Igiene e Sanità Pubblica 2024; 88 (1): 1-18

Potentially inappropriate prescriptions for poly-treated patients in long-term care facilities: retrospective pharmacoutilization analysis.

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ABSTRACT

BACKGROUND

This study aimed to investigate, among elderly patients in long-term care (LTC) facilities, potentially inappropriate drug prescriptions, potentially interactions and verify whether they can be traced back to hospitalisations or accesses to the Emergency Department (ED). The study data were acquired by means of a case report form investigating the medication management process in LTCs.

MATERIAL AND METHODS

Analysis of pharmacutilisation in LTCFs patients aged ≥65 years on polypharmacy or excessive polypharmacy, January-July 2023. Data was extracted from a database (DB) containing the monthly prescriptions of medicines supplied by direct distribution (DD) to LTCs. The prevalence of PIMs was evaluated by applying the Beers and STOPP criteria to the medication profile of each patient.

RESULTS

The overall prevalence of polypharmacy and hyperpolypharmacy was 83% and 17%, respectively. PIMs were defined using Beers and STOPP criteria. The most frequent PIMs were proton pump inhibitors (19% e 15%), antiplatelets agent (17% e 13%) and non-associated sulfonamides (14% e 12%). Of the 1,921 PIMs, 121 were contraindicated or very serious (6%) and 1,800 were major (94%).The most common medicaments involved in drug-drug interaction are furosemide (21%), sertraline (19%), pantoprazole (16%) e trazodone (15%). LTCs participating in the study (56%) excluded polypharmacy as a cause of access to the ED and ADRs. Therefore no case was ever reported (100%).

Igiene e Sanità Pubblica 2024; 88 (1): 1-18

CONCLUSIONS

Polypharmacy or excessive polypharmacy among elderly patients may increase PIMs and ADRs. A constant review of the therapeutic regimens and deprescribing decrease inappropriate use of medications and interactions, ADRs, and accesses to the ED with consequent reduction of pharmaceutical spending.

INTRODUCTION

The phenomenon of population aging, which is associated with an increase in risk factors and/or pathologies, is growing, leading to increased social impact in terms of social security, assistance and healthcare spending[1].

The prevalence of chronic diseases increases in older adults and the presence of multimorbidity affects 75% of sixty-five year olds and almost every adult over eighty year olds[2].

Direct consequence of comorbidities is polypharmacy, the use of 5 or more drugs, in the same individual to treat these pathologies, which is associated with increased risk of drug-drug interactions, adverse drug reactions (ADRs) and may affect adherence to treatment[3,4].

Inappropriate and unnecessary drug use can cause, in addition to administration errors, adverse outcomes such as functional (disability) and cognitive decline, increased number of geriatric syndromes (GS) (delirium, falls, incontinence, eating disorders, etc.), risk of institutionalization and mortality[5]. Pharmacokinetic and pharmacodynamic alterations may occur in older adults due to age-related physiological changes such as organ failure (kidney, liver and cardiovascular diseases), modifying the pharmacological profile of drugs with consequent significant differences in response. To achieve a balance between risk and benefit in older adults is challenging, therefore, many therapies are considered inappropriate[6-8]. Potentially inappropriate medications (PIMs) in geriatric patients are drugs or drug classes that should be avoided because the risk of adverse reactions exceeds the expected benefit of treatment, especially when there are safer and/or more effective alternative treatments for the same clinical condition[9]. Explicit criteria based on predefined measures have been developed to detect prescriptive inappropriateness and aimed at analyzing the drug or pathology, which can also be applied without knowledge of the patient's clinical characteristics. Among other criteria used to detect PIMs among older adults, the most widely known are Beers criteria[10] that identify drugs to be avoided in the elderly, and STOPP criteria wich identify both potentially useful drugs in older patients and drugs that should be suspended in older patients that are potentially inappropriate in particular clinical conditions[11]. Their application improves the quality in patient care through a more aware use of medications and drug-related problems, especially in high-risk patients (elderly people with multiple pathologies and polypharmacy).

The main objective of this study is to analyze PIMs prescriptions and potential interactions between drugs of different clinical relevance within the care setting among patients in long-term care (LTC) facilities.

Secondary objective is to investigate potentially inappropriate drug prescriptions associated with the risk of very serious and increased potential interactions in patients on polypharmacy are associated with access to emergency departments with consequent

Igiene e Sanità Pubblica 2024; 88 (1):1-18

increase in hospital admissions. The information, including that relating to pharmacovigilance, was obtained from a cognitive questionnaire administered to the patients residing in LTCFs and aimed at investigating the drug management process.

MATERIALS AND METHODS

SETTING AND STUDY DESIGN

A retrospective study of drug utilization was conducted in patients hosted in LTCFs in the province of Vercelli, Italy, included in the prescriptive appropriateness project[12,13].

The drug prescriptions, supplied under Direct Distribution (DD), were extracted from a database ACCESS (DB LTCFs), for the period January - July 2023, which includes the data from the DB of each LTCF, limited to drugs from the affiliate (CONV), distribution on behalf (DPC) and occasionally to drugs outside therapeutic handbook (PTA)/ emergency prescriptions[14-17].

Patients of both genders, aged > 65 years, were included in this study if they were receiving polypharmacy (patients taking 5 or more drug therapies with different Anatomical Therapeutic Chemical Classification [ATC] at level 5°), or excessive polypharmacy (patients taking more than 10 drugs with different ATC at level 5°).

Patients were characterized according to: gender, age, number of active ingredients prescribed. Dispenseding medications were classified according to: ATC level 1°, ATC level 5°, number of prescriptions, and number of packages.

PIMs were evaluated according to Beers and STOPP criteria using INTERCheck® software (a prescription support system with the aim of evaluating prescriptive appropriateness developed by Istituto di Ricerche Farmacologiche Mario Negri of Milan IRCCS).

To detect PIMs, according to Beers' criteria, appropriateness notes and drugs to be used with caution were included, without excluding drug-disease or drug-syndrome interactions. Using STOPP's criteria, medications that increase the risk of falls in predisposed individuals and indicators by pathophysiological-target system were included. Potential clinically relevant interactions are classified according to severity type C (major) and type D (contraindicated or very serious), as an increase in their incidence represents a high risk to the patient's health[18].

Direct access to reporting data in the National Pharmacovigilance Network, hospital discharge records (SDO) or the Emergency Department (ED) was not available therefore it was not possible to monitor emergency department admissions with a principal diagnosis or secondary to trauma, fall or fracture. To overcome the problem and obtain information on the matter, a fact-finding survey was conducted involving the 32 LCTFs enrolled in the prescriptive appropriateness project of the Local Health Authority (ASL VC): the answers provided to the questionnaires on the management of the drug, distributed from 23 August to 24 September 2023, which returned data not only on aspects relating to reception, taking charge of drugs, management of therapy (storage, preparation and administration of drugs and DM) including gases medicines, but above all relating to pharmacovigilance[19-23].

Igiene e Sanità Pubblica 2024; 88 (1): 1-18

RESULTS

The number of patients in the LTCFs in the province of Vercelli, included in the study, who received at least one prescription drug between January and July 2023 was 1,628, of which 1,530 (94%) were ≥65 years old. Of this group, 667 (44%) received less than 5 active substances and 863 (56%) were on polypharmacy, 712 (83%) received from 5 to 9 active substances, and 151 (17%) received more than 10 active ingredients (excessive polypharmacy). Subjects on polypharmacy and excessive polypharmacy were divided by sex and age groups (Table 1): female were 604 (70%) and men 259 (30%); the prevalent age groups were ≥90 years for female (277, 46%) and 85-89 years for men (65, 25%). Polypharmacy was prevalent in female starting from age group 75-79 years (37 patients in polypharmacy out of 74); in men starting from age group 65-69 years (20 patients in polypharmacy out of 34).

Table 1. Distribution of patients in LTCFs by age group for polytherapy (5-9 active substance) and excessive polytherapy (≥10 active substance).

Distribution of patients in LTCFs by age group for polytherapy and excessive polytherapy

Females (F)								
Age groups (years)	**λ_1**	**α_1**	**(%) α_1 *vs* Total $\alpha_1+\beta_1$**	**β_1**	**(%) β_1 *vs* Total $\alpha_2+\beta_2$**	**$\alpha_1+\beta_1$**	**(%) $\alpha_1+\beta_1$ *vs* Total $\alpha+\beta$**	**(%) $\alpha_1+\beta_1$ *vs* Total $\alpha_1+\beta_1$**
65 -69	32	10	*2%*	6	*1%*	16	*2%*	*3%*
70 - 74	40	17	*3%*	2	*0%*	19	*2%*	*3%*
75 -79	74	34	*6%*	3	*0%*	37	*4%*	*6%*
80 - 84	158	77	*13%*	12	*2%*	89	*10%*	*15%*
85 -89	295	135	*22%*	31	*5%*	166	*19%*	*27%*
≥90	514	237	*39%*	40	*7%*	277	*32%*	*46%*
Total	**1,113**	**510**	***84%***	**94**	***16%***	**604**	***70%***	***100%***
Males (M)								
Age groups (years)	**λ_2**	**α_2**	**(%) $\alpha 2$ *vs* Total $\alpha_2+\beta_2$**	**β_2**	**(%) $\beta 2$ *vs* Total $\alpha_2+\beta_2$**	**$\alpha_2+\beta_2$**	**(%) $\alpha_2+\beta_2$ *vs* Total $\alpha+\beta$**	**(%) $\alpha_2+\beta_2$ *vs* Total $\alpha_2+\beta_2$**
65 -69	34	18	*7%*	2	*1%*	20	*2%*	*8%*
70 - 74	61	29	*11%*	5	*2%*	34	*4%*	*13%*
75 -79	61	28	*11%*	9	*3%*	37	*4%*	*14%*
80 - 84	76	47	*18%*	14	*5%*	61	*7%*	*24%*
85 -89	102	47	*18%*	18	*7%*	65	*8%*	*25%*
≥90	83	33	*13%*	9	*3%*	42	*5%*	*16%*
Total	**417**	**202**	***78%***	**57**	***22%***	**259**	***30%***	***100%***
Females + Males (F+ M)								
Age groups (years)	**λ**	**α**	**(%) α *vs* Total $\alpha+\beta$**	**β**	**(%) β *vs* Total $\alpha+\beta$**	**$\alpha+\beta$**	**(%) $\alpha+\beta$ *vs* Total $\alpha+\beta$**	**(%) $\alpha+\beta$ *vs* Total $\alpha+\beta$**
65 -69	66	28	*3%*	8	*1%*	36	*4%*	*4%*
70 - 74	101	46	*5%*	7	*1%*	53	*6%*	*6%*
75 -79	135	62	*7%*	12	*1%*	74	*9%*	*9%*
80 - 84	234	124	*14%*	26	*3%*	150	*17%*	*17%*
85 -89	397	182	*21%*	49	*6%*	231	*27%*	*27%*
≥90	597	270	*31%*	49	*6%*	319	*37%*	*37%*
Total	**1530**	**712**	***83%***	**151**	***17%***	**863**	***100%***	***100%***

Data source: DB LTCFs – SC Farmaceutica Territoriale ASL VC

Number of female patients aged > 65 years divided by age group ($\lambda 1$); Number of male patients aged > 65 years divided by age groups ($\lambda 2$); Number of female and male patients aged > 65 years divided by age groups (λ).

Number of female patients in polypharmacy aged > 65 years divided by age groups ($\alpha 1$); Number of male patients in polypharmacy aged > 65 years divided by age groups ($\alpha 2$); Number of female and male patients in polypharmacy aged > 65 years divided by age groups (α).

Number of female patients in excessive polypharmacy aged > 65 years divided by age groups ($\beta 1$); Number of male patients in excessive polypharmacy aged > 65 years divided by age groups ($\beta 2$); Number of female and male patients in excessive polypharmacy aged > 65 years divided by age groups (β).

Number of females aged >65 years in polypharmacy and excessive polypharmacy divided by age groups ($\alpha 1+\beta 1$); Number of males aged >65 years in polypharmacy and excessive polypharmacy divided by age groups ($\alpha 2+\beta 2$); Number of females and males aged >65 years in polypharmacy and excessive polypharmacy divided by age groups ($\alpha+\beta$).

Igiene e Sanità Pubblica 2024; 88 (1): 1-18

Table 2 shows pharmaceutical prescriptions distributed by ATC level 1°, by gender and age group. Cardiovascular drugs (ATC C) were the most widely used (33.3 %) followed by central nervous system drugs (ATC N 22.8%), blood pressure and hematopoiesic drugs (ATC B 17.2%). The highest number of prescriptions occured in the age group ≥90 years (38 %) and between 85-89 years (28%) considering both genders. Both female and men used more cardiovascular system drugs (ATC C), respectively, 8,970 and 3,154 prescriptions (34% and 32%), no gender difference was reported. Total analysis of prescriptions by gender and age group showed the highest utilization in female in the ≥90 years age group (12,496; 47%) and in men between 85-89 years (2,865; 29%).

Table 2. Distribution of pharmaceutical prescriptions by age group and gender for ATC level 1°.

Number of prescriptions for ATC level 1°															
Females (F)	ATC A	ATC B	ATC C	ATC D	ATC G	ATC H	ATC J	ATC L	ATC M	ATC N	ATC P	ATC R	ATC S	ATC V	Total
65-69	140	89	204	0	0	80	19	0	26	242	0	5	0	7	812
70-74	149	127	221	0	0	33	22	0	6	311	0	17	0	2	888
75-79	192	208	411	0	0	76	33	10	15	429	7	6	0	12	1,399
80-84	643	579	1.057	0	0	171	62	16	44	914	0	25	0	23	3,534
85-89	1,125	1,261	2,520	0	0	312	138	50	135	1,638	7	88	4	46	7,324
90	1,900	2,351	4,557	0	0	538	223	47	252	2,460	6	87	0	75	12,496
Subtotal F	4,149	4,615	8,970	0	0	1,210	497	123	478	5,994	20	228	4	165	26,453
Males (M)	ATC A	ATC B	ATC C	ATC D	ATC G	ATC H	ATC J	ATC L	ATC M	ATC N	ATC P	ATC R	ATC S	ATC V	Total
65-69	115	69	179	0	40	14	16	0	29	310	0	4	0	14	790
70-74	226	191	343	0	33	17	24	0	45	435	0	17	0	18	1,349
75-79	281	237	409	0	25	17	23	0	48	366	0	35	0	2	1,443
80-84	320	306	755	0	69	37	42	1	34	425	0	18	0	9	2,016
85-89	360	526	949	0	146	72	83	7	87	526	0	80	7	22	2,865
90	283	309	519	0	56	36	35	0	35	237	0	29	6	18	1,563
Subtotal M	1,585	1,638	3,154	0	369	193	223	8	278	2,299	0	183	13	83	10,025
(F +M)	ATC A	ATC B	ATC C	ATC D	ATC G	ATC H	ATC J	ATC L	ATC M	ATC N	ATC P	ATC R	ATC S	ATC V	Total
65-69	255	158	383	0	40	94	96	0	55	552	0	9	0	21	1,663
70-74	375	318	564	0	33	50	46	0	51	746	0	34	0	20	2,237
75-79	473	445	820	0	25	93	56	10	63	795	7	41	0	14	2.842
80-84	963	885	1,812	0	69	208	104	17	78	1,339	0	43	0	32	5,550
85-89	1,485	1,787	3,469	0	146	384	221	57	222	2,164	7	168	11	68	10,189
90	2,183	2,660	5,076	0	56	574	258	47	287	2,697	6	116	6	93	14,059
Total	5,734	6,253	12,124	0	369	1,403	781	131	756	8,293	20	411	17	248	36,540

Data source: DB LTCFs - SC Farmaceutica Territoriale ASL VC

Table 3 shows the top 20 most prescribed drugs and the corresponding number of packages dispensed during the analysis period. Pantoprazole was the most prescribed drug (3,303; 9%), followed by acetylsalicylic acid/lysine acetylsalicylate (2,948; 8%) and furosemide (2,646; 7%).

Igiene e Sanità Pubblica 2024; 88 (1): 1-18

Table 3. Top 20 most prescribed substances.

ATC	Drug	Prescriptions N. (%)	Packaging N.
A02BC02	Pantoprazole	3303 (9%)	3925
B01AC06	Acetylsalicylic acid/Lysine acetylsalicylate	2948 (8%)	3046
C03CA01	Furosemide	2646 (7%)	3546
C07AB07	Bisoprolol	2376 (7%)	2608
N05AH04	Quetiapine	1262 (4%)	2574
N06AB06	Sertraline	1198 (3%)	1409
N06AX05	Trazodone	1091 (3%)	1490
C09AA05	Ramipril	984 (3%)	1637
H03AA01	Levothyroxine Sodium	832 (2%)	904
C08CA01	Amlodipine	826 (2%)	1327
B03AA07	Ferrous Solphate	646 (2%)	653
B01AC04	Clopidogrel	565 (2%)	609
A12BA01	Potassium Chloride	552 (2%)	664
M04AA01	Allopurinol	533 (1%)	544
C03EB01	Furosemide + Spironolactone	508 (1%)	692
C10AA01	Simvastatin	490 (1%)	570
B01AF02	Apixaban	479 (1%)	961
C10AA05	Atorvastatin	454 (1%)	468
N03AX16	Pregabalin	428 (1%)	853
N03AE01	Clonazepam	399 (1%)	1006

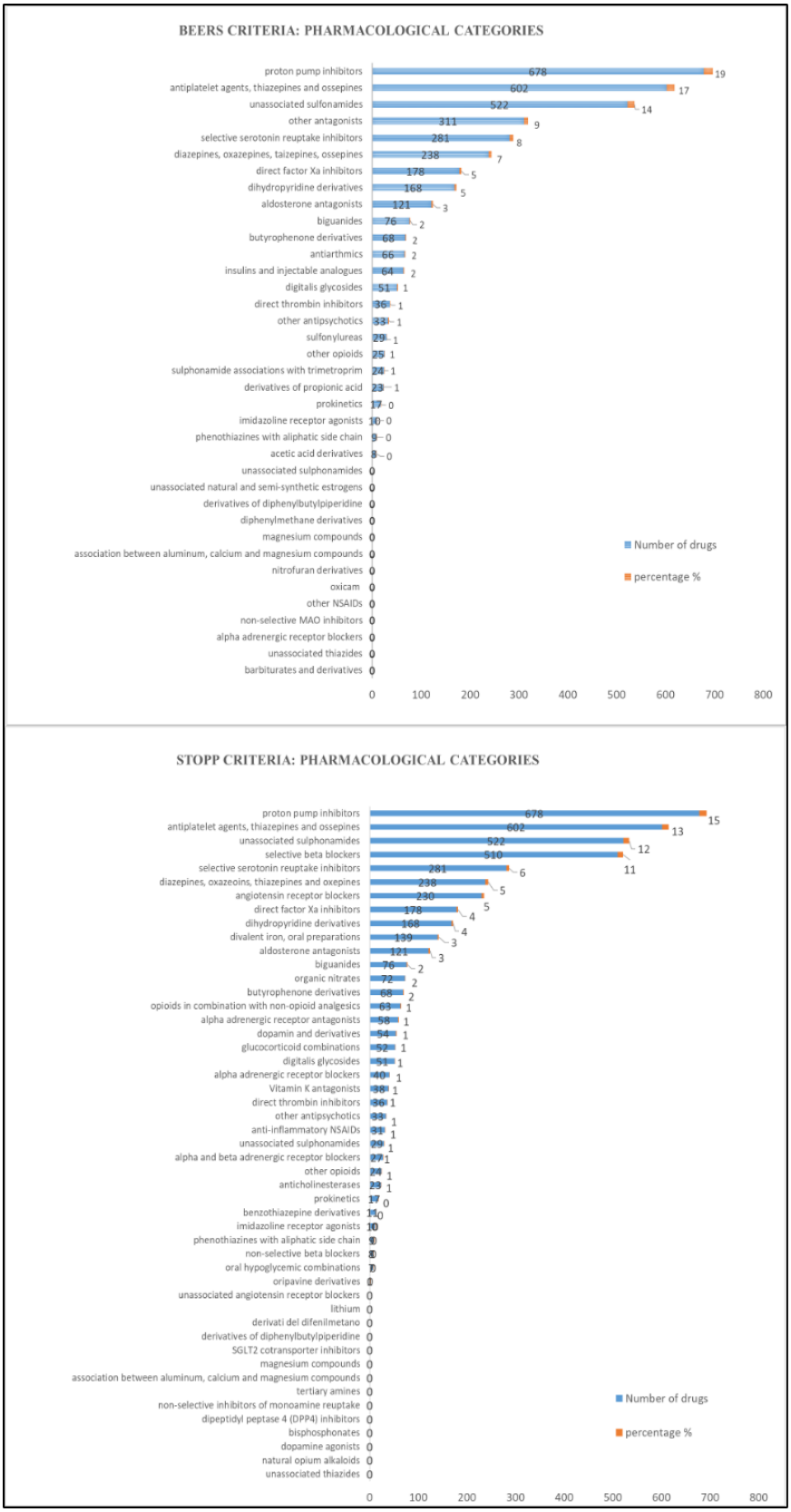
Data source: DB LTCFs - SC Farmaceutica Territoriale ASL VC

Figure 1 shows potentially inappropriate prescribing among patients on polytherapy aged ≥65 years was 3,638 according to Beers criteria and 4,504 according to STOPP criteria.

Most frequently used PIMs according to Beers and STOPP criteria in patient therapy were proton pump inhibitors (PPIs) 678 (19% and 15% respectively), followed by antiplatelet medications 602 (17% and 13% respectively) and nonassociated sulfonamides 522 (14% and 12% respectively) (Figure 1).

Igiene e Sanità Pubblica 2024; 88 (1): 1-18

Figure 1. Number of potentially inappropriate drugs according to the Beers and STOPP criteria, for level ATC 3°.



Igiene e Sanità Pubblica 2024; 88 (1):1-18

A total of 1,921 potential drug interactions were detected of which 121 (6%) contraindicated or very serious and 1,800 (94%) major. Analysis data were divided by gender, polypharmacy and age group (Table 4). Potential contraindicated and/or major interactions were 1,194 in patients on polypharmacy (62%) and 727 (38%) in patients on overtreatment. The age group with the most recurrence of interactions was ≥90 years for female with 560 potential interactions (29%) and 85-89 years for men with 258 potential interactions (13%). Female on polypharmacy reported 809 potential interactions (42%), female on excessive polypharmacy 428 (22%). Men on polypharmacy reported 385 potential interactions (20%), men on excessive polypharmacy 299 (16%).

Table 4. Potential contraindicated and greater interactions in LTCFs patients.

Potential major (type C) and contraindicated (type D) interactions						
Females						
Age groups (years))	**σ_1**	**(%) σ_1 *vs* Total σ**	**ψ_1 (5-9)**	**(%) ψ_1 (5-9) *vs* Total σ**	**ϕ1 (>10)**	**(%) ϕ1 (>10) vs Total σ**
65 -69	30	*2%*	9	*0%*	21	*1%*
70 - 74	38	*2%*	27	*1%*	11	*1%*
75 -79	84	*4%*	58	*3%*	26	*1%*
80 - 84	192	*10%*	142	*7%*	50	*3%*
85 -89	333	*17%*	207	*11%*	126	*7%*
≥90	560	*29%*	366	*19%*	194	*10%*
Total	**1,237**	***64%***	**809**	***42%***	**428**	***22%***
Males						
Age groups (years)	**σ_2**	**(%) σ_2 vs Total σ**	**ψ_2 (5-9)**	**(%) ψ2 (5-9) vs Total σ**	**ϕ2 (>10)**	**(%) ϕ1 (>10) vs Total σ**
65 -69	54	*3%*	43	*2%*	11	*1%*
70 - 74	86	*4%*	61	*3%*	25	*1%*
75 -79	63	*3%*	46	*2%*	17	*1%*
80 - 84	153	*8%*	83	*4%*	70	*4%*
85 -89	258	*13%*	108	*6%*	150	*8%*
≥90	70	*4%*	44	*2%*	26	*1%*
Total	**684**	***36%***	**385**	***20%***	**299**	***16%***
Females + Males						
Age groups (years)	**σ**	**(%) σ vs Total σ**	**ψ (5-9)**	**(%) ψ (5-9) vs Total σ**	**ϕ (>10)**	**(%) ϕ1 (>10) vs Total σ**
65 -69	84	*4%*	52	*3%*	32	*2%*
70 - 74	124	*6%*	88	*5%*	36	*2%*
75 -79	147	*8%*	104	*5%*	43	*2%*
80 - 84	345	*18%*	225	*12%*	120	*6%*
85 -89	591	*31%*	315	*16%*	276	*14%*
≥90	630	*33%*	410	*21%*	220	*11%*
Total	**1,921**	***100%***	**1,194**	***62%***	**727**	***38%***

Data source: DB LTCFs - SC Farmaceutica Territoriale ASL VC

Number of interactions in females divided by age group (σ1); Number of interactions in males divided by age group (σ2); Number of interactions in females e males divided by age group (σ).

Potential major (type C) and contraindicated (type D) interactions in polypharmacy (5-9) in females (ψ1); Potential major (type C) and contraindicated (type D) interactions in polypharmacy (5-9) in males (ψ2); Potential major (type C) and contraindicated (type D) interactions in polypharmacy (5-9) in females and males (ψ).

Potential major (type C) and contraindicated (type D) interactions in excessive

Igiene e Sanità Pubblica 2024; 88 (1): 1-18

polypharmacy in females (φ1); Potential major (type C) and contraindicated (type D) interactions in excessive polypharmacy in males (φ2); Potential major (type C) and contraindicated (type D) interactions in excessive polypharmacy in females and males (φ).

Table 5 shows the top 20 most common drugs of potential drug interactions detected: an active substance may be counted more than once if it was present in more than one pair of potential interactions (Table 6), so the total of all percentages of single active ingredients exceeds 100 percent.

Table 5. Top 20 drugs present in drug interactions.

Main drugs in potential interactions	Number	%
Furosemide	400	21
Sertraline	371	19
Pantoprazole	308	16
Trazodone	282	15
Acetylsalicylic acid	273	14
Amiodarone	151	8
Aloperidol	142	7
Azithromycin	141	7
Levetiracetam	134	7
Quetiapine	119	6
Oxicodone	108	6
Mirtazapine	93	5
Ramipril	77	4
Ciprofloxacin	68	4
Citalopram	67	3
Paroxetine	60	3
Naloxone	54	3
Clarithromycin	52	3
Lansoprazole	49	3
Potassium	49	3

Data source: DB LTCFs - SC Farmaceutica Territoriale ASL VC

Igiene e Sanità Pubblica 2024; 88 (1): 1-18

Drugs that were most frequently involved in a drug interaction were furosemide (21% of total interactions), followed by sertraline (19%), pantoprazole (16%) and trazodone (15%). The major categories found were antidepressants (972 potential interactions), diuretics (496), antithrombotics (488), antipsychotics (367), PPIs (357) and antibiotics (356).

The most frequent drug interactions with contraindicated severity were the following combinations: fentanil/sertraline (10%), aloperidol /levetiracetam (8%), amiodarone/ azithromycin (8%). The drugs most commonly implicated in major interactions were pantoprazole/trazodone (13%), acetylsalicylic acid/sertraline e furosemide/sertraline (12%). Table 6 shows the number of cases and the % value of the total number of potential interactions contraindicated and major, respectively.

Table 6. Top 20 contraindicated and major interactions.

Contraindicated associations (type D)				Major associations (type C)			
AS1	**AS2**	**N.**	**%**	**AS1**	**AS2**	**N.**	**%**
Fentanil	Sertraline	5	10	Pantoprazole	Trazodone	89	13
Aloperidol	Levetiracetam	4	8	Acetylsalicylic acid	Sertraline	88	12
Amiodarone	Azithromycin	4	8	Furosemide	Sertraline	86	12
Spironolactone	Sulfametoxazole	3	6	Oxicodone	Naloxone	47	7
Aloperidol	Aripiprazole	3	6	Amiodarone	Furosemide	35	5
Fentanil	Trazodone	3	6	Sertraline	Trazodone	31	4
Aloperidol	Amiodarone	3	6	Digoxin	Furosemide	30	4
Spironolactone	Trimetoprim	3	6	Levetiracetam	Pantoprazole	30	4
Aloperidol	Levomepromazine	3	6	Furosemide	Tamsulosin	28	4
Amiodarone	Levetiracetam	2	4	Aloperidol	Furosemide	27	4
Bisoprolol	Diltiazem	2	4	Amiodarone	Pantoprazolo	26	4
Chlorpromazine	Clozapine	2	4	Acetylsalicylic acid	Clopidogrel	25	4
Ciprofloxacin	Levetiracetam	2	4	Furosemide	Levetiracetam	25	4
Clarithromycin	Donepezil	2	4	Azithromycin	Pantoprazole	23	3
Duloxetine	Fentanil	2	4	Acetylsalicylic acid	Prednisone	21	3
Azithromycin	Ciprofloxacin	2	4	Aloperidol	Pantoprazole	21	3
Citalopram	Tapentadolo	2	4	Aloperidol	Quetiapine	20	3
Azithromycin	Mirtazapine	2	4	Amiodarone	Bisoprolol	20	3
Ciprofloxacin	Citalopram	2	4	Azithromycin	Salbutamol	20	3
Clarithromycin	Levetiracetam	2	4	Acetylsalicylic acid	Betamethasone	19	3
Miscellaneous *		51	43	Miscellaneous *		711	27

Data source: DB LTCFs - SC Farmaceutica Territoriale ASL VC

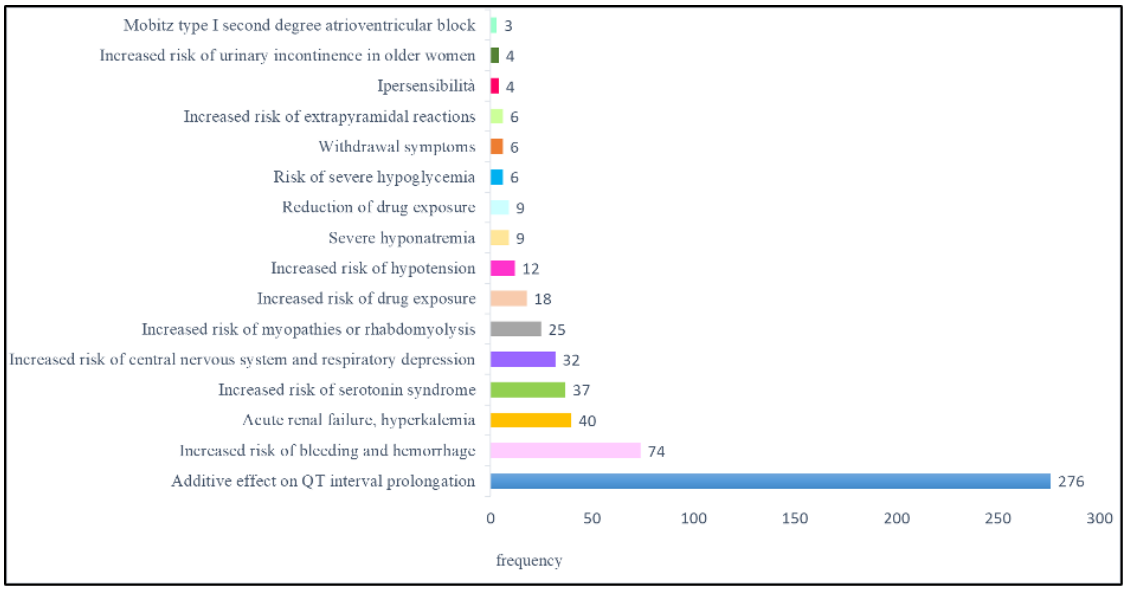
AS1: active substance 1; AS2 active substance 2

** All other AS1/AS 2 combinations outside the top 20.*

Igiene e Sanità Pubblica 2024; 88 (1): 1-18

Figure 2 shows the main effects caused by potential contraindicated and major interactions. The most frequent were: additive effect of QT interval prolongation (n=276, 48%), increased risk of bleeding and hemorrhage (n=74, 13%) and increased risk of kidney diseases and hyperpotassemia (n=40, 7%).

Figure 2. Potential effects of potential interactions detected with INTERCheck® database



For the specific secondary objective, responses from administered questionnaires to the 32 LTCFs enrolled and included in the ASL VC appropriateness project were analysed. Of these, 19 LTCFs (59%) participated in the survey. The investigation conducted on pharmacovigilance reported the following outcome: it was unanimously highlighted that ADRs have never occurred and that in this regard, no reports have ever been made to the local health unit (ASL) which they belong to, the more it was excluded that the accesses to the ED were caused by ADRs nor that there was any correlation with polypharmacy (100% of the responses). (See appendicies for data questionnaire results).

DISCUSSION

The analysis showed that 94% of LTCFs patients enrolled in the appropriateness project were ≥65 years old, 57% aged between 65 and 89 years old, and 37% ≥90 years old.

Compared to the total number of patients in LTCFs aged over 65 years, 44% take less than 5 drugs, 46% are on polypharmacy (5-9 drugs) and 10% are on excessive polypharmacy (≥10 drugs) [24]. The most prescribed drugs are cardiovascular drugs (antihypertensives), CNS-active medications (antidepressants and antipsychotics), blood pressure and hematopoietic drugs (antiplatelet drugs), which match those published in the OsMed Report on drug consumption in the elderly population in Italy[25].

The most common potentially inappropriate prescriptions identified were diuretics (11.1%), of which the most frequent inappropriate prescription was furosemide (fall risk); antithrombotic drugs (10.9%) of which antiplatelet agents (acetylsalicylic acid is the most

Igiene e Sanità Pubblica 2024; 88 (1): 1-18

prescribed) and oral anticoagulants (high risk of severe bleeding) and high-dose PPIs (8.0%) for > 8 weeks (risk of infection and loss of bone mass and fractures); regarding CNS agents, antidepressants (21.7%) (fall risk, dyspraxia and parkinsonism, increased risk of cerebrovascular events, stroke, cognitive impairment, mortality in individuals with dementia), and antipsychotics (8.2%) (syndrome of inappropriate antidiuretic hormone secretion or hyponatremia)[26]. Prescription trends are nationally validated by the OsMed Report in patients on polytherapy in LTCFs.

The most frequent potential adverse drug reaction is the increased risk of QT interval prolongation (48%), which can lead to cardiotoxicity, arrhythmias such as torsade de pointes ventricular tachycardia often associated with sudden death due to concurrent drug administration (furosemide and antidepressants, antipsychotics and antibiotics) [27].

Another potential ADR is the increased risk of gastrointestinal and intracranial bleeding and/or hemorrhage (13%) resulting from the combination of antithrombotics with antidepressants and antithrombotics with NSAIDs, and eventually the increased risk of hyperkalemia (7%) manifested as muscle weakness, abdominal pain, diarrhea, flaccid paralysis, and may lead to cardiac toxicity and renal failure. These effects are also reported nationally in the OsMed Report 2021 in a group of elderly people exposed to polypharmacy[25,28]. The drug most recurrent within an interaction was furosemide (9%) as confirmed by two Italian studies on potential drug-drug interactions prescribed at discharge. In this setting it represents 47% of very serious interactions and is found in most associations responsible for moderate interaction[29,30].

Regarding the secondary objective of the study, the review of the literature shows that ADRs are frequent in the ED and are not always properly recognized by doctors, especially when the drug is involved in a multifactorial disease condition[31]. Healthcare staff at residential care homes for older adults have ruled out that the accesses to ED were either caused by ADRs or by a correlation with polypharmacy.

Responses to the questionnaires do not highlight critical issues on patients on polypharmacy and the correlation with accesses to the ED caused by falls, fractures or traumas, which are particularly significant in older adults as they can trigger a series of adverse events that increase the number of hospitalizations and risk of death.

Analysis limitations are the lack of essential and chronic disease medications ("fascia A"), dispensed by affiliated pharmacies and medications for minor health conditions charged to the citizen ("fascia C") (including benzodiazepines and laxatives), SOPs/OTCs, supplements and phytotherapeutic, which are responsible for potential additional interactions and ADRs, therefore PIMs and potential drug interactions are underestimated. Further limit is the sample size, lack of information on patients' clinical conditions (diagnosis or comorbidities) and the impossibility of accessing emergency department admission records and hospital discharge records.

CONCLUSION

LTCFs are the ideal health care setting to conduct a periodic review of personalized therapies and to implement drug deprescribing for the following reasons: there are few ongoing acute situations, medications are managed by health care personnel, and there is the possibility of prescribing without urgency and strictly monitoring outcomes.

To support and implement systematic medication review, identification of the causes of

Igiene e Sanità Pubblica 2024; 88 (1):1-18

polypharmacy, and deprescribing by the physician, a multidisciplinary team with the presence and active participation of a pharmacist is essential. Indeed, only through constant monitoring of prescriptions is it possible to reduce inappropriate use of drugs and potentially serious interactions resulting in a reduction of side effects, ADRs and accesses to the ED, as well as cost-containment in pharmaceutical spending[32]. Therefore, the pharmacist is the figure of reference necessary for proper enhancement of standards of care, such as to guide prescribing decisions to ensure better quality of life, health and well-being of the patient.

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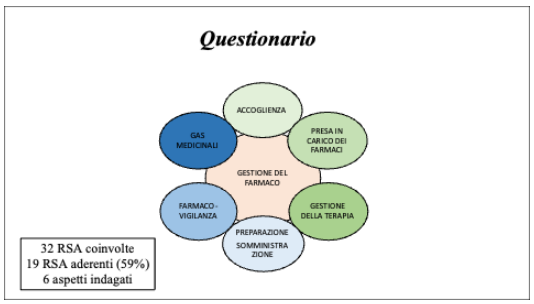
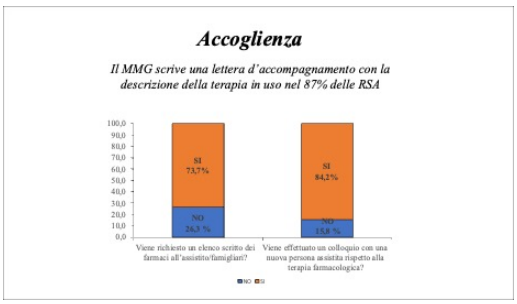
Igiene e Sanità Pubblica 2024; 88 (1): 1-18

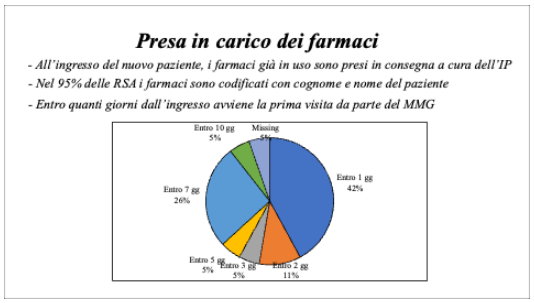
APPENDICES: DATA QUESTIONNAIRE RESULTS AT THE LTC FACILITIES



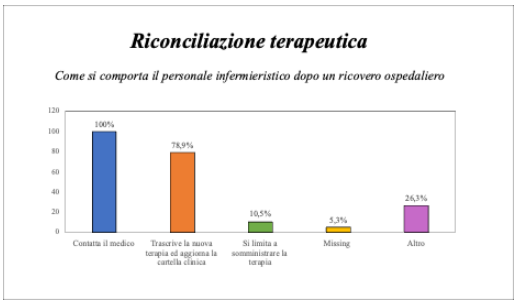
A.1_N. 6 Aspects investigated



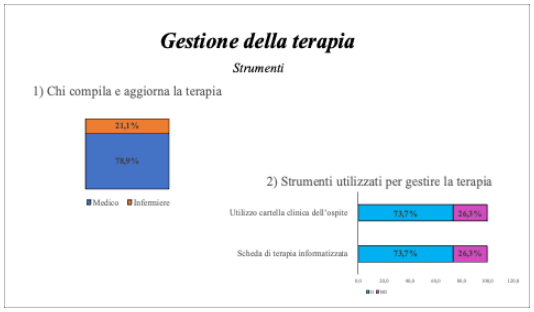
A.2_Hospitality



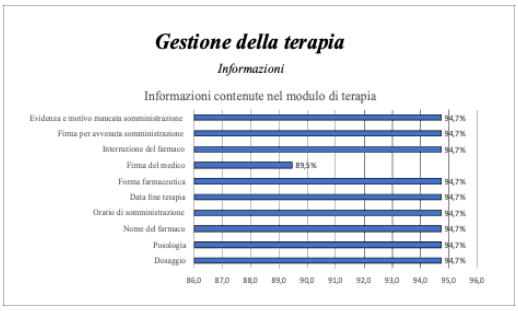
A.3_ Taking charge of drugs



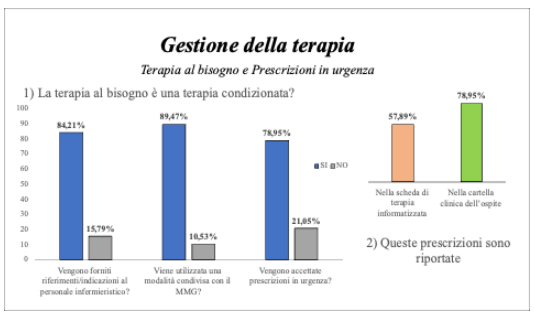
A.4_ Therapeutic reconciliation



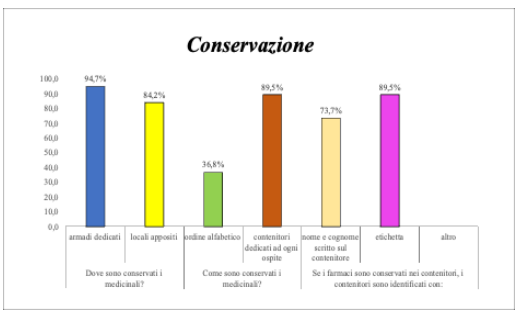
A.5_ Therapy management: instruments



A.6_ Therapy management: informations

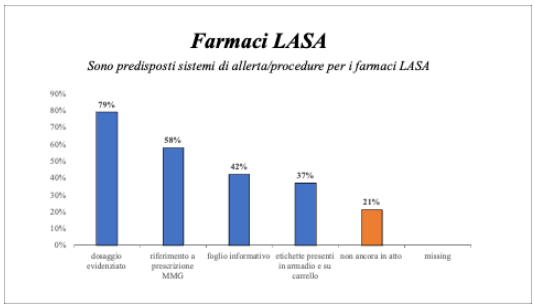


A.7_ Therapy management: therapy as needed and emergency prescriptions

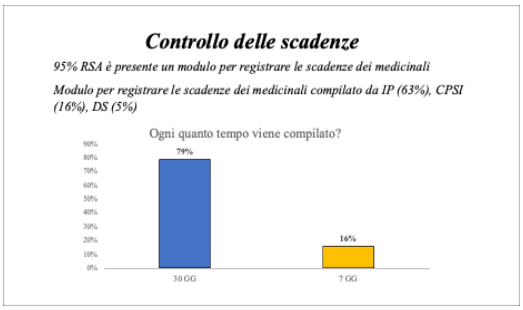


A.8_ Storage

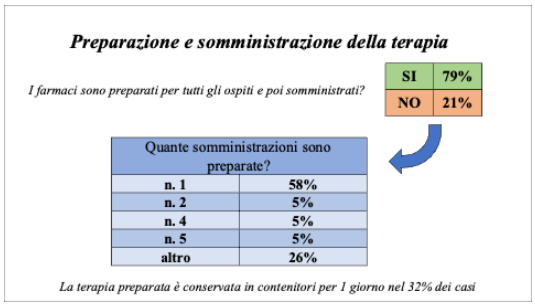
Igiene e Sanità Pubblica 2024; 88 (1): 1-18



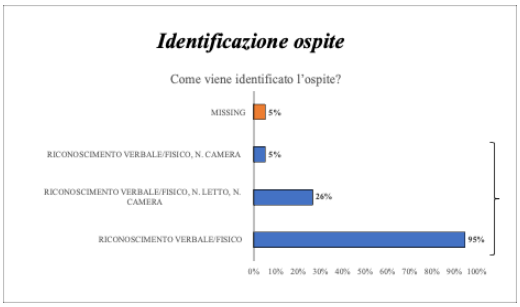
A.9_LASA Drugs



A.10_ Checking drug expiration dates

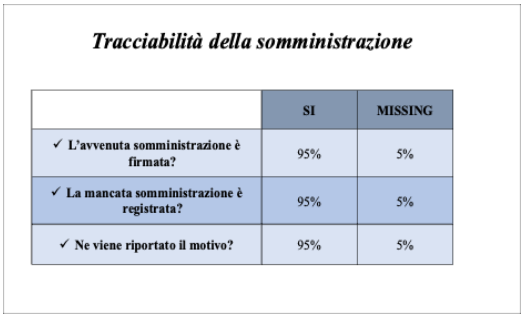


A.11_ Preparation and administration of therapy

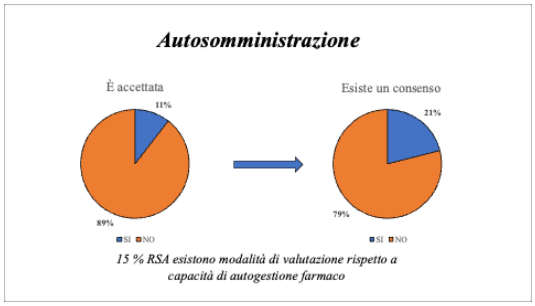


A.12_ Identification

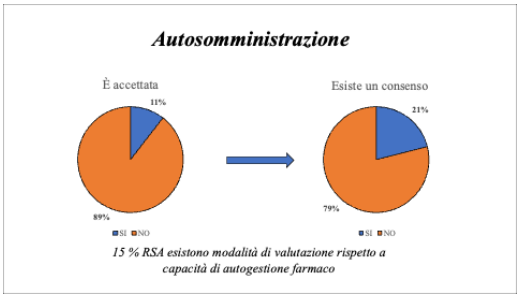
A.13_ Healthcare professional involved



A.14_ Traceability of administration

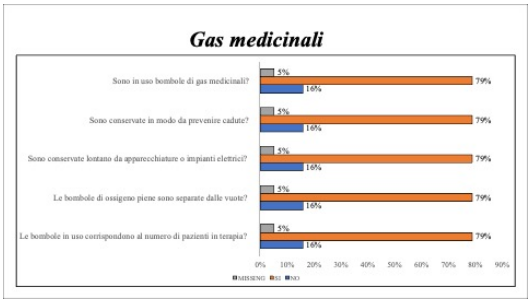


A.15_ Self-administration



A.16_ Pharmacovigilance

Igiene e Sanità Pubblica 2024; 88 (1): 1-18



A.17_Medicinal gases