				0,33		0,54			
351–450	2 (1,5)	8	6	2,0 %	3,00	0,00		2	2,4 %				2	2,4 %				1,00		1,41			
451–550	8 (5,9)	22	18	6,1 %	2,25	1,98		4	4,7 %				4	4,7 %				0,50		0,53			
651–750	3 (2,2)	27	14	4,8 %	4,67	1,15		13	15,3 %				13	15,3 %				4,33		2,08			
751–850	3 (2,2)	2	2	0,7 %	0,67	1,15		0	0,0 %				0	0,0 %				0,00		0,00			
>850	44 (32,6)	147	114	38,8 %	2,59	2,11		33	38,8 %				33	38,8 %				0,75		0,87			
Age grouped																							
<55	6 (4,4)	0	0	0,0 %	0,00	0,00		0	0,0 %				0	0,0 %				0,00		0,00			
55–59	3 (2,2)	0	0	0,0 %	0,00	0,00		0	0,0 %				0	0,0 %				0,00		0,00			
60–64	6 (4,4)	0	0	0,0 %	0,00	0,00		0	0,0 %				0	0,0 %				0,00		0,00			
65–69	11 (8,2)	28	24	8,2 %	2,18	1,66		4	4,7 %				4	4,7 %				0,36		0,67			
70–74	15 (11,1)	45	35	11,9 %	2,33	1,59	0,015	10	11,8 %				10	11,8 %				0,67		0,90		0,031	
75–79	40 (29,6)	158	112	38,1 %	2,80	1,79		46	54,1 %				46	54,1 %				1,15		1,25			
80–84	30 (22,2)	85	70	23,8 %	2,33	1,84		15	17,6 %				15	17,6 %				0,50		0,73			
85–89	20 (14,8)	50	43	14,6 %	2,15	1,84		7	8,2 %				7	8,2 %				0,35		0,59			
90–94	4 (2,7)	13	10	3,4 %	2,50	1,73		3	3,5 %				3	3,5 %				0,75		0,50			
Number of drugs																							
0–4	11 (8,2)	8	7	2,4 %	0,64	0,92		1	1,2 %				1	1,2 %				0,09		0,30			
5–9	44 (32,6)	89	71	24,1 %	1,61	1,69		18	21,2 %				18	21,2 %				0,41		0,50			
10–14	45 (33,3)	134	100	34,0 %	2,22	1,44	0,096	34	40,0 %				34	40,0 %				0,76		1,26		0,001	
15–19	22 (16,3)	88	69	23,5 %	3,14	2,14		19	22,4 %				19	22,4 %				0,86		0,83			
20–24	13 (9,6)	60	47	16,0 %	3,62	1,85		13	15,3 %				13	15,3 %				1,00		1,08			
Health Departments																							
Gandía	25 (18,5)	73	61	20,7 %	2,44	1,64		12	14,1 %				12	14,1 %				0,48		0,59			
La Ribera	3 (2,2)	27	14	4,8 %	4,67	1,15		13	15,3 %				13	15,3 %				4,33		2,08			
Manises	6 (4,4)	23	17	5,8 %	2,83	2,48		6	7,1 %				6	7,1 %				1,00		0,89			
Requena	8 (5,9)	7	7	2,4 %	0,88	0,99	0,024	0	0,0 %				0	0,0 %				0,00		0,00		0,001	
Sagunto	6 (4,4)	18	15	5,1 %	2,50	2,07		3	3,5 %				3	3,5 %				0,50		0,55			
Valencia-Arnau Vilanova Llíria	9 (6,7)	14	10	3,4 %	1,11	0,93		4	4,7 %				4	4,7 %				0,44		0,53			
Xàtiva-Ontinyent	78 (57,8)	217	170	57,8 %	2,18	1,86		47	55,3 %				47	55,3 %				0,60		0,80			

N (%): total number of patients included in the study and the percentage they represent in each of the variables analyzed. n: number of incidents (DRP/PIP) identified for each of the variables analyzed. Total: total number of incidents detected in the patients included according to the category of incidence typified by the PCNE criteria. %: percentage represented by each of the values of the total according to its category and variable. Mean: average number of incidences detected in a given category according to the associated variable. SD: standard deviation of the mean number of incidents. p-value: value obtained from the statistical analysis of each of the variables. Obtained by Chi-square, Fisher's exact test and t-test.

Table 2
Comparison of the differences in the incidences (DRPs/PIPs) detected before and after the pharmacist-led intervention following medication review.

		Incidences (DRP/PIP) before-after pharmacy-led intervention											
		Initial incidences					Final incidences					Δ Total	Before-after intervention
		N (%)	Total	%	Mean	SD	p-value	Total	%	Mean	SD	p-value	p-value
Sex	53	515					471						
Male	17 (32,1)	184	35,7 %	10,82	6,98	0,431	172	36,5 %	10,12	6,93	0,383	0,71	0,001
Female	36 (67,9)	331	64,3 %	9,19	6,98		299	63,5 %	8,31	7,04		0,89	
N. Inhabitants													
151–250	19 (35,9)	180	35,0 %	9,47	8,68	0,451	166	35,2 %	8,74	8,59	0,513	0,74	0,001
251–350	25 (47,2)	255	49,5 %	10,20	6,36		230	48,8 %	9,20	6,54		1,00	
351–450	1 (1,9)	16	3,1 %	16,00	–		16	3,4 %	16,00	–		–	
451–550	5 (9,4)	41	8,0 %	8,20	3,42		38	8,1 %	7,60	3,78		0,60	
>550	3 (5,7)	23	4,5 %	7,67	5,86		21	4,5 %	7,00	5,29		0,67	
Age grouped													
55–64	5 (9,4)	30	5,8 %	6,50	6,75	0,629	26	5,5 %	5,67	6,32	0,595	0,83	0,001
65–74	12 (22,6)	125	24,3 %	10,42	7,08		112	23,8 %	9,33	7,52		1,08	
75–84	28 (52,8)	313	60,8 %	11,18	7,42		292	62,0 %	10,43	7,37		0,75	
85–94	8 (15,1)	47	9,1 %	5,88	3,14		41	8,7 %	5,13	3,14		0,75	
Number of drugs													
5–9	35 (66,0)	219	42,5 %	4,40	2,36	0,001	189	40,1 %	3,48	2,74	0,001	0,92	0,001
10–14	15 (28,3)	218	42,3 %	14,53	5,01		207	43,9 %	13,80	4,93		0,73	
15–19	3 (5,7)	78	15,1 %	26,00	5,29		75	15,9 %	25,00	4,58		1,00	

N (%): total number of patients included in the pre-post pharmaceutical intervention study and the percentage they represent in each of the variables analyzed. Total: total number of incidents detected before and after the pharmaceutical intervention. %: percentage represented by each of the values of the total according to its category and variable. Mean: average number of incidents detected in a given category according to the associated variable. SD: standard deviation of the mean number of incidents. p-value: value obtained from the statistical analysis of each of the variables. Obtained by Chi-square, Fisher's exact test and t-test.

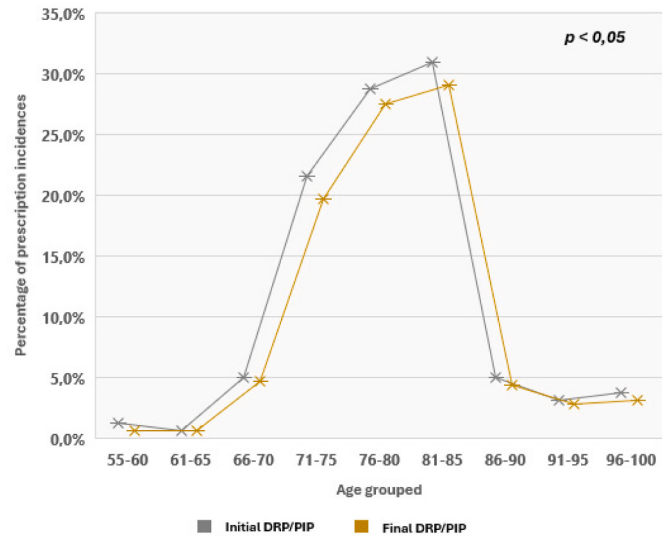


Fig. 2. Comparison of the percentage of initial and final DRPs/PIPs in the rural population of Valencia, before and after the pharmaceutical intervention according to the age group.

0.05). A total of 44 fewer drug-related issues (DRPs and PIPs) were quantified in the 53 patients who received intervention.

3.2.2. Changes in treatment

The 73 complete PLI involving 53 patients resulted in 35 (47.9 %) changes in treatment. When comparing whether there was a change in the patient's final pharmacotherapy with or without PLI after the medication review, a significant change ($p < 0.05$) was observed in those patients who underwent PLI. This analysis was performed with a contingency table using the Chi-Squared probability statistics.

3.2.3. Detected incidents and pharmacist-led interventions

Table 3 shows the overall breakdown of the characteristics of the PLI performed in the 53 patients, with interactions being the most frequent type of incidence (47.6 %; $n = 39$). The communication between

pharmacist and patient was mostly verbal (77.0 %; $n = 57$), while communication of the pharmacist with the physician was mostly written through the patient (45.0 %; $n = 27$). Drug substitution (22.2 %; $n = 18$) or change of dose/administration (17.3 %; $n = 11$) were the most prevalent proposals made by the pharmacists performing a type 1 medication review, and almost half of them were accepted by the physician (45.2 %; $n = 33$). The therapeutic groups with the highest percentage of PLI were A02BC, corresponding to PPIs, with 12.2 % of the total number of interventions, followed by N02AJ, corresponding to opioids combined with other analgesics, with 9.8 % of the total number of interventions. Collectively, these two groups account for 22.0 % of the total number of incidences that underwent intervention. Fig. 3 shows the total percentage of incidences involved and the percentage represented by each of the above-mentioned ATC groups.

4. Discussion

A comprehensive analysis of data from the InPRESC pilot study revealed significant findings on the prevalence of DRPs and PIPs in polymedicated elderly patients attending pharmacies in rural areas of the province of Valencia, Spain. It also assessed the effectiveness of PLI in significantly reducing the total number of incidences identified in 135 patients, with interactions being the most common type of incidence. It is noteworthy that the recommendation in 4.4 % of the interactions identified was to avoid co-administration of diazepam with omeprazole due to the significant risk of intoxication by pharmacokinetic interaction at the metabolic level. Therefore, the present study emphasizes the importance of pharmaceutical interventions in the detection and resolution of DRPs and PIPs in polymedicated patients, thereby helping to prevent adverse health outcomes.

In this way, Revisem® plays an essential role for detecting a vast number of DRPs and PIPs. Its ability to automatically analyze a patient's pharmacotherapeutic history and provide specific recommendations facilitated the pharmacists' work in identifying and addressing clinical problems. However, it was the pharmacists' clinical judgment and communication with physicians that ultimately enabled the necessary interventions to resolve these drug-related issues previously identified.

Table 3

Descriptive analysis of the types of incidences on which the pharmacist has intervened, as well as the interventions conducted with the patient/physician, the proposals to optimize pharmacotherapy, and the final result of the intervention. The two pharmacotherapeutic groups with the highest percentage of intervention are also detailed.

Incidence type	N (%)	Total medication		A02BC		N02AJ	
				PPI		Combined opioids	
		Total	%	Total	%	Total	%
STOPP criteria	18 (29,0)	21	25,6 %	0	0,0 %	2	2,4 %
START criteria	6 (9,7)	6	7,3 %	0	0,0 %	3	3,7 %
Interactions	25 (40,3)	39	47,6 %	9	11,0 %	3	3,7 %
Precaution of Use	8 (12,9)	10	12,2 %	1	1,2 %	0	0,0 %
Contraindication	0 (0,0)	0	0,0 %	0	0,0 %	0	0,0 %
Duplicity	1 (1,6)	1	1,2 %	0	0,0 %	0	0,0 %
Inadequate dosage, dosage interval and/or duration	4 (6,5)	5	6,1 %	0	0,0 %	0	0,0 %
Total	62	82	100,0 %	10	12,2 %	8	9,8 %
Patient intervention	53						
Oral	35 (70,0)	57	77,0 %	8	10,8 %	5	6,8 %
Oral and written	8 (16,0)	9	12,2 %	1	1,4 %	0	0,0 %
Written	7 (14,0)	8	10,8 %	2	2,7 %	0	0,0 %
Total	50	74	100,0 %	11	14,9 %	5	6,8 %
Physician intervention	53						
Written reports through patient	20 (48,8)	27	45,0 %	9	15,0 %	0	0,0 %
Telephone	8 (19,5)	10	16,7 %	0	0,0 %	3	5,0 %
Oral	9 (22,0)	16	26,7 %	0	0,0 %	3	5,0 %
Oral through patient	3 (7,3)	6	10,0 %	0	0,0 %	0	0,0 %
Telephonic, Oral, Oral through patient	1 (2,4)	1	1,6 %	0	0,0 %	0	0,0 %
Total	41	60	100,0 %	9	15,0 %	6	10,0 %
Proposal	53						
Add a medication	4 (6,2)	4	4,9 %	0	0,0 %	2	2,5 %
Modify dose	11 (21,5)	14	17,3 %	0	0,0 %	2	2,5 %
Modify duration	2 (3,1)	2	2,5 %	0	0,0 %	0	0,0 %
Modify regimen	11 (21,5)	14	17,3 %	4	4,9 %	0	0,0 %
Remove a medication	7 (12,3)	8	9,9 %	1	1,2 %	0	0,0 %
Substitute a medication	15 (27,7)	18	22,2 %	6	7,4 %	0	0,0 %
No proposal	16 (32,3)	21	25,9 %	0	0,0 %	4	4,9 %
Total	66	81	100,0 %	11	13,6 %	8	9,9 %
Intervention result	53						
Accepted	26 (54,2)	33	45,2 %	5	6,8 %	3	4,1 %
Not accepted	10 (20,8)	16	21,9 %	4	5,5 %	0	0,0 %
Not accepted but modification	2 (4,2)	2	2,7 %	0	0,0 %	0	0,0 %
Unknown	10 (20,8)	22	30,1 %	0	0,0 %	5	6,8 %
Total	48	73	100,0 %	9	12,3 %	8	11,0 %

N (%): total number of patients who underwent pharmaceutical intervention and the percentage they represent in each of the variables analyzed. Total: total number of drugs on which pharmaceutical intervention was conducted. %: percentage represented by each of the values of the total according to its category and variable.

4.1. Comparison with the existing literature

The main findings of this study agree with previously published articles: (1) The most prevalent DRPs was interactions with 43.7 % of the detected incidences in the studied patients, similar to the 49.0 % of the total DRPs previously reported.²⁶ (2) PPIs, specifically omeprazole, are the drugs with the highest number of interactions, consistent with other studies conducted in hospitals in which PPIs account for 17.2 % of the identified DRPs, followed by nootropic drugs (16.1 %) and hypnotics-anxiolytics (13.9 %).^{26,27} (3) Pharmaceutical interventions carried out by community pharmacies have significantly reduced the number of total incidences in patients undergoing intervention.

However, it is important to highlight some differences in the findings from rural areas when compared to hospital settings. For instance, the frequency of interactions including PPIs might be influenced by the higher self-medication practices in rural areas, where patients have less frequent contact with healthcare professionals.²⁸ Furthermore, the lower acceptance rate of pharmacist interventions in community settings, suggests that some of the strategies that fit well in hospitals may not be directly applicable in rural contexts.²⁹ These differences underline the need for more research to adapt pharmaceutical care protocols to rural settings.

In addition, there are two relevant findings related to the therapeutic groups in our study. Firstly, the high prevalence of DRPs involving PPIs (ATC A02BC) described above. One of the possible explanations for this high frequency is the elevated consumption of PPIs in Spain, mainly

omeprazole, whereas the use of PPIs other than omeprazole is higher in other European countries.³⁰ PPIs (ATC A02BC) ranked first as the pharmacotherapeutic group with the highest consumption in packs (6.9 %) in the Spanish National Health System (Spanish NHS), according to the Report on Pharmaceutical Provision of 2023,³¹ which increases the probability of DRPs.

The second relevant finding affects the combined opioids (ATC N02AJ). This latter pharmacotherapeutic group is one of the 15 most widely used in Spain in recent years, with total consumption expressed as defined daily dose/1000 inhabitants/day (DHD) increasing every year.³¹ Several articles have warned of the problems associated with the misuse of these drugs, particularly because of their tolerance and dependence, which can lead to overdose or even death.^{32,33} Studies in rural areas have demonstrated the importance of community interventions to improve the use and knowledge of opioid medicines, highlighting the pivotal role of pharmacists in solving incidences related to this therapeutic group through the PLI.^{34,35}

In the current study, 39.3 % of patients with detected drug-related issues underwent PLI, a dwindling number compared to other studies in the hospital setting, where medication review and clinical care practice are established daily routines. Medication review is an essential practice in hospital pharmaceutical care, especially in polymedicated patients. In Spain, as in other countries, there are well-established protocols and programs for medication review in hospitalized patients; however, this is not a widespread practice in community pharmacies.^{36,37}

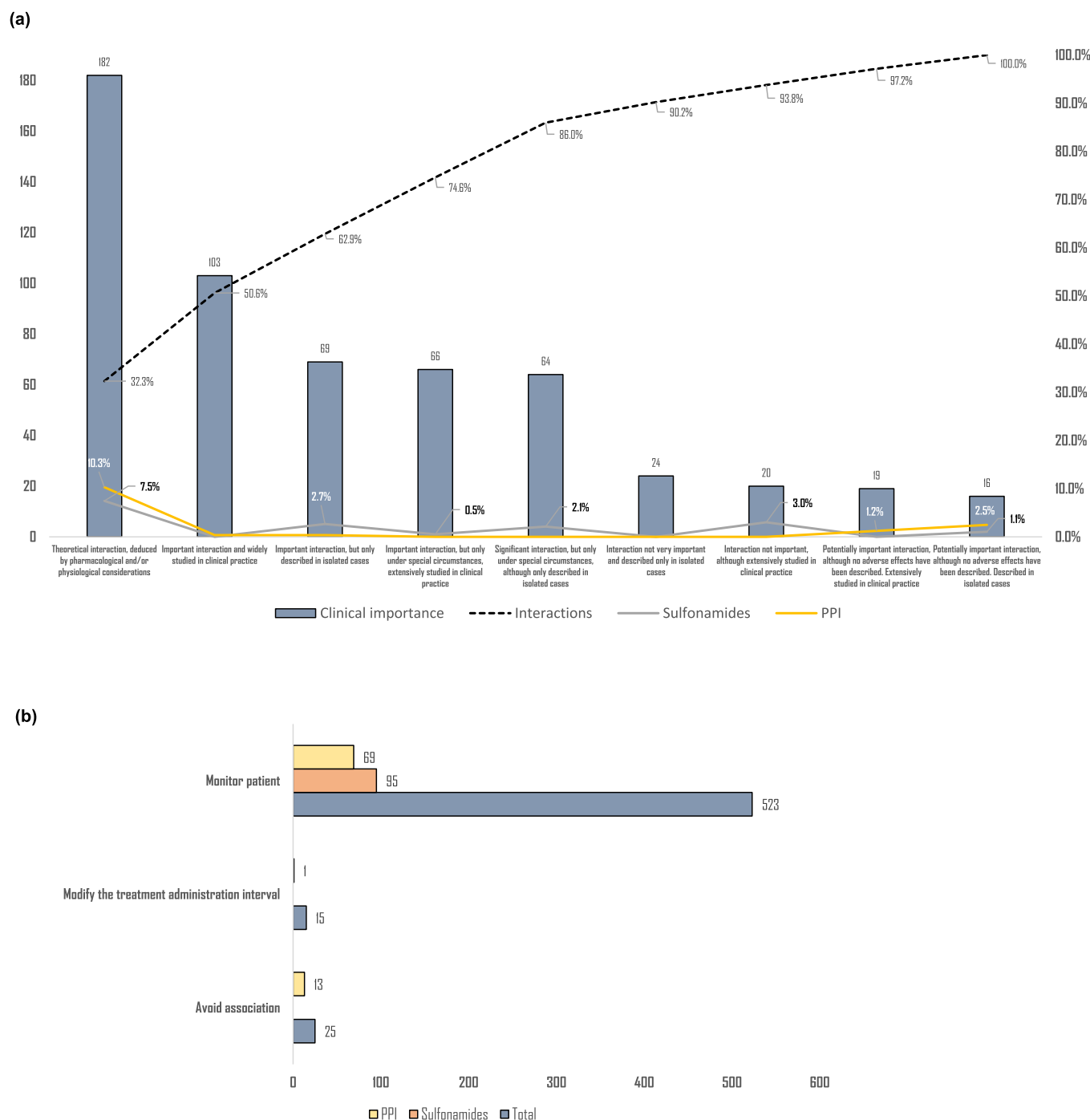


Fig. 3. (a) Prevalence (columns), percentages (lines), and severity of total interactions identified with Revisem® compared to the ATC percentages of the main drugs with interactions. (b) Suggested recommendations to be addressed by the pharmacist from the interactions detected obtained by Revisem®.

Acceptance of pharmacist-suggested interventions constitutes another relevant difference between hospital and community pharmacy settings. In the hospital setting, the acceptance rate is remarkably high, ranging from 70.8 % to 90.8 % according to several studies,^{11,38} whereas in our study it was 45.2 %. The lower acceptance rate in rural pharmacies could stem from several factors, including the lack of multidisciplinary teamwork with other healthcare professionals due to the particular characteristics of the Spanish NHS, in which the community pharmacy is only granted access to drug-prescription, but not the clinical history. In addition, there is no fluid communication between the community pharmacist and the primary care physician. Cultural

differences in rural populations, such as a stronger reliance on traditional remedies or reluctance to modify long-standing prescriptions, may also play a role.²⁹

It is also worth noting the means of communication used by pharmacists. Some studies confirm greater acceptance of PLI when proposed directly by the pharmacist.³⁹ However, community pharmacists have great difficulty in contacting the prescribing physician directly, prompting a lower number of accepted suggestions than in other settings, such as hospitals, where physicians and pharmacists are more disposed to communicate directly, achieving acceptance rates of up to 97 % of PLI.^{36,40,41} Tools such as Revisem® highlight the need to

continue to explore the best ways to communicate in order to optimize patient treatment.

4.2. Strengths

The pilot study has three strong points. Firstly, it is the first study to evaluate a computer program, specifically designed by a professional college, for the type 1 medication review in rural pharmacies in the province of Valencia. Secondly, the seventeen pharmacies that conducted the recording and review of the 135 patients received specific training, and participating pharmacists were evaluated and qualified in the CPS before implementing the service, in order to guarantee data collection and record-keeping in a protocolized manner and the standardization of the review criteria. These aspects contributed to the reliability and accuracy of the data, ensuring that the findings can serve as a basis for future research and practice improvements in similar settings. Finally, the study has not only provided a better understanding of the most common DRPs, and PIPs identified in rural areas, highlighting the need to standardize reviews as a daily activity in pharmaceutical care practice but has also revealed the existing communication gap between pharmacists and primary care doctors, hence the low degree of PLI acceptance, showcasing the need for improvement.

4.3. Limitations

As this was a pilot study in rural pharmacies (<5000 inhabitants), the number of patients willing to participate was limited. This small sample size may reduce the generalizability of the findings to other rural populations or urban settings. This problem has been mitigated by extending the duration of the study and including a greater number of rural pharmacies in the province of Valencia. On the other hand, type 1 medication review only requires the patient's pharmacotherapeutic history, so for future research it is intended to extend it to the type 3 medication review, in which a clinical interview is conducted with the patient, allowing the identification, quantification, and resolution of adverse drug reactions and health problems caused by the medication. Future studies could also benefit from including larger, more diverse populations, and developing strategies to overcome communication barriers between pharmacists and other healthcare professionals, which could enhance the applicability of pharmaceutical interventions.

5. Conclusion

The results of InPRESC pilot study using Revisem® software evidence a high prevalence of drug-related problems and potentially inappropriate prescriptions in the rural population from Valencia (Spain). Pharmacological interactions and STOPP criteria were the most frequent incidences detected. Pharmacist-led interventions played a crucial role in reducing the drug-related issues detected in rural patients. These findings highlight the importance of the pharmacist as a member of the healthcare team in preventing adverse outcomes and improving pharmaceutical care, especially in rural settings where access to medical resources may be more limited.

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.rcsop.2024.100536>.

Ethics approval and consent to participate

This study was approved by the Ethics Committee for Drug Research of the Hospital Clínico Universitario of Valencia (CEIm 2023.093). Written informed consent was obtained from all patients.

Funding

This work was funded by the Chair for the Rational Use of Medicines, MICOOF-University of Valencia.

CRedit authorship contribution statement

Salvador Gutiérrez-Igual: Writing – review & editing, Writing – original draft, Visualization, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Rut Lucas-Domínguez:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Methodology, Investigation, Formal analysis, Conceptualization. **José Sendra-Lillo:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization. **Alberto Martí-Rodrigo:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Conceptualization. **Isabel Romero Crespo:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Conceptualization. **M. Carmen Montesinos:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare no conflict of interest.

Acknowledgments

Authors would like to acknowledge the MICOOF's Informatic team for they helpfully contribution to the development of Revisem®. They also want to give a recognition to M^a Teresa Vicedo, member of MICOOF's Rural Pharmacy Commission for all her support in this study.

References

- Griese-Mammen N, Hersberger KE, Messerli M, et al. PCNE definition of medication review: reaching agreement. *Int J Clin Pharmacol*. 2018;40(5):1199–1208. <https://doi.org/10.1007/s11096-018-0696-7>.
- Ni XF, Yang CS, Bai YM, Hu ZX, Zhang LL. Drug-related problems of patients in primary health care institutions: a systematic review. *Front Pharmacol*. 2021;12, 698907. <https://doi.org/10.3389/fphar.2021.698907>.
- Ayalew MB, Tegegn HG, Abdela OA. Drug related hospital admissions; a systematic review of the recent literatures. *Bull Emerg Trauma*. 2019;7(4):339–346. <https://doi.org/10.29252/beat-070401>.
- Tharanon V, Putthipokin K, Sakthong P. Drug-related problems identified during pharmaceutical care interventions in an intensive care unit at a tertiary university hospital. *SAGE Open Med*. 2022;10. <https://doi.org/10.1177/20503121221090881>, 20503121221090881.
- Sheleme T, Sahilu T, Feyissa D. Identification and resolution of drug-related problems among diabetic patients attending a referral hospital: a prospective observational study. *J Pharm Policy Pract*. 2021;14(1):50. <https://doi.org/10.1186/s40545-021-00332-9>.
- Kaae S, Hedegaard U, Andersen A, et al. What are the drug-related problems still faced by patients in daily life?—a qualitative analysis at the pharmacy counter. *Pharmacy*. 2023;11(4):124. <https://doi.org/10.3390/pharmacy11040124>.
- Chaomuang N, Dede AJO, Saokaew S, Umuaypornlert A. Effects of home drug delivery on drug-related problems: preliminary evidence for improved patient outcomes during the COVID-19 pandemic in Thailand. *J Am Pharm Assoc*. 2022;62(4):1206–1213. e3 <https://doi.org/10.1016/j.japh.2022.01.015>.
- Garin N, Sole N, Lucas B, et al. Drug related problems in clinical practice: a cross-sectional study on their prevalence, risk factors and associated pharmaceutical interventions. *Sci Rep*. 2021;11:883. <https://doi.org/10.1038/s41598-020-80560-2>.
- Ferrández O, Urbina O, Grau S, et al. Computerized pharmacy surveillance and alert system for drug-related problems. *J Clin Pharm Ther*. 2017;42(2):201–208. <https://doi.org/10.1111/jcpt.12495>.
- Gutiérrez-Igual S, Lucas-Domínguez R, Martí Rodrigo A, Romero Crespo I, Montesinos Mezquita MC. Nuevas herramientas para la revisión de la medicación: PRM en pacientes en tratamiento con inhibidores de la bomba de protones. *Aten Primaria*. 2024;56(5), 102836. <https://doi.org/10.1016/j.aprim.2023.102836>.
- Ruiz-Millo O, Clemente-Martí M, Galbis-Bernácer AM, Navarro-Sanz JR. Clinical impact of an interdisciplinary patient safety program for managing drug-related problems in a long-term care hospital. *Int J Clin Pharmacol*. 2017;39(6):1201–1210. <https://doi.org/10.1007/s11096-017-0548-x>.
- Tasaka Y, Tanaka A, Yasunaga D, Asakawa T, Araki H, Tanaka M. Potential drug-related problems detected by routine pharmaceutical interventions: safety and economic contributions made by hospital pharmacists in Japan. *J Pharm Health Care Sci*. 2018;4(1):33. <https://doi.org/10.1186/s40780-018-0125-z>.
- Lee H, Ryu K, Sohn Y, Kim J, Suh GY, Kim E. Impact on patient outcomes of pharmacist participation in multidisciplinary critical care teams: a systematic review

- and meta-analysis*. *Crit Care Med.* 2019;47(9):1243. <https://doi.org/10.1097/CCM.0000000000003830>.
14. Kellow N. Evaluation of a rural community pharmacy-based waist management project: bringing the program to the people. *Aust J Prim Health.* 2011;17(1):16–22. <https://doi.org/10.1071/PY10030>.
 15. Hilsenrath P, Woelfel J, Shek A, Ordanza K. Redefining the role of the pharmacist: medication therapy management. *J Rural Health.* 2012;28(4):425–430. <https://doi.org/10.1111/j.1748-0361.2012.00417.x>.
 16. Tan ACW, Emmerton L, Hattingh HL. A review of the medication pathway in rural Queensland, Australia. *Int J Pharm Pract.* 2012;20(5):324–339. <https://doi.org/10.1111/j.2042-7174.2012.00193.x>.
 17. Chambers B, Fleming C, Packer A, Botha L, Hawthorn G, Nott S. Virtual clinical pharmacy services: a model of care to improve medication safety in rural and remote Australian health services. *Am J Health-Syst Pharm.* 2022;79(16):1376–1384. <https://doi.org/10.1093/ajhp/zxac082>.
 18. Cole SL, Grubbs JH, Din C, Nesbitt TS. Rural inpatient telepharmacy consultation demonstration for after-hours medication review. *Telemed J E-Health.* 2012;18(7): 530–537. <https://doi.org/10.1089/tmj.2011.0222>.
 19. Fletcher J, Hogg W, Farrell B, et al. Effect of nurse practitioner and pharmacist counseling on inappropriate medication use in family practice. *Can Fam Physician.* 2012;58(8):862–868.
 - 20.. Afí. Farmacéuticos Consejo General de Colegios Farmacéuticos. La aportación de valor del modelo de farmacia a la cohesión territorial y al reto demográfico. Accessed June 12, 2024 <https://www.farmacéuticos.com/wp-content/uploads/2023/01/Informe-Contribucion-farmacia-reto-demografico.pdf>; 2023.
 21. Keasberry J, Scott IA, Sullivan C, Staib A, Ashby R. Going digital: a narrative overview of the clinical and organisational impacts of eHealth technologies in hospital practice. *Aust Health Rev.* 2017;41(6):646–664. <https://doi.org/10.1071/AH16233>.
 22. Söling S, Köberlein-Neu J, Müller BS, et al. From sensitization to adoption? A qualitative study of the implementation of a digitally supported intervention for clinical decision making in polypharmacy. *Implement Sci.* 2020;15:82. <https://doi.org/10.1186/s13012-020-01043-6>.
 23. Corny J, Rajkumar A, Martin O, et al. A machine learning-based clinical decision support system to identify prescriptions with a high risk of medication error. *J Am Med Inform Assoc.* 2020;27(11):1688–1694. <https://doi.org/10.1093/jamia/ocaa154>.
 24. BOE-A-2007-21493. Ley 45/2007, de 13 de diciembre, para el desarrollo sostenible del medio rural. Accessed March 7, 2024 <https://www.boe.es/buscar/act.php?id=BOE-A-2007-21493>; 2007.
 25. INE Instituto Nacional de Estadística. Valencia: Population by municipality and sex. INE; 2023. Accessed December 14, 2023. <https://www.ine.es/jaxiT3/Tabla.htm?t=2903&L=1>.
 26. Babelghaith SD, Wajid S, Alrabiah Z, et al. Drug-related problems and pharmacist intervention at a general hospital in the Jazan Region, Saudi Arabia. *Risk Manag Healthc Policy.* 2020;13:373–378. <https://doi.org/10.2147/RMHP.S247686>.
 27. Chen Q, Jin Z, Zhang P, Sun S, Li L, Liao Y. Characteristics of drug-related problems among hospitalized ischemic stroke patients in China. *Int J Clin Pharmacol.* 2020;42(4):1237–1241. <https://doi.org/10.1007/s11096-020-01081-6>.
 28. Ahmad A, Patel I, Mohanta G, Balkrishnan R. Evaluation of self medication practices in rural area of town Sahaswan at northern India. *Ann Med Health Sci Res.* 2014;4 (suppl 2):S73–S78. <https://doi.org/10.4103/2141-9248.138012>.
 29. Miller EE, Hunt A, Middendorf A, et al. Comparing South Dakota pharmacist perspectives of pharmacy services in rural versus urban settings. *Explor Res Clin Soc Pharm.* 2024;15, 100490. <https://doi.org/10.1016/j.rcsop.2024.100490>.
 30. García Del Pozo J. Estudio de utilización de antiulcerosos en España (2000–2008). *Inf Ter Sist Nac Salud.* 2009;33(2):49–54.
 31. Ministerio de Sanidad. Sanidad en datos - Informe anual del Sistema Nacional de Salud. Accessed December 14, 2023 https://www.sanidad.gob.es/estadEstudios/estadisticas/sisInfSanSNS/tablasEstadisticas/InfAnualSNS2023/INFORME_ANUAL_2023.pdf; 2023.
 32. Gadd S, Cox N, Samuelson J, Kenney A, Turner K, Cochran G. Abuse-deterrent opioid formulations and the opioid crisis: a pharmacist's perspective. *Ther Drug Monit.* 2021;43(1):35–41. <https://doi.org/10.1097/FTD.0000000000000844>.
 33. Viktil KK, Blix HS, Reikvam A, et al. Comparison of drug-related problems in different patient groups. *Ann Pharmacother.* 2004;38(6):942–948. <https://doi.org/10.1345/aph.1D531>.
 34. Chisholm-Burns MA, Spivey CA, Sherwin E, Wheeler J, Hohmeier K. The opioid crisis: origins, trends, policies, and the roles of pharmacists. *Am J Health-Syst Pharm.* 2019;76(7):424–435. <https://doi.org/10.1093/ajhp/zxy089>.
 35. Curcija K, Zittleman L, Fisher M, et al. Does a rural community-based intervention improve knowledge and attitudes of opioid use disorder and medication-assisted treatment? A report from the IT MATTTs study. *J Rural Health.* 2022;38(1): 120–128. <https://doi.org/10.1111/jrh.12545>.
 36. Li XX, Zheng SQ, Gu JH, et al. Drug-related problems identified during pharmacy intervention and consultation: implementation of an intensive care unit pharmaceutical care model. *Front Pharmacol.* 2020;11, 571906. <https://doi.org/10.3389/fphar.2020.571906>.
 37. Delgado Silveira E, Fernandez-Villalba EM, García-Mina Freire M, Albiñana Pérez MS, Casajús Lagranja MP, Peris Martí JF. The impact of pharmacy intervention on the treatment of elderly multi-pathological patients. *Farm Hosp.* 2015;39(4): 192–202. <https://doi.org/10.7399/fh.2015.39.4.8329>.
 38. Herledan C, Falandry C, Huot L, et al. Clinical impact and cost-saving analysis of a comprehensive pharmaceutical care intervention in older patients with cancer. *J Am Geriatr Soc.* October 11, 2023. <https://doi.org/10.1111/jgs.18585>. Published online.
 39. Onatibia-Astibia A, Larranaga B, Iribar J, et al. A communication procedure between community pharmacists and primary care professionals resolves medication errors and other administrative issues. *Int J Pharm Pract.* 2022;30(3):235–240. <https://doi.org/10.1093/ijpp/riac008>.
 40. Ilardo ML, Speciale A. The community pharmacist: perceived barriers and patient-centered care communication. *Int J Environ Res Public Health.* 2020;17(2):536. <https://doi.org/10.3390/ijerph17020536>.
 41. Weissenborn M, Haefeli WE, Peters-Klimm F, Seidling HM. Interprofessional communication between community pharmacists and general practitioners: a qualitative study. *Int J Clin Pharmacol.* 2017;39(3):495–506. <https://doi.org/10.1007/s11096-017-0450-6>.