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RESEARCH ARTICLE

Clinical impact of an interdisciplinary patient safety program for managing drug-related problems in a long-term care hospital

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Abstract *Background* Medication reviews intended to identify drug-related problems (DRPs) have been researched in primary care, acute care and nursing homes rather than in long-term care hospitals (LTCHs). *Objectives* To assess the clinical impact of an interdisciplinary pharmacotherapy quality improvement and patient safety program in elderly patients with polypharmacy admitted to an LTCH. *Setting* An interventional, longitudinal, prospective study was conducted in a Spanish LTCH *Method* A total of 162 elderly (≥ 70 years) patients with polypharmacy (≥ 5 medications) were included. Pharmacist conducted the pharmacotherapy follow-up of patients (reconciliation, pharmacotherapeutic optimization, educational interviews) from admission to discharge. Demographic, clinical and treatment-related variables were recorded. *Main outcome measured* Clinical impact of the program by DRP-based effectiveness and drug-related morbidity (DRM)-based safety indicators. *Results* 895 DRPs (median of 5 (1–23)) were identified in 153 (94.4%) patients. The most common DRPs were unnecessary drug (25.3%), dosage too high (24.9%) and a need for additional drug (24.8%). The most frequent pharmacotherapy recommendations were individualizing the dosage regimen (29.6%) and stopping (27.3%) or starting (21.9%) a drug. The mean implementation rate of pharmacotherapy recommendations was 90.9%. The effectiveness indicator revealed a 94.9% of prevented or resolved DRPs. The safety indicator showed an 89.3% of prevented or resolved DRM. Therefore, the program prevented or resolved 92.5% of adverse effects and 91.7% of suboptimal responses or therapeutic failures. *Conclusion* This interdisciplinary patient safety program seems to be a valuable approach to identify, prevent and resolve the high number of DRPs and potential DRM that elderly patients with polypharmacy admitted to an LTCH present.

Keywords Drug-related problem · Elderly · Interdisciplinary care · Long-term care · Pharmacotherapy · Quality improvement · Patient safety · Spain

Impact of practice

- The number of drug-related problems in elderly patients with polypharmacy, and admitted to a long term care hospital, is high.
- An interdisciplinary pharmacotherapy quality improvement and patient safety program implemented in a high-risk population is likely to be a valuable interdisciplinary approach to identify, prevent and resolve their drug-related problems.
- A structured, proactive pharmacotherapy follow up conducted by pharamacists in a long-term care hosdpital will reduce the number of drug-related problems and consequently the drug-related morbidity.

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Introduction

Based on current demographic trends, the percentage of population aged 65 or older in Europe, which is now at 18%, would rise to 28% in 2060 [1]. This progressive aging of our population causes a higher prevalence of chronic diseases and multiple comorbidities, leading to polypharmacy, complex treatments and medication inappropriate use. Therefore, an ageing population presents new challenges to health, long-term care, and welfare systems [2].

Interventions to improve care for elderly patients with polypharmacy should be planned with an interdisciplinary and multifactorial approach. Several studies have shown that interventions performed by coordinated interdisciplinary teams with a common goal improve various outcomes, such as reducing drug-related problems (DRPs), improving clinical outcomes and achieving cost savings [3–8]. The interdisciplinary team approach must take into account multiple factors such as multimorbidity, frailty, polypharmacy, multiple prescribers, pharmacokinetic and pharmacodynamic changes, functional decline, cognitive impairment, nutritional status, social situation and length of patient stay. These factors are known to increase the risk of inappropriate drug prescription and the development of DRPs in elderly patients [9–12].

DRPs have been defined as "an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes" [13]. DRPs comprise both non-preventable adverse drug events and medication errors. Otherwise, a potential consequence of DRPs is drug-related morbidity (DRM). It has been defined as "the incidence and prevalence of disease and illness or harm associated with the use (or lack) of drug therapy". DRM is the phenomenon of therapeutic malfunction, or failure of a therapeutic agent to produce a desired outcome [14].

A multitude of initiatives have been developed to assess the appropriateness of drugs prescribed in elderly patients. Explicit methods, which are developed from published reviews and expert opinions, are drug or disease oriented. Among the explicit methods are the START/STOPP criteria [15], the Beers criteria [16], the PRISCUS list [17] and the FORTA list [18]. Implicit methods use patient-specific information and published evidence to form judgments regarding medication appropriateness. The more commonly used implicit methods are the Medication Appropriateness Index [19] and the pharmacotherapy review focused on DRPs' detection, such as the IASER method® [20]. The latter classifies DRPs in four categories (indication, effectiveness, safety and compliance) according to the Cipolle and Strand methodology [14], and assesses patient outcomes in clinical, economical and humanistic terms [20]. Therefore, a combination of both explicit and implicit criteria would offer a more thorough assessment of medication appropriateness [21].

Elderly patients with polypharmacy and multimorbidity are often discharged from hospital after an acute admission and, transferred to other health care settings as primary care, home hospitalization units, nursing homes or long-term care hospitals (LTCH). Concretely, an LTCH is a hospital for patients with physical and/or psychiatric chronic disease and functional decline in activities of daily living, requiring health care which cannot be provided at home and, causing a prolonged period of hospitalization.

Furthermore, care transitions represent points of increased risk for these patients, which can result in suboptimal use of medications, confusions about the care plan, unintended lapses in treatment, and increased cost and use of resources [22]. Hence, medication reconciliation must be an integrated part of care transitions process in which health care professionals collaborate to improve medication safety [23]. Appropriate pharmacotherapy united with holistic assessment of patients' clinical and functional parameters and integration of skills from different healthcare professionals are needed to address medical complexity of older adults. A major challenge nowadays is to integrate valuable information obtained by combinations of these methods in a multifaceted, complete, and global approach targeting all potential factors involved in onset of DRPs [24].

Consequently, the identification, resolution and prevention of DRPs is one of the foci of healthcare professionals that are truly proactive and patient-focused, and contribute to positive patient outcomes. The patient, and not the drug product, must be the major focus of the pharmacist's decisions and actions [25]. However, patient-centred clinical pharmacy services are still poorly developed in much of Europe, especially in long-term care facilities.

Many studies have demonstrated that systematic medication reviews are effective in identifying and resolving DRPs in primary care [26–29], acute hospitals [5, 30] and nursing homes [4, 31–33]. Furthermore, there is increasing evidence that pharmacists' involvement in interdisciplinary teams has a positive influence on the quality of medication use and patient safety by rationalizing the pharmacotherapy and reducing medication errors and DRPs in these settings [5, 7, 32–39]. Nevertheless, as far as we know, no studies have been published that evaluate this impact in an LTCH.

Aim of the study

The aims of this study were to (1) evaluate the incidence and nature of identified DRPs, (2) examine the implementation rates of the associated pharmacotherapy recommendations made by pharmacist, and (3) assess the clinical impact of an interdisciplinary pharmacotherapy quality improvement

and patient safety program for identifying, preventing and resolving DRPs in elderly patients with polypharmacy admitted to an LTCH.

Ethics approval

The study was approved by the Clinical Research Ethics Committee of the Doctor Peset University Hospital (a reference acute care hospital). Written informed consent was obtained from all individual participants included in the study.

Method

Study population and setting

An interventional, longitudinal, prospective study was conducted at the Comprehensive Medical Unit (CMU) of a 125-bed non-teaching LTCH in Valencia (Spain), between October 2013 and July 2014, when the last included patient was discharged. The recruitment period extended from October 2013 to April 2014. The follow-up period lasted until January 2016 to check the vital status of patients. The CMU, comprising 75 single-patient rooms, was a hospital resource for patients with complex chronic disease requiring post-acute convalescent, medium-term rehabilitation care or palliative care. The median length of stay in the CMU was 42.5 days at the time of the study.

The inclusion criteria were elderly patients (≥ 70 years of age) with polypharmacy (≥ 5 medications at admission) discharged from acute hospitals and admitted to the CMU. Patients who had an expected length of stay < 48 h or were actively dying, or were not willing to participate in the study were excluded. During the recruitment period, a total of 285 possible candidates were admitted to the CMU. Of these, 123 patients were excluded if aged under 70 years (n = 99), took less than 5 medications (n = 7), were actively dying (n = 15), or if unwilling to participate in the study (n = 2). In total, 162 patients were included in the study. The median follow-up period was 2.5 (range: 0.1–27.1) months per patient.

The program was implemented in the CMU, in which a consensual stepwise protocol (see Appendix A) was followed by an interdisciplinary team of physicians, nurses, pharmacist, and other healthcare providers. One full-time clinical pharmacist with advanced training (e.g., hospital pharmacy residency and extensive work experience in pharmaceutical care) was involved in the program. Figure 1 shows the seven-step protocol applied in the program.

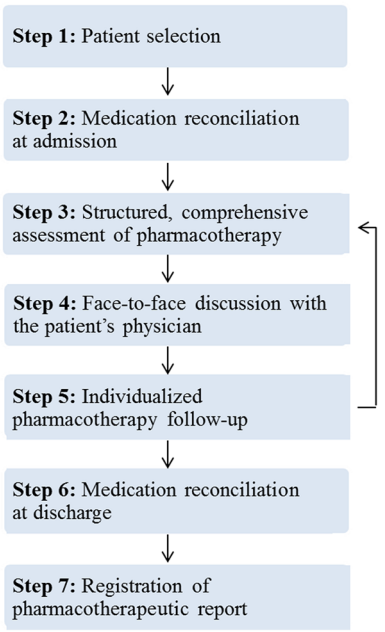

Fig. 1 Flowchart describing seven-step protocol of the interdisciplinary patient safety program

Outcome measures

The following variables were recorded:

1. Demographic-related: age, sex, weight, height, care objective defined by interdisciplinary team (post-acute convalescent, medium-term rehabilitation care or palliative care), hospitalizations in the last year.
2. Clinical-related: main diagnosis, pluripathology [40], comorbid conditions and patient comorbidity according to the Charlson Comorbidity Index (CCI) and the age-adjusted CCI [41] (the higher the score, the more likely the predicted outcome would result in mortality or higher resource use), physical problems, Barthel Index to evaluate functional status (it yields a score of 0–100, lower scores are associated with greater dependence), Pfeiffer questionnaire to assess cognitive status (scores of 0–10, score ≥ 3 indicates cognitive impairment), length of stay, in-hospital mortality.
3. Treatment-related: (a) Number and type of prescribed medications at admission, including medications for regular use and as needed, (b) DRPs: number, point of care (admission, follow-up or discharge), type (actual or potential -whether it reached or not the patient-, preventable or non-preventable, reconciliation-related), category (indication, effectiveness, safety and compliance), subcategory (needs additional drug therapy, unnecessary drug therapy, inappropriate medication, dosage too low, adverse drug reaction, dosage too high, and non-com-

pliance), consequences (DRM, cost-effectiveness and humanistic) and scoring of severity. The initial severity was documented considering the potential DRM and the final severity according to actual DRM, both rated from grades 1—would not cause harm or would cause reversible harm that would require monitoring—to 5—would cause lethal harm—, by agreement between pharmacist and physician according to IASER method® [20]. The Anatomical Therapeutic Chemical (ATC) Classification System was used to classify the drug involved in DRPs [42]. (c) Pharmacotherapy recommendations (PRs): number, type (individualization of dosage regimen, cessation of drug, initiation of drug, change of drug, initiation of therapeutic drug monitoring/clinical monitoring and change to more cost-effectiveness drug), impact (effectiveness, safety, cost-effectiveness and humanistic issues), level of acceptance (accepted, partially accepted, or rejected).

The implementation rate of PRs was defined as the percentage of PRs that were fully or partially implemented during the study period. A DRP was prevented or resolved if a PR was implemented and a desired pharmacotherapeutic outcome was achieved, thus avoiding inappropriate drug use according to clinical guidelines in elderly patients. It was confirmed by a clinical pharmacist through individualized follow-up of patient, by talking with the physician, or by checking the patient's clinical records.

The impact of the program was assessed in clinical terms by calculating effectiveness and safety indicators. The effectiveness indicator was the *percentage of prevented or resolved DRPs* defined as the percentage of prevented or resolved DRPs with respect to the total amount of DRPs identified by the program. The safety indicator was the *percentage of prevented or resolved DRM* defined as the percentage of prevented or resolved DRPs with final severity grade 1 with respect to the identified DRPs with initial severity grade ≥ 2, by selecting DRPs which potential consequences were DRM.

Statistical analysis

To determine the sample size for estimating the proportion of patients with DRPs, we considered a DRP percentage of 40.6% from a previously non-published pilot study conducted in the LTCH and a finite population of 571 patients admitted to the CMU the previous year. Using a 95% confidence level, a 5% two-sided alpha level and, no drop-out rate, a sample size of 162 patients was calculated. The recruitment period was closed when the calculated sample size was achieved.

Statistical analysis was performed using PASW version 17.0 for Windows (SPSS™, Inc., Chicago, IL, USA). The demographic and clinical variables of the patients, prescribed medications and registered information on individualized pharmacotherapeutic monitoring form were described using univariate analysis. The Shapiro–Wilks test with the evaluation of skewness and kurtosis was used to assess normality. Categorical variables were reported as frequencies (%) and quantitative variables, as mean and standard deviation (normally distributed data) or median and range (non-normally distributed data). Non-parametric tests (Spearman's ρ correlation coefficient, Mann–Whitney test or Kruskal–Wallis test, according to the type of variable) were used to evaluate any association with the number of DRPs per patient. The Wilcoxon signed-ranks test was used to examine the difference in severity of DRP after implementing PRs. A p value < 0.05 was considered as statistically significant.

Results

One hundred and sixty-two elderly patients with polypharmacy who met eligibility criteria were consecutively recruited with median of 2 (1–6) hospitalizations in the last year. Cancer (27.2%), cerebral vascular disease (21.6%) and pneumonia (13.6%) were the most common main diagnoses among included patients at admission. The 80.9% were 131 pluripathological patients with median 3 (2–6) pathologies. Patient demographic and clinical characteristics are presented in Table 1.

On admission, the mean (SD) number of medications was 12.2 (3.7), of which 9.6 (3.3) were for regular use. Major polypharmacy (≥ 10 medications prescribed) was presented in 72.8% of patients and, at least one sedative drug as antipsychotics (65.4%), benzodiazepines (61.1%) or opioids (45.7%) was taken by 93.8% of them.

Incidence and nature of identified DRPs

In total, 895 DRPs were identified in 153 patients (94.4% of patients had one or more DRPs) during the study period. Of these, 398 DRPs (44.5%) were detected on admission, 417 (46.6%) in the follow-up period and 80 (8.8%) at discharge. A median (range) of five (1–23) DRPs were identified per patient.

Six-hundred-and-thirty-two DRPs (70.6%) were potential and did not reach the patient and 751 (83.9%) were preventable. Regarding preventable DRPs, all were caused by medication errors occurring mostly in the process of selecting and/or prescribing a drug (n = 447, 59.5%) and on monitoring of therapy (n = 235, 31.3%). A total of 251 (28.0%) DRPs were detected during the medication reconciliation, 202 (80.5%) on admission and 49 (19.5%) at discharge.

Table 1 Demographics and clinical characteristics of patients (n = 162)

Patient characteristics	Value
Age, years, median (range)	80.3 (70.3–97.9)
Gender, female, n (%)	86 (53.1)
Weight, kg, mean (SD)	65.2 (13.2)
Height, meters, mean (SD)	1.64 (0.08)
Care objectives, n (%)	
Post-acute convalescent care	90 (55.6)
Palliative care	50 (30.9)
Medium-term rehabilitation care	22 (13.6)
Comorbid conditions, n (%)	
Hypertension	124 (76.5)
Moderate-severe renal disease (eFGR < 60 ml/min/1.73 m^2)	87 (53.7)
Dyslipidaemia	84 (51.9)
Dementia	78 (48.1)
Congestive heart failure	71 (43.8)
Diabetes mellitus	70 (43.2)
Cancer	66 (40.7)
Cerebrovascular disease	55 (34.0)
Chronic pulmonary disease	49 (30.2)
Physical problems, n (%)	
Immobility	136 (84.0)
Pain	118 (72.8)
Malnutrition	109 (67.3)
Constipation	94 (58.0)
Dysphagia	93 (57.4)
Pressure ulcers	90 (55.6)
Multidimensional assessments	
CCI score, median (range)	5 (1–13)
Age-adjusted CCI, median (range)	8 (4–16)
Barthel index ≤ 20 points, n (%)	137 (84.6)
Pfeiffer score, median (range)	4.5 (0–10)
Length of stay, days, median (range)	42.5 (3–160)
In-hospital mortality, n (%)	83 (51.2)

CCI charlson comorbidity index, *eGFR* estimate glomerular filtration rate, *n* number of patients, *SD* standard deviation, % percentage

The most common category of DRP was indication (n = 448, 50.1%), followed by safety (n = 293, 32.7%), effectiveness (n = 148, 16.5%) and compliance (n = 6, 0.7%). Table 2 describes the frequency of DRPs in each of the subcategories and lists the three most frequent drug classes involved in them.

The most frequent potential consequences of DRPs were DRM (n = 764, 85.4%), followed by cost-effectiveness (n = 123, 13.7%) and humanistic (n = 8, 0.9%) issues. Considering DRM, the most common types were adverse effects (n = 399, 52.2%) and suboptimal responses to treatment or therapeutic failures (n = 264, 34.6%).

Overall, 56.8% (n = 508) of DRPs were classified as initial severity grade 2 (reversible harm that would require change of therapy), followed by 22.5% (n = 201), as grade 3 (reversible harm that would require additional therapy or increase length of stay) and 20.8% (n = 186), as grade 1 (would not cause harm or would cause reversible harm that would require monitoring). No potentially lethal harm was detected in our study. Table 3 summarizes the ten drug classes most commonly involved in detected DRPs.

Patients requiring post-acute convalescent ($p < 0.001$) with a higher number of medications at admission ($p = 0.023$) and a higher age-adjusted CCI ($p = 0.034$) were found to present higher number of DRPs. Patients with longer hospital stay ($p < 0.001$) and discharged from LTCH ($p < 0.001$) had also higher number of DRPs.

Pharmacotherapy recommendations (PRs)

During the study period, 963 PRs were made by the pharmacist in 93.8% (n = 152) of patients to prevent or resolve 835 DRPs (93.3% of all detected DRPs). The most common PRs were individualizing the dosage regimen (27.5%), followed by stopping a drug (27.3%) and starting a drug (21.9%). The mean implementation rate of PRs was 90.9%. An overview of all proposed PRs and their implementation rates can be found in Table 4.

The PRs had impact on safety, effectiveness, cost-effectiveness and humanistic issues in 46.6% (n = 417), 41.0% (n = 367), 26.3% (n = 235) and 4.8% (n = 43) of identified DRPs, respectively.

Among the 963 PRs, 875 (90.9%) were accepted and implemented by healthcare professionals, mostly by physicians in 98.9% (n = 865). Of these, 89.1% (n = 780) were accepted, while 10.9% (n = 95) were partially accepted during the study period. Only 9.0% (n = 87) of PRs were rejected, being 54.0% (n = 47) of these PRs justified by the physician. A 37.5% (n = 15) and 35.0% (n = 14) of non-justified PRs were safety and cost-effectiveness-related issues, respectively.

After implementing PRs, the most frequent (n = 819, 91.5%) final severity of DRPs was grade 1 (did not cause harm or caused reversible harm that required monitoring). A Wilcoxon signed rank test revealed a statistically significant reduction in severity of DRPs ($z = -23.4$, $p < 0.001$). Figure 2 illustrates the comparison between initial and final severity of the detected DRPs by the program.

Clinical impact of the program

As a result of the program, of the 895 identified DRPs, 589 (65.8%) DRPs were prevented and 260 (29.1%) were resolved. The effectiveness indicator revealed a 94.9% of prevented or resolved DRPs. Considering potential

Table 2 Subcategories of identified DRPs and the three drug classes (ATC therapeutic subgroups) most frequently involved

Classification of DRP	n (%)	Drug classes most frequently involved in the DRPs listed	n
Indication			
Unnecessary drug therapy	226 (25.3)	Antibacterials for systemic use (J01)	32
		Psycholeptics (N05)	17
		Cough and cold preparations (R05)	17
Need for additional drug therapy	222 (24.8)	Antithrombotic agents (B01)	22
		Antianemic preparations (B03)	21
		Drugs for acid related disorders (A02)	21
Safety			
Dosage too high	223 (24.9)	Antibacterials for systemic use (J01)	89
		Cardiac therapy (C01)	34
		Antithrombotic agents (B01)	13
Adverse drug reaction	70 (7.8)	Psycholeptics (N05)	12
		Psychoanaleptics (N06)	12
		Drugs for functional gastrointestinal disorders (A03), and for constipation (A06)	6
Effectiveness			
Dosage too low	100 (11.2)	Antithrombotic agents (B01)	19
		Antibacterials for systemic use (J01)	13
		Cardiac therapy (C01)	8
Inappropriate medication	48 (5.4)	Agents acting on the RA system (C09)	11
		Antibacterials for systemic use (J01)	9
		Drugs for acid related disorders (A02)	5
Compliance			
Non-compliance	6 (0.7)	Ophthalmologicals (S01)	3
		Intestinal antiinfective agents (A07)	2
		Thyroid therapy (H03)	1
Total	895 (100)		

ATC anatomical therapeutic chemical, *DRP* drug-related problem, % percentage, *RA* renin-angiotensin

Table 3 The 10 drug classes (ATC therapeutic subgroups) most commonly involved in detected DRPs

Therapeutic subgroups (ATC classification)	Number (%) of DRPs
Antibacterials for systemic use (J01)	150 (16.6)
Antithrombotic agents (B01)	74 (8.2)
Cardiac therapy (C01)	54 (6.0)
Psycholeptics (N05)	53 (5.9)
Drugs for acid related disorders (A02)	52 (5.8)
Antianemic preparations (B03)	45 (5.0)
Psychoanaleptics (N06)	33 (3.7)
Agents acting on the renin-angiotensin system (C09)	31 (3.4)
Diuretics (C03)	29 (3.2)
Drugs for obstructive airway diseases (R03)	28 (3.1)
Total	549/895 (61.3)

ATC anatomical therapeutic chemical, *DRP* drug-related problem, % percentage

consequences of DRPs, the safety indicator showed an 89.3% of prevented or resolved DRM.

Among the 399 potential (n = 284) or actual (n = 115) identified adverse effects, 369 (92.5%) were prevented (n = 261) or resolved (n = 108) and among the 264 potential (n = 185) or actual (n = 79) identified suboptimal responses or therapeutic failures, 242 (91.7%) were also prevented (n = 169) or resolved (n = 73).

Table 4 Prevalence and implementation rate of associated pharmacotherapy recommendations with identified DRPs by the program. The three drug classes (ATC therapeutic subgroups) most frequently involved in pharmacotherapy recommendations

Type of pharmacotherapy recommendation	n (%)	Implementation rate (%)	Drug classes most frequently involved	n
Individualization of dosage regimen	285 (29.6)	92.6	Antibacterials for systemic use (J01)	59
			Cardiac therapy (C01)	38
			Antithrombotic agents (B01)	32
Drug cessation	263 (27.3)	90.0	Antibacterials for systemic use (J01)	67
			Antianemic preparations (B03)	16
			Psycholeptics (N05)	16
			Cough and cold preparations (R05)	16
Initiation of drug	211 (21.9)	91.0	Antithrombotic agents (B01)	20
			Drugs for acid related disorders (A02)	19
			Antianemic preparations (B03)	19
Drug change	82 (8.5)	89.0	Agents acting on the RA system (C09)	12
			Antibacterials for systemic use (J01)	10
			Psycholeptics (N05)	9
Initiation of therapeutic drug monitoring/clinical monitoring	70 (7.3)	91.4	Cardiac therapy (C01)	25
			Antibacterials for systemic use (J01)	20
			Antianemic preparations (B03)	9
Change to a more cost-effective drug	52 (5.4)	92.3	Antithrombotic agents (B01)	10
			Drugs for acid related disorders (A02)	8
			Antibacterials for systemic use (J01)	5
Total	963 (100)			

ATC anatomical therapeutic chemical, *DRPs* drug-related problems, *n* number of pharmacotherapy recommendations, % percentage

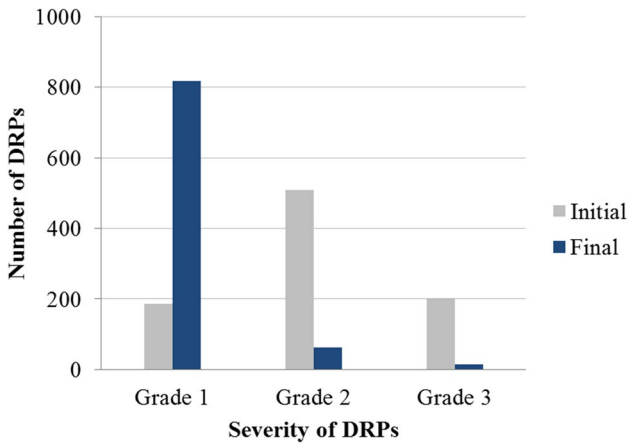

Fig. 2 Comparison of initial and final severity of the detected DRPs by the program. *DRPs* drug-related problems

Discussion

DRPs are well known in patients attended in different clinical settings such as primary care [26, 28, 29], acute-care hospitals [5, 37] and nursing homes [4, 31, 34]. However, to the best of our knowledge, this is the first interventional prospective study in Europe that assesses the number and the nature of DRPs, associated PRs and the clinical impact of an interdisciplinary patient safety program for identifying, preventing and resolving DRPs in elderly patients with polypharmacy admitted to an LTCH.

Our study patients constituted a complex population with a high level of comorbidity and pluripathology combined with functional and cognitive deterioration, high complexity of the treatment and high in-hospital mortality. Based on the high incidence of DRPs and the high implementation rate for solving these, clinical pharmacists should be integrated in interdisciplinary teams to participate in conducting a structured comprehensive assessment of pharmacotherapy and individualized pharmacotherapy follow-up during hospital stay in LTCHs, as our study suggest.

DRPs were identified in nearly 95% of the included patients, with a median of 5 (1–23) DRPs per patient. This number is in the upper limit of the range of 2–5 DRPs found for these patients in research settings [4, 5, 28, 32, 37]. DRPs were identified not only at admission, but also during the follow-up period and at discharge. Moreover, approximately nine hundred DRPs were identified of whom most had the potential to cause DRM. It might be explained by the selection of patients at risk for developing DRPs and pharmacotherapy follow-up of patients from admission to discharge.

The most common category of DRP was indication (50.1%), followed by safety (32.7%). Moreover, in line with some nursing home [4, 32] and primary care [26, 28] studies the most commonly identified DRPs were unnecessary drug therapy and dosage too high, in contrast with acute hospitals, whose most common DRPs are drug interactions and untreated indications [5, 37, 38]. This is possibly explained by the different approach in acute hospital admission, more focused on looking for a solution for the acute clinical situation leading to hospitalization. Additionally, in the LTCH most interactions were considered of minor clinical importance or risk–benefit analyses were justified by the clinical characteristics of these elderly patients with polypharmacy.

Medication reconciliation is a key process required to improve patient safety and outcomes in care transitions, but pharmacist are often not involved in the discharge planning process [23]. There is a need for increased use of pharmacists as part of the patient care team during a patient's care transition [22]. In our study, almost a third of DRPs were detected through the medication reconciliation during care transitions, mostly at admission. Consequently, it reinforces the importance of medication reconciliation as a crucial part of the program to bridge the gaps in continuity of patient care, and further ensure a comprehensive medication history of patients.

In agreement with our results, a systematic review from 2016 [12] revealed that the most frequent types of drugs reported to be associated with DRPs leading to a hospital pharmaceutical intervention are intravenous antimicrobials, anticoagulants and thrombolytics, cardiovascular drugs, and central nervous system drugs. Moreover, factors such as post-acute convalescent care, multiple comorbidities, polypharmacy and, prolonged length of stay were associated with a greater incidence of DRPs, which is consistent with previous findings [12, 28, 43]. Therefore, by giving more attention to these factors, which cause a high number of DRPs, the number of DRPs may decrease. Nevertheless, optimal management of complex medication regimens in older adults with numerous comorbidities remains a challenge for health care professionals due to the still limited evidence for effective interventions. In most cases, polypharmacy and multi-morbidity can be managed through an interdisciplinary approach as our study shows.

A secondary point of emphasis for this study is to examine the implementation rates of the proposed PRs to prevent or resolve DRPs. Over 91% of PRs were accepted and implemented by healthcare professionals. The observed high implementation rate of PRs were consistent with the implementation rates described in the literature in hospital settings [37, 39], but higher than in community [28, 29] and nursing home [4, 28, 34] settings. These differences could be justified, mainly, by direct communication "face-to-face" with the interdisciplinary team when PRs were suggested and pharmacist' experience in conducting comprehensive medication assessment with a systematic methodology. Both were crucial to improve implementation rates. Although, it was not an aim of this study to measure time spent on each activity of the program, one full-time pharmacist worked directly with healthcare professionals and each patient and/or primary caregiver to individually adjust dosage regimens, discontinue unnecessary medications, add medications to prevent illness, and personally explain how to properly use each medication during LTCH stay. In this sense, many opportunities were found to improve pharmacotherapy quality and patient safety in the included patients admitted to an LTCH.

According to other nursing home studies [4, 32], the most common PRs were *individualization of dosage regimen* and *drug cessation*. Particularly, it was more frequently patients required their drug dosages to be decreased in order to provide safety therapy. Moreover, after implementing PRs, a reduction in severity of DRPs was obtained and final severity of mostly DRPs was grade 1 that did not cause harm or caused reversible harm that required monitoring. These findings suggest that pharmacists not only can effectively identify DRPs but also appropriately manage DRPs to solve and prevent them, and subsequently, to solve and prevent potentially associated DRM. The small percentage of rejected PRs by physicians were justified by different criteria about the clinical situation (e.g. the therapeutic objectives, life expectancy) of the patient or the non-willingness to modify chronic treatments indicated by other specialist physician.

In the present study, pharmacist intervention integrated in an interdisciplinary team to develop the program achieved a high clinical impact in elderly patients with polypharmacy admitted to an LTCH. This impact, confirmed by effectiveness and safety indicators, permitted to prevent or resolve most of identified DRPs (94.9%), and consequently, DRM (89.3%). This great impact might be partly explained by the integration of pharmacist. Thus, the best results are obtained when the pharmacist reviews pharmacotherapy actively, in a structured way, and within the context of an interdisciplinary approach [4]. This sum of efforts is essential in case of elderly and patients with polypharmacy, who typically present complex treatment regimens, multiple comorbidities, and other factors of risk of DRM related with patients, their setting, and the health system [44]. Because of this, the role of pharmacists in optimizing geriatric pharmacotherapy is significantly increasing, and their involvement in interdisciplinary cooperation using a patient-centred approach is being critically important in different settings of care [33, 45].

The strength of this study is the use of a prospective approach and an interdisciplinary and multifactorial intervention conducted in real-life context. The seven-step protocol designed to improve the pharmacotherapy quality

and patient safety, included medication reconciliation at admission and discharge, structured comprehensive assessment of pharmacotherapy by using a combination of both explicit and implicit criteria, face-to-face discussion with the patient's physician and individualized pharmacotherapy follow-up during hospital stay. Based on the results shown, our program seems to be helpful to identify, prevent or resolve DRPs and DRMs among these high-risk patients recently discharged from acute hospitals, and consequently, improve procedures in LTCHs.

There were limitations to the present study that should be considered when interpreting the findings. First limitation is the lack of a control group and a randomized design. In our study, patients were their own control group before the interventions of the interdisciplinary team and the intervention of pharmacist was not randomized. A control group would have prevented the main confounding factor, being detection and resolution of DRPs by physicians themselves, without the implementation of the program. Nevertheless, a control group would have caused an ethical conflict in the LTCH, so it was discarded. Second, this study uses process outcomes instead of final clinical endpoints. In the program, DRP-based effectiveness indicator and DRM-based safety indicator were used as endpoint measurements of clinical impact. Yet, more patient-relevant endpoints such as drug-related readmissions, time-to-readmission, possible cost-savings or humanistic outcomes should be measured in further studies. Third, the key limitation of our study was that it was performed on a single LTCH with unique population. Our findings are of interest as a description of the types of DRPs and associated PRs most often detected in elderly patients with polypharmacy of an LTCH and show a trend that should be confirmed on a large scale. Hence, to strengthen these findings, a multicentre future study could involve other medical units from other LTCH.

Conclusion

The patient safety program identified a high incidence of DRPs, especially indication and safety-related DRPs, in elderly patients with polypharmacy admitted to an LTCH. The majority of PRs were accepted and implemented by healthcare professionals. This high level of the PRs' acceptance demonstrates that the interdisciplinary team members recognized the ability of pharmacists to provide responsible, accurate, and appropriate pharmaceutical care to patients admitted at LTCH. This interdisciplinary program also showed a high clinical impact by preventing or resolving more than 90% of adverse effects and suboptimal responses or therapeutic failures.

The proactive participation of pharmacists in these coordinated interdisciplinary teams, conducting medication reconciliation at admission and discharge, structured comprehensive assessment of pharmacotherapy, face-to-face discussion with the patient's physician and individualized pharmacotherapy follow-up from admission to discharge is useful to identify, prevent and resolve DRPs, and consequently DRM, allowing the impact of the program to be maximized in this high-risk population.

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