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SHORT COMMUNICATION

Prevention of Inappropriate Prescribing in Hospitalized Older Patients Using a Computerized Prescription Support System (INTERcheck®)

Simona Ghibelli · Alessandra Marengoni · Codjo D. Djade · Alessandro Nobili · Mauro Tettamanti · Carlotta Franchi · Silvio Caccia · Flavio Giovarruscio · Andrea Remuzzi · Luca Pasina

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Abstract

Background Polypharmacy is very common among older adults and can lead to inappropriate prescribing, poor adherence to treatment, adverse drug events and the prevalence of potential drug–drug interactions (DDIs). Electronic prescription database software may help to prevent inappropriate prescribing and minimize the occurrence of adverse drug reactions. INTERcheck® is a Computerized Prescription Support System (CPSS) developed in order to optimize drug prescription for elderly people with multimorbidity.

Objectives The objectives of this study were (i) to evaluate the applicability of INTERcheck® as a means of reviewing the pharmacological profiles of elderly patients hospitalized in an acute geriatric ward in Northern Italy; and (ii) to evaluate the effectiveness of INTERcheck® in reducing potentially inappropriate medications (PIMs), potentially severe DDIs and the anticholinergic burden in daily practice.

Methods Two samples of elderly patients (aged 65+ years) hospitalized in a geriatric ward in Italy were enrolled throughout 2012. During the first (observation) phase, medications prescribed to 74 patients at admission and discharge were analyzed with INTERCheck® without any kind of interference based on information obtained from the software. During the second (intervention) phase, the treatment of 60 patients was reviewed and changed at discharge according to INTERCheck® suggestions.

Results In the observational period, the number of patients exposed to at least one PIM remained unchanged on both admission ($n = 29$; 39.1 %) and discharge ($n = 28$; 37.8 %). In the intervention phase, 25 patients (41.7 %) were exposed to at least one PIM at admission and 7 (11.6 %) at discharge ($p < 0.001$). The number of patients exposed to at least one potentially severe DDI decreased from 27 (45.0 %) to 20 (33.3 %), although the difference was not statistically significant ($p = 0.703$), while the number of new-onset potentially severe DDIs decreased from 37 (59.0 %) to 9 (33.0 %) [$p < 0.001$].

Conclusions The use of INTERCheck® was associated with a significant reduction in PIMs and new-onset potentially severe DDIs. CPSSs combining different prescribing quality measures should be considered as an important strategy for optimizing medication prescription for elderly patients.

Electronic supplementary material The online version of this article (doi:10.1007/s40266-013-0109-5) contains supplementary material, which is available to authorized users.

S. Ghibelli · A. Marengoni
Geriatric Unit, Spedali Civili, Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy

C. D. Djade · A. Nobili · M. Tettamanti · C. Franchi · S. Caccia · F. Giovarruscio · A. Remuzzi · L. Pasina (✉)
Laboratory for Quality Assessment of Geriatric Therapies and Services, Drug Information Service for the Elderly, IRCCS, Istituto di Ricerche Farmacologiche "Mario Negri", Via Giuseppe La Masa, 19, 20156 Milan, Italy
e-mail: luca.pasina@marionegri.it

1 Introduction

Polypharmacy is very common among older adults and is often adopted as a strategy for alleviating symptoms, reducing disease-related problems and improving quality of life [1–3]. However, it may entail inappropriate prescribing, poor adherence, adverse drug events, and high prevalence of drug–drug interactions (DDIs) [4–11]. Inappropriate prescribing is highly prevalent in older

people and has been found to be associated with adverse drug reactions (ADRs), acute hospitalization and health resource utilization [12]. In order to reduce the prescription of drugs with a high risk of adverse side effects in elderly patients [13], different sets of explicit criteria for potentially inappropriate medications (PIMs) have been developed; the most widely used are the Beers criteria [14]. In addition, there is strong evidence that certain drugs, especially those with anticholinergic properties, can cause adverse conditions, such as delirium, falls, loss of independence and worsening cognitive impairment [15–25]. Among older subjects, the use of anticholinergic drugs has also been associated with impaired physical performance and functional status [26]. These adverse health events are mainly linked to age-related changes such as decrease in cholinergic neurons or receptors in the brain, reduction in hepatic and renal clearance of drugs and increase in blood–brain barrier permeability, particularly during acute physical illness [27, 28]. Indeed, the effect of anticholinergic drugs on cognitive and physical performance may be due to the cumulative effect of multiple medications with modest antimuscarinic effects [29]. Polypharmacy and aging have also been identified as independent risk factors for potential DDIs [4, 30] because of the age-related physiological changes that affect the pharmacokinetic and pharmacodynamic properties of medications. The most important age-related change affecting drug excretion is the decrease in renal drug clearance [31]. Changes in pharmacodynamic responses also contribute to susceptibility to DDIs [32] and decreased homeostasis which may result in greater sensitivity to ADRs [33]. A review of recent literature shows that DDIs were responsible for 4.8 % of hospital admissions in the elderly [34]. Integrated software with electronic prescription databases and the involvement of a clinical pharmacist within multidisciplinary geriatric teams may help to highlight inappropriate prescribing and minimize the occurrence of ADRs [35–37]. Computerized Prescription Support Systems (CPSSs) have been developed for the general adult population but, to date, none has been developed to specifically address prescribing in older people with altered pharmacokinetics and pharmacodynamics and complex co-morbidity [12]. INTERcheck® is a CPSS developed by Istituto di Ricerche farmacologiche Mario Negri in order to optimize drug prescription in elderly people.

The aims of the present study were, first, to evaluate the applicability of INTERcheck® as a means of reviewing the pharmacological profiles of elderly patients hospitalized in an acute geriatric ward in Northern Italy; and second, to evaluate the effectiveness of INTERcheck® in reducing the use of PIMs, potentially severe DDIs and anticholinergic burden in daily practice.

2 Methods

2.1 Computerized Prescription Support System

A computer-based application (INTERCheck®) was developed in order to collect, store and automatically provide drug information in order to reduce or prevent inappropriate prescriptions. INTERCheck® is stand-alone software developed in Java with an embedded database that stores information on explicit criteria for PIMs, anticholinergic load, potential DDIs, dose adjustment in cases of renal impairment and the calculation of the GerontoNet ADR Risk Score. The latter is a method used to identify elderly patients who are at increased risk of ADRs. The variables associated with ADRs, and included in the risk score, were four or more co-morbid conditions (1 point), heart failure (1 point), liver disease (1 point), number of daily drugs (0–4 points according to the number of drugs), previous ADR (2 points) and renal failure (1 point). The range of the score was 0–10 points. A cut point between 3 and 4 may be used to identify patients at high risk for ADRs [38]. An illustrative case of a simulated patient showing the output of INTERCheck® is reported in the electronic supplementary material (see S1). In addition, INTERCheck® keeps track of all user instances in the database by storing alerts and risks detected in each drug prescription. The drug database and all of the other related information described above is automatically updated using an Internet connection.

2.2 Data Collection

The study was conducted in the geriatric ward of the Civili Hospital in Brescia, an academic urban hospital with 1,500 in-patient beds. The Civili Hospital is the main hospital of the city, evaluating approximately 250 patients per day in the emergency room. In emergency situations, elderly persons are admitted to the nearest of the city's three hospitals. Thus, subjects admitted to the Civili Hospital may be considered representative of the ill elderly population in its specific catchment area. The hospital's Geriatric Unit (20 in-patient beds) discharges about 700 patients per year. The study design consisted of two phases with a duration of 2 months each, one observational and one experimental. During the 'observation phase' (April–May 2012), 74 patients aged 65 years or over were consecutively included. During the second 'intervention' phase (June–July 2012), 60 subjects were included. The only exclusion criteria were severe malignancy (life expectancy less than 6 months) or terminal illness. During the observation phase, treatment received by patients both at admission and discharge was analyzed with INTERCheck® without any kind of interference based on information

provided by the software, while during the intervention phase, medications prescribed on admission were reviewed and changed at discharge according to INTERCheck® indications, in order to reduce PIMs, DDIs and anticholinergic burden. Participation was voluntary and all patients signed an informed consent form. The study was approved by the hospital's Ethics Committee.

All medications were encoded according to the Anatomical Therapeutic Chemical (ATC) classification system [39], which groups drugs according to the organ or system on which they act and/or their therapeutic and chemical characteristics. During hospitalization, a multidimensional geriatric assessment was performed. Multimorbidity was assessed using the Cumulative Illness Rating Scale (CIRS) [40], according to which diseases and impairment of major organ systems are rated on a scale from 1 (no impairment) to 5 (life-threatening impairment). A severity index and comorbidity index are thus derived. The comorbidity index is calculated according to the number of organ systems affected by a severity of at least 3, a score associated with a moderate impairment of major organ systems.

Functional status was assessed according to the Barthel Index, which assesses independence in basic activities of daily living [41] and yields a score of 0–100. Higher scores are associated with greater independence.

Cognitive status was evaluated according to the Mini-Mental State Examination (MMSE) [42], a widely used test of cognitive function among the elderly that includes tests of orientation, attention, memory, language and visual-spatial skills. Scores range from 0 to 30, and a score of <24 is the generally accepted cutoff indicating the presence of cognitive impairment.

2.3 Potentially Inappropriate Medications (PIMs)

Explicit criteria for PIMs are usually developed from literature reviews, expert opinion and consensus methodology. They usually consist of lists of drugs or drug classes and dosages that are known to cause harmful effects. In 1991, Beers et al. published the first set of explicit criteria for inappropriate prescribing in older patients. These criteria, based on consensus opinion, were updated in 1997, 2003 and 2012 [43], and can be applied to all patients aged 65 years and over irrespective of place of residence. The explicit criteria available in INTERcheck® are the Beers criteria (recently updated in the 2012 version). For the purpose of this study, the 2003 Beers criteria were used.

2.4 Anticholinergic Drugs

Several drugs have anticholinergic properties and different scales have been proposed to classify medications according to their anticholinergic effects [44–46]. The Anticholinergic Cognitive Burden (ACB) Scale [46] is a practical tool used to identify the severity of any anticholinergic effect on cognition. Drugs with potential anticholinergic effects are defined as those with serum anticholinergic activity or in vitro affinity for muscarinic receptors but without known clinically relevant cognitive effects (ACB score = 1). Drugs with established, clinically significant cognitive effects are considered positively anticholinergic (ACB score = 2 or 3). INTERcheck® calculates the drug-related anticholinergic burden of each patient using the sum score of each anticholinergic medication included in the ACB scale.

2.5 Potential Drug–Drug Interactions (DDIs)

Potential DDIs were analyzed by a computerized system, using the drug interaction database developed by the Istituto di Ricerche farmacologiche Mario Negri, which has been previously validated and described in detail [47, 48]. In brief, all drug interactions are classified in terms of clinical significance as severe, moderate or minor, taking into account 'potential' clinical outcomes, type, quality and relevance of supporting clinical and pharmacological documentation. Each potential DDI is classified in terms of clinical significance as severe (the drug combination should usually be avoided or may potentially have serious clinical consequences, such as severe adverse effects or lack of clinical effects; close monitoring is required), moderate (the drugs may be combined, the precipitant drug may modify the effect of the object drug, but the resulting effect can be controlled by adjusting the individual dose and/or by controlling drug plasma concentration) and minor (the drug combination probably has no clinical significance or has not been completely assessed).

2.6 Statistical Analysis

The sociodemographic and clinical characteristics of the two samples of patients and medication prescribed to them were described using univariate analysis (with mean or percentage values). 95 % confidence intervals (CI) were calculated for means and proportions. Differences were tested using the Student *t* test for continuous variables and the Pearson Chi-square test for dichotomous and unordered categorical data. All statistical calculations were performed with Stata software release 12 (StataCorp LP, College Station, TX, USA). The number of patients to be recruited for the present study was chosen on the assumption that the percentage reduction in patient numbers from the intervention to the observation phase would be at least 15 % (specifically, 5 % in patients recruited in the observation phase as opposed to 20 % in patients recruited in the intervention phase). The significance criterion (alpha) was

set at 0.05, 2-tailed. With the proposed sample size of 75 and 75 for the two groups, the statistical power of the study is 80.0 %.

3 Results

Table 1 describes the characteristics of the two populations enrolled. Sixty-five percent of the first sample were women, with a mean age of 81.3 years. Around 46 % of patients still lived with their spouse; however, 40.5 % of them needed a 24-h caregiver. Their Barthel Index mean score was 76.8, indicating moderate functional dependency. Their global health status, as indicated by the mean Comorbidity Index Score of 4.6, was poor, while their mean MMSE score was 22.3. The mean number of drugs for each patient was 7.4 (range 6.7–8.1) on admission and 8.5 (range 7.8–9.2) at discharge. The GerontoNet ADR Risk Score was 4.2 (range 3.6–4.8) at admission and 4.9 (range 4.3–5.5) at discharge (Table 1).

Women accounted for 58.3 % of patients in the second sample. Their mean age was 81 years; 36.7 % of patients lived with their spouse and 48.3 % of them needed a caregiver. Their mean Barthel Index Score was 76, while their mean MMSE score was 22.4. Finally, their mean Comorbidity Index Score was 4.2. The mean number of prescribed drugs was 7.0 (range 6.3–7.8) at admission and 7.0 (range 6.3–7.7) at discharge. The GerontoNet ADR Risk Score was 4.1 (range 3.4–4.8) at admission and 4.1 (range 3.4–4.8) at discharge (Table 1).

The review of each patient's medication using INTERcheck® took approximately 5 min.

The length of patients' hospital stays was similar in the observation phase (mean ± SD 10.1 days ± 6.1) and intervention phase (mean ± SD 10.4 days ± 7.0; $p = 0.84$).

3.1 Prevalence of PIMs

In the observation phase, 29 (39.1 %) patients were exposed to at least one PIM on admission and 28 (37.8 %) at discharge; the mean number of PIMs per patient was similar on admission (0.5) and at discharge (0.4). In the intervention phase, 25 (41.7 %) patients were exposed to at least one PIM at admission, and 7 (11.6 %) at discharge ($p < 0.001$). Similarly, the mean number of PIMs per patient significantly decreased at discharge from 0.5 to 0.1 ($p < 0.001$). The most frequent PIMs at both hospital admission and discharge are shown in Table 2.

3.2 Potential DDIs

In the observation phase, on hospital admission 67 (90.5 %) patients were exposed to at least one potential DDI. Of these, 64 (86.5 %) were exposed to at least one potentially moderate or severe DDI and 28 (37.8 %) to at least one potentially severe DDI. Of all 301 potential DDIs, 46 (15.3 %) were severe and 174 (57.8 %) moderate. The mean number of potential DDIs per patient at admission was 4.1 (range 0–14). At discharge, 65 patients (87.8 %) were still exposed to at least one potential DDI, 63 (85.1 %) patients to at least one potentially moderate or severe DDI and 40 (54 %) to at least one potentially severe DDI. Of all of the 330 potential DDIs, 63 (19.1 %) were severe and 164 (49.7 %) moderate. Moreover, 37 (59.0 %) potentially severe DDIs were created during hospitalization. The mean number of potential DDIs per patient at discharge was 4.5 (range 0–17).

In the intervention phase, at admission, 51 (85.0 %) patients were exposed to at least one potential DDI. Of these, 44 (73.3 %) were exposed to at least one potentially moderate or severe DDI, and 27 (45.0 %) to at least one potentially severe DDI. Of all 223 potential DDIs, 37

Table 1 Characteristics of the two samples of elderly patients

Variable	Observation phase		Intervention phase	
	Mean or %	95 % CI	Mean or %	95 % CI
Female (%)	64.8	53.7–76.0	58.3	45.5–71.1
Age (mean)	81.3	79.8–82.8	81.1	79.4–82.7
Living with spouse (%)	45.9	24.1–49.2	36.7	24.1–49.2
Needs caregiver (%)	40.5	29.1–52.0	48.3	35.3–61.3
Barthel Index Score (mean)	76.8	70.3–83.3	76.0	69.4–82.7
Comorbidity Index Score (mean)	4.6	4.2–5.0	4.2	3.8–4.6
MMSE score (mean)	22.3	20.8–23.8	22.4	21.0–23.8
WBC, ×1,000/μL (mean)	7.1	6.6–7.6	6.8	6.2–7.4
Hb, g/dL (mean)	11.5	11.2–11.8	11.8	11.4–12.1
Creatinine, mg/dL (mean)	1.1	1.0–1.3	1.3	0.9–1.7
Glycemia, mg/dL (mean)	114.2	103.3–125.1	105.8	98.6–113.0
Albumin, g/dL (mean)	3.4	3.3–3.5	3.3	3.2–3.4

Hb hemoglobin, *MMSE* Mini-Mental State Examination, *WBC* white blood cell count

Table 2 Most frequent potentially inappropriate medications (PIMs) at hospital admission and discharge

PIMs	Observation phase [n (%)]		Intervention phase [n (%)]	
	Admission	Discharge	Admission	Discharge
High-dose short-acting benzodiazepines[a]	12 (16.2)	16 (21.6)	12 (20)	4 (6.7)
Ticlopidine	12 (16.2)	4 (5.4)	10 (16.7)	0
Digoxin >0.125 mg/day[b]	3 (4.1)	4 (5.4)	6 (10)	1 (1.7)
Doxazosin	3 (4.1)	1 (1.3)	3 (5)	1 (1.7)
Clonidine	3 (4.1)	1 (1.3)	1 (1.7)	0

[a] Daily dose exceeding: lorazepam 3 mg, oxazepam 60 mg, alprazolam 2 mg, temazepam 15 mg, zolpidem 5 mg, triazolam 0.25 mg

[b] With the exception of patients with supraventricular arrhythmias

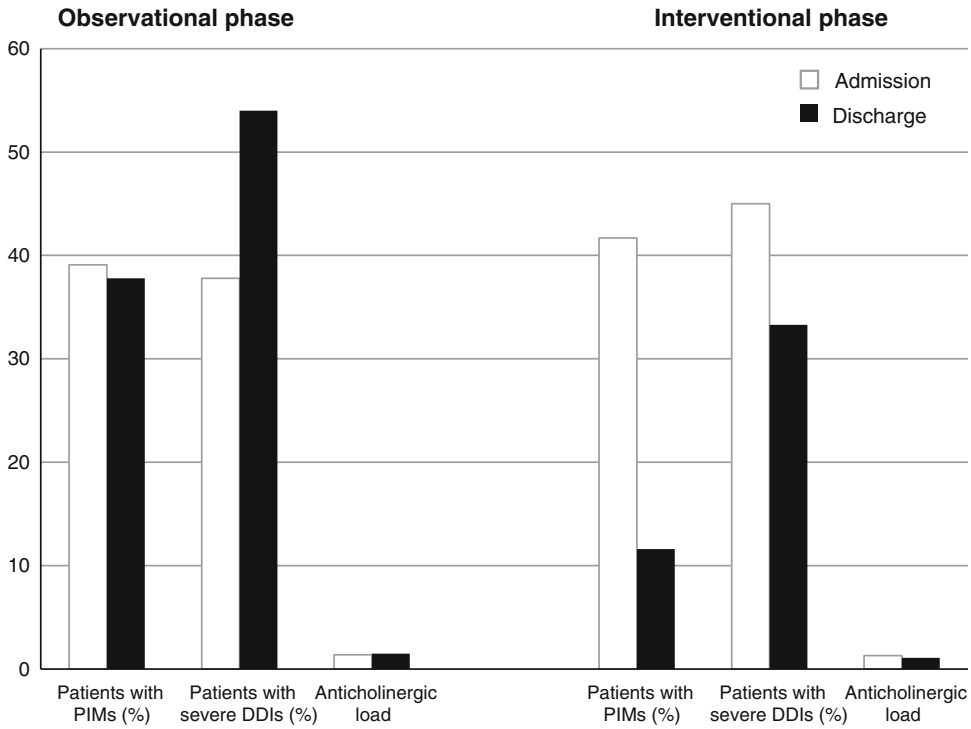

Fig. 1 Main results of observational and interventional phases of the study. *DDIs* drug–drug interactions, *PIMs* potentially inappropriate medications

(16.6 %) were severe and 116 (52.0 %) moderate. The mean number of potential DDIs per patient at admission was 3.7 (range 0–16). At discharge, 53 (88.3 %) patients were exposed to at least one potential DDI, 42 (70.0 %) patients to at least one potentially moderate or severe DDI, and 20 (33.3 %) to at least one potentially severe DDI. Of all of the 224 potential DDIs, 27 (12.0 %) were severe and 104 (46.4 %) moderate. The mean number of potential DDIs per patient at discharge was 3.7 (range 0–11). Although the mean number of potential DDIs was similar at admission and at discharge, the prevalence of patients exposed to potentially severe DDIs decreased, respectively, from 27 (45.0 %) to 20 (33.3 %) [$p = 0.703$]. The number of newly created potentially severe DDIs decreased from 37 (59.0 %) in the observation phase to 9 (33.0 %) in the intervention phase ($p < 0.001$). The main results are illustrated in Fig. 1. The most frequent potential DDIs at both admission and discharge are reported in Table 3.

3.3 Anticholinergic Burden

In the observation phase, the median ACB scale score was 1.4 at admission and 1.5 at discharge, while in the intervention phase this value decreased from 1.3 at admission to 1.1 at discharge. The most frequent drugs with possible or established anticholinergic effects at admission and at discharge for both phases are shown in Table 4.

Table 3 Most frequent potentially severe drug–drug interactions (DDIs) at hospital admission and discharge

DDIs	Potential adverse events	Observation phase [*n* (%)]		Intervention phase [*n* (%)]	
		Admission	Discharge	Admission	Discharge
Warfarin + canrenone	Increased risk of bleeding	4 (5.4)	8 (10.8)	1 (1.7)	4 (6.7)
Ramipril + canrenone	Increased risk hyperkalemia	4 (5.4)	8 (10.8)	1 (1.7)	4 (6.7)
Digoxin + furosemide	Increased risk of digoxin toxicity	3 (4.1)	3 (4.1)	5 (8.3)	1 (1.7)
Aspirin (acetylsalicylic acid) + clopidogrel	Increased risk of bleeding	1 (1.3)	4 (5.4)	4 (6.7)	5 (8.3)
Amlodipine + simvastatin	Increased risk of myopathy (rhabdomyolysis)	2 (2.7)	3 (4.1)	2 (3.3)	1 (1.7)
Amiodarone + simvastatin	Increased risk of myopathy (rhabdomyolysis)	3 (4.1)	4 (5.4)	1 (1.7)	2 (3.3)
Simvastatin + diltiazem	Increased risk of myopathy (rhabdomyolysis)	3 (4.1)	3 (4.1)	1 (1.7)	1 (1.7)

Table 4 Most frequently prescribed drugs with anticholinergic effects at hospital admission and discharge, according to the Anticholinergic Cognitive Burden (ACB) Scale

Drug	ACB score	Observation phase [n (%)]		Intervention phase [n (%)]	
		Admission	Discharge	Admission	Discharge
Furosemide	1	37 (50)	49 (66.2)	27 (45)	33 (55)
Warfarin	1	13 (17.6)	18 (24.3)	7 (11.7)	8 (13.3)
Trazodone	1	6 (8.1)	5 (6.7)	8 (13.3)	6 (10)
Digoxin	1	4 (5.4)	4 (5.4)	6 (10)	1 (1.7)
Paroxetine	3	4 (5.4)	5 (6.7)	4 (6.7)	1 (1.7)
Atenolol	1	1 (1.3)	1 (1.3)	3 (5)	1 (1.7)
Prednisone	1	4 (5.4)	4 (5.4)	2 (3.3)	2 (3.3)
Haloperidol	1	2 (2.7)	3 (1.7)	2 (3.3)	1 (1.7)
Carbamazepine	2	2 (2.7)	2 (2.7)	1 (1.7)	1 (1.7)
Promazine	3	1 (1.3)	1 (1.3)	0	1 (1.7)

4 Discussion

In the present study, the review of patients' medication prescription with a CPSS was associated with a significant reduction in PIMs among hospitalized older adults. Prevalence of inappropriate prescription was near 40 % at admission in both phases of the study, but in the intervention phase it was significantly reduced to 11.6 % at discharge.

Although experience in geriatric pharmacotherapy is desirable, it is unrealistic to expect that the majority of clinicians have enough knowledge about drug-related appropriateness and interactions when prescribing to older people with multimorbidity. In Europe, several large-scale epidemiological studies have used the Beers criteria to quantify the prevalence of inappropriate prescribing in older people in primary, secondary and long-term care. PIMs were identified in 14–66 % of hospitalized older adults [53–55]. A reliable CPSS with instant feedback to the prescriber might improve prescribing quality, thereby reducing the incidence of ADRs in older people [12]. CPSSs have been used in hospital and community settings, showing that they reduce the prescription of PIMs [49–51]. A randomized study among family doctors showed no reduction in the discontinuation of inappropriate medications. However, there was a significantly lower prevalence of newly prescribed PIMs during the study period [52].

The absolute number of concurrently prescribed drugs is the strongest risk factor for the development of ADRs [38]. In our study, patients recruited in both phases were at high risk for ADRs according to their GerontoNet ADR Risk Score [38]. Although the mean number of drugs and mean GerontoNet ADR Risk Score increased between admission and discharge in the observation phase, they both remained unchanged in the intervention phase.

Little is known about the efficacy of CPSSs in reducing potentially severe DDIs and related outcomes in the hospitalized elderly. Despite different classifications for DDIs, which make comparison between studies difficult, in our study the prevalence of potentially severe DDIs was slightly higher than in other hospital-based studies [56–58]. These findings may be due to the study sample consisting of very elderly patients characterized by severe multimorbidity and polypharmacy. Indeed, aging and a high number of prescribed drugs are associated with a higher prevalence of potential DDIs [4]. Medication review with

INTERcheck® proved effective in reducing the prevalence of potentially severe DDIs, and especially of those created during hospitalization, which are those that entail higher risk of associated harm [59].

As the mean ACB score at admission was relatively low we could not evaluate the utility of INTERcheck® in reducing the anticholinergic burden. Lack of follow-up also prevented assessment of the relationship between longitudinal cumulative anticholinergic exposure and cognitive and physical performance. In a previous study we found an association between the drug-related anticholinergic burden and cognitive and physical impairment for patients who scored 5 or more [28].

The main limitation of this study is the lack of follow-up information on clinical outcomes; other limitations include the small sample of patients recruited and single-center design of the study. However, it is a pilot study, the main aim of which is to evaluate the applicability of the INTERcheck® system to the hospitalized elderly and to test its effectiveness in reducing PIMs, potentially severe DDIs and the anticholinergic burden in daily practice. A multicenter longitudinal study with 3- and 12-month follow-ups will follow.

5 Conclusion

This study shows that reviewing elderly patients' medication using a CPSS is not time-consuming and is associated with a significant reduction in PIMs and potentially severe new-onset DDIs. The combination of different prescribing quality measures (e.g. criteria of inappropriate prescription, DDIs, anticholinergic load or dose adjustment) with an ADR risk factor analysis should be considered a strategy to optimize polypharmacy in elderly people affected by multimorbidity.

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