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Original Article

Gender difference in drug use in hospitalized elderly patients

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ABSTRACT

Purpose: The aims of this study were to evaluate whether or not there are gender differences in drug use at hospital admission and prescription at discharge and to evaluate the effect of hospitalization on medication patterns in the elderly.
Method: In-patients aged >65 years included in the REPOSI registry during a recruitment period of 3 years (2008–2010–2012) were analyzed in order to evaluate drug use at hospital admission and prescription at discharge according to gender.
Results: A total of 3473 patients, 52% women and 48% men, were considered. Polypharmacy (>5 drugs) is more frequent in men both at hospital admission and discharge. At hospital discharge, the number of prescriptions increased in both sexes at all age groups. Neuropsychiatric drugs were significantly more prescribed in women ($p < 0.0001$). At admission men were more likely to be on antiplatelets (41.7% vs 36.7%; $p = 0.0029$), ACE-inhibitors (28.7% vs 24.7%; $p = 0.0072$) and statins (22.9% vs 18.3%; $p = 0.0008$). At discharge, antiplatelets (43.7% vs 37.3%; $p = 0.0003$) and statins (25,2% vs 19.6%; $p < 0.0001$) continued to be prescribed more often in men, while women were given beta-blockers more often than men (21.8% vs 18.9%; $p = 0.0340$). Proton pump inhibitors were the most prescribed drugs regardless of gender. At discharge, the medication pattern did not change according to gender.
Conclusion: Our study showed a gender difference in overall medications pattern in the hospitalized elderly. Hospitalization, while increasing the number of prescriptions, did not change drug distribution by sex.

1. Introduction

Elderly are the largest medication users in the general population, often taking several different drugs on a regular basis [1,2] Although polypharmacy is the consequence of multiple chronic conditions, socio-demographic factors (including age, sex, education, living and functional status) may have a role in the medication needs and use [3,4]. Gender and sex differences in medication use and prescription represent a complex issue, pertaining also to sex-related physiologic characteristics of drugs metabolism and response [5–8]. In addition, factors such as socio-demographic profiles and living arrangements might play a contributing role in medication pattern in elderly women, in whom widowhood and loneliness are often associated with depressed mood and over-utilization of neuropsychiatric drugs [9–12]. Finally, differences between sexes in risk factor distribution [13] and clinical manifestations [14] of the most frequent chronic conditions such as cardiovascular and inflammatory diseases might have contributed to a model of medication prescription based on physician's misperception of disease gender specificity [15–17]. Women and the elderly are historically under-represented in large clinical trials of pharmacological intervention, mainly in the cardiovascular field, despite the disease global burden being equally represented in women and men [18]. As a consequence, specific pharmacological treatments in women and in the elderly are frequently administered on the basis of indirect evidence. Furthermore until recently epidemiological studies and clinical trials failed to systematically report gender differences in medication profile, leading to a knowledge gap that contributed to an increase of the risk of inappropriate medication use [19,20]. With this background, the REPOSI

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registry [21] was finalized to investigate issues related to multimorbidity and polypharmacy in elderly patients (>65 years) acutely admitted to internal medicine and geriatrics wards in Italy. The aims of this study were to describe whether or not there were gender differences in drug use at hospital admission and in prescription discharge, and to evaluate the effect of hospitalization on medication patterns in the elderly women and men included in this registry.

2. Methods

The REPOSI (REgistro POliterapie SIMI) is a collaborative and independent study of the Italian Society of Internal Medicine (SIMI), IRCCS Fondazione Cà Granda Policlinico and the IRCCS—Istituto di Ricerche Farmacologiche "Mario Negri". The design was described in details elsewhere [21]. Briefly, patients aged 65 years or older consecutively admitted to internal medicine and geriatric wards during 2008, 2010 and 2012 in four periods of four weeks each 3 months apart from each other were included in the registry. Participation was voluntary and all patients provided signed informed consent. The study was approved by the Ethical Committes of the IRCCS Cà Granda Maggiore Policlinico Hospital Foundation, Milan, and of all participating hospitals. All data of the patients included in the 3 years of the REPOSI registry were analyzed according to gender. Medications recorded at hospital admission and discharge were considered and compared between sexes. All drugs were encoded according to the Anatomical Therapeutic Chemical classification system (ATC) (WHO 1990), by first and third levels. Drug distribution by gender at hospital admission and discharge has also been analyzed according to age subgroups (65–69, 70–74, 75–79, 80–84, 85+). Out of a whole population of 4035 subjects recruited in the 3-year study, 3473 were included in this analysis, after exclusion of 158 cases who died in hospital, 339 transferred to other wards, 29 in critical conditions and 36 missing at discharge for whom we didn't have information about drugs at discharge.

Number of diagnoses at admission and discharge was also evaluated by gender. Socio-demographic variables (such as age, education, marital status and living arrangement) were all considered. Data were analyzed according to the cognitive status and mood disorders, as tested by the Short Blessed Test (SBT) [22] and Geriatric Depression Scale (GDS)[23] respectively; and to the functional status at hospital admission measured by means of the Barthel index (BI) [24] classified as mild (BI 75–90), moderate (BI 50–74), severe (BI 25–49) and total dependence (BI 0–24). The Cumulative Illness rating Scale (CIRS-s and CIRS-c) severity and comorbidity indexes [25], were also included in the gender analysis.

3. Statistical analysis

Prevalence was calculated by sex and percentages for categorical variables and mean (standard deviation) for continuous variables were reported. The comparison between groups was made using the chi squared test for contingency tables and the *t* test for the comparison of proportions. A two-tailed *p* value less than 0.05 was considered statistically significant. Analyses were carried out with JMP Pro 11 (SAS Institute Inc.)

4. Results

Socio-demographic and clinical characteristics of the study population according to gender at hospital admission and discharge are shown in Table 1. Overall, women were older than men, the main age difference was among the oldest old (>85 years). A significantly higher proportion of women was widow and living alone. At hospital admission, the mean number of diagnoses was > 5 in both sexes and a higher percentage of men presented 5 or more diagnoses ($p = 0.002$). At discharge, the number of diagnoses increased in both sexes, and again a higher percentage of men reported 5 or more diagnoses ($p = 0.02$). At admission, the CIRS comorbidity and severity index scores were higher in men ($p < 0.0001$): the first increased in both sexes at discharge, the latter remained almost unchanged. Women were functionally more impaired according to the Barthel index (BI) score in all the classified disability categories. SBT and GDS mean scores were also significantly higher in women ($p < 0.0001$). A previous hospitalization within the past 6 months was more frequent in men ($p = 0.002$).

At admission, the mean number of drugs was >5 in both sexes and higher percentage of men reported the intake of 5 or more drugs ($p = 0.005$). At discharge, the mean number of drugs increased in both sexes contributing to a reduction of the gender gap among those patients taking 5 or more drugs, however a higher percentage of men (+3%) reported 10 or more drugs ($p = 0.04$).

Fig. 1A and B show the mean number of drugs by gender at different age groups, at hospital admission and discharge. In both situations, the mean number of drugs is higher in men for all age groups > 70 years, and in women only for the age class 65–69 years. In the 75–79 and 80–84 ($p = 0.02$) age groups the difference was statistically significant. At discharge, the mean number of drugs increased from admission in both sexes for all age groups.

Fig. 2A and B show the drug distribution according to the 1st ATC level analyzed by gender at hospital admission and discharge. At admission, women used more drugs in the anatomical main groups C (cardiovascular system) although not significantly, in group H (systemic hormonal preparations) ($p < 0.0001$) and group N (nervous system) ($p < 0.0001$). At discharge, H and N group drugs were still more prescribed in women. More specifically, among the drugs in the N group, antidepressants (13% at admission versus 14% at discharge) and anxiolytics (13% at admission versus 15% at discharge) were the most prescribed medications. Either at admission and discharge, men were more prescribed with drugs belonging to the main anatomical group A (alimentary tract and metabolism) ($p < 0.04$), B (blood and blood-forming organs) ($p < 0.004$), G (genito-urinary system and sex hormones) ($p < 0.0001$), J (anti-infectives for systemic use) (not significant), M (muscoloskeletal system) ($p < 0.006$), and R (respiratory system) ($p < 0.0001$).

Table 2 shows the distribution of the most frequent diseases at admission according to gender and Table 3 shows the distribution of the 10 most frequently prescribed drugs at hospital admission and discharge. Pattern of diseases distribution approximately reflects the drugs distribution by gender. Hypertension and diabetes are the most frequent diseases at admission for both sexes, accordingly, drugs for cardiovascular diseases were the most prescribed. Specifically, at hospital admission, antiplatelet drugs, ACE-inhibitors and statins were more prescribed in men. On the other hand beta-blockers, dihydropyridine derivatives and angiotensin II antagonists were more prescribed in women, although the difference was not statistically significant. The medication pattern between sexes did not change at discharge. Overall drug prescription increased at hospital discharge compared with admission, but we failed to find a statistically significant difference within sexes. The most marked increase was for proton pump inhibitors (PPI) in both sexes, mostly in women in whom the number of cases on this therapy is about 30% higher than at admission (+264 women). Similarly, with respect to admission women were more prescribed than men at discharge with sulfonamides (+109 subjects), ACE-inhibitors (+83 subjects), vitamin K antagonists (+45 subjects), dihydropyridine derivatives (+26 subjects) and angiotensin II antagonists (+14 subjects). On the other hand, men were more prescribed with statins (+37 subjects). No differences were found for organic nitrates prescriptions.

Fig. 3A and B show the prevalence of patients according to the number of drugs by gender at hospital admission and discharge. The number of women admitted to hospital taking 1 to 8 drugs is higher than that of men, while at discharge the number of men taking 10 or more drugs is higher.

Table 1
Socio-demographic and clinical characteristics of the total population (N = 3473) according to gender at hospital admission and discharge.

Variables		Women (N = 1819)	Men (N = 1654)	
Age (years), mean (SD)		80.12 (7.6)	77.96 (7.1)	*<0.0001*
Age class, N (%)	65–74	495 (27.2)	589 (35.6)	*<0.0001*
	75–84	820 (45.1)	766 (46.3)	
	≥85	504 (27.7)	299 (18.1)	
Education (years), mean (SD)		6.06 (3.7)	7.26 (4.3)	*<0.0001*
Marital status[a], N (%)	Single (unmarried, divorced, separated)	151 (8.5)	149 (9.2)	*<0.0001*
	Married	618 (34.6)	1173 (72.2)	
	Widow/er	1018 (57.0)	303 (23.0)	
Living arrangement[b], N (%)	Alone	559 (31.2)	245 (15.3)	*<0.0001*
	With spouse	468 (26.9)	979 (61.0)	
	With sons	436 (25.1)	121 (7.5)	
	With spouse and sons	82 (4.7)	158 (9.9)	
	Other	193 (11.1)	101 (6.3)	
Number of diagnoses at admission, mean (SD)		5.07 (2.8)	5.36 (2.7)	*0.0019*
Number of patients at admission with 5 or more diagnoses, N (%)		977 (53.7)	976 (59.0)	*0.0017*
Number of drug at admission, mean (SD)		5.08 (2.8)	5.38 (3.0)	*0.0030*
Number of patient at admission with 5 or more drugs, N (%)		989 (54.4)	978 (59.1)	*0.0047*
Number of drug at admission	0	49 (2.7)	54 (3.3)	*0.0001*
	1–4	781 (42.9)	622 (37.6)	
	5–9	872 (47.9)	814 (49.2)	
	≥10	117 (6.4)	164 (9.9)	
Numbers of diagnosis at discharge, mean (SD)		6.12 (2.8)	6.38 (2.7)	*0.0060*
Number of patients discharged with 5 or more diagnoses, N (%)		1272 (69.9)	1215 (73.5)	*0.0211*
Number of drugs at discharge, mean (SD)		6.09 (2.8)	6.36 (3.0)	*0.0066*
Number of drug at discharge	0	26 (1.4)	21 (1.3)	*0.0365*
	1–4	534 (29.4)	446 (27.0)	
	5–9	1042 (57.38)	937 (57.0)	
	≥10	217 (11.9)	250 (15.1)	
Number of patients discharged with 5 or more drugs, N (%)		1259 (69.2)	1187 (71.8)	*0.0997*
CIRS—severity index at admission[c], mean (SD)		1.62 (0.3)	1.67 (0.3)	*<0.0001*
CIRS—comorbidity index at admission[c], mean (SD)		2.80 (1.8)	3.11 (1.8)	*<0.0001*
CIRS—severity index at discharge[c], mean (SD)		1.66 (0.3)	1.72 (0.3)	*<0.0001*
CIRS—comorbidity index at discharge[c], mean (SD)		2.96 (1.9)	3.28 (1.9)	*<0.0001*
Barthel at admission, mean (SD)		77.42 (29.0)	81.20 (28.0)	*0.0255*
Short Blessed Test (SBT), mean (SD)		10.04 (8.2)	8.43 (7.4)	*<0.0001*
Geriatric Depression Scale (GDS), mean (SD)		1.41 (1.3)	1.18 (1.2)	*<0.0001*
Patients with at least one hospitalization in the previous 6 months[d], N (%)		324 (17.8)	364 (22.0)	*0.0020*

[a] Sample size = (3412/1787/1625).
[b] Sample size = (3342/1738/1604).
[c] It should be noted that severity and comorbidity indices are calculated only on the Reposi 2010 and 2012.
[d] Sample size = (1136/588/548).

5. Discussion

Data on gender differences in medication patterns in hospitalized patients are lacking. Several possible factors, other than the overall gender difference in diseases distribution, related to patient behavior and physician prescribing may contribute to diversities in medication use according to gender.

Treatment seeking, education, social status, compliance and adherence to therapy, are all factors that can affect the population medication pattern. Women are known to be more aware of preventive care issues and more proactive in seeking medical attention than men, nevertheless it has been reported that less often than men they persist in medication use over time [26]. Higher rate of side effects in women and/or failure to meet expectations of efficacy, especially for chronic treatments, along with socio-demographic issues, such as responsabilities for taking care of relatives or spouses, likely affect the adherence to medications [27]. On the physician perspective, sex differences in metabolism, drugs distribution activity and related adverse reactions may affect the prescribing choices and ultimately determine gender differences in specific treatments [28]. Women and men also differ in terms of anatomy, physiology and effect of aging on body functions and systems other than reproductive, mainly muscoloskeletal and cardiovascular ones, reflecting differences in drug responses especially in elderly. To this regard, data are scarse due to under-representation of elderly and women in clinical trials [29] as well as failure to report systematically sex-difference analyses on drug response and side effect rate. In the general population, there are more women than men and despite the higher prevalence of chronic disease in women they live longer and therefore are numerical prevalent in the old ages. Our study stemming from a prospective registry showed significant gender differences in overall medication patterns in people >65 years of age acutely admitted Italian internal medicine and geriatric wards. In our observation, the most relevant difference was observed for drugs acting on the nervous system, higher in women. Indeed, gender differences are known for a number of drugs acting on central nervous system [30]. Anxiety disorders are the most common psychiatric diseases and women are twofold more likely than men to develop them during lifetime [31]. Treatments with anxiolytics are therefore largely prescribed with different effects gender related including dependency-producing properties which are more pronounced in women [28].

Depression also is twice as common in women than men likely related to the hormonal profile and gender differences in serotonin levels and activities [32]. In our population of subjects 65 years of age or older, other factors such as socio-demographic differences between sexes may contribute to the differences between sexes in the use of drugs acting on the central nervous system. Indeed, women were older, more often widow and living alone than men, and were also more functionally impaired. All these conditions are likely to represent contributing factors for the higher request and prescription of neuropsychiatric medications. Moreover, it has been observed that women

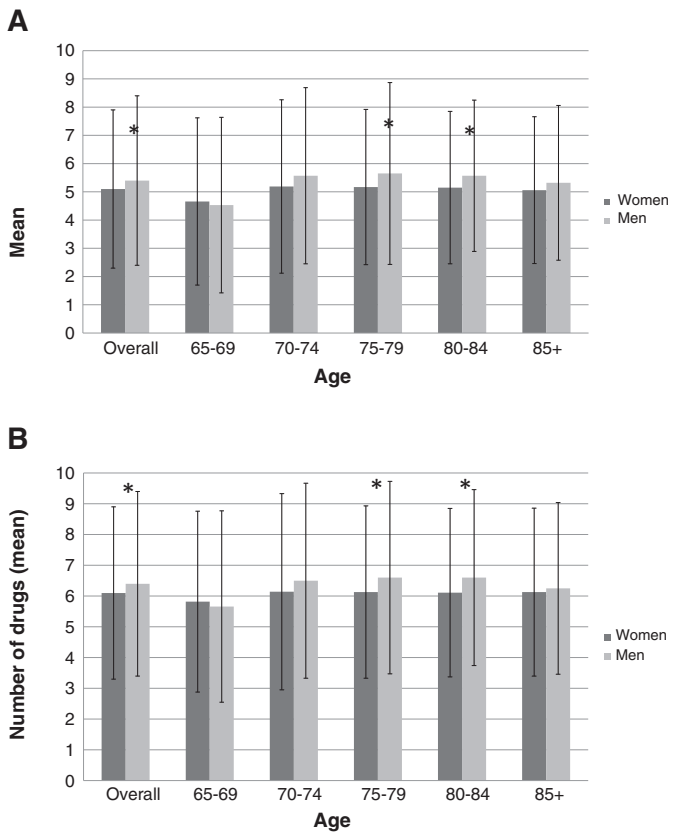

Fig. 1. A. Number of drugs (mean) at hospital admission by groups of age in according to gender. B. Number of drugs (mean) at hospital discharge by groups of age in according to gender.

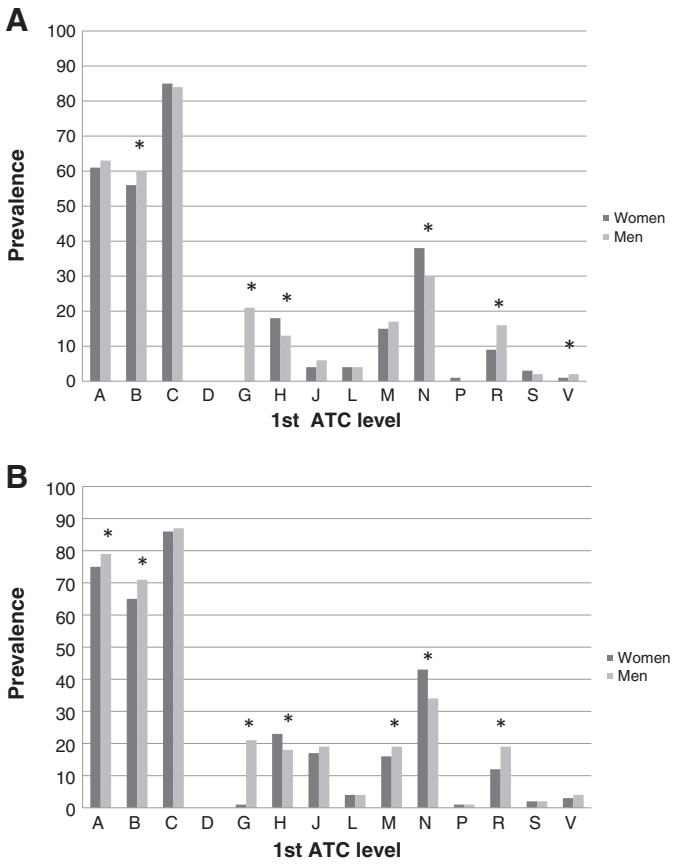

Fig. 2. A. Drugs distribution (1st ATC level) according to gender at hospital admission. B. Drugs distribution (1st ATC level) according to gender at hospital discharge.

consider themselves as suffering more than men of poor health and presenting greater morbidity leading to a higher request of medical attention and prescription of specific medications [33,34].

Antidepressants and anxiolytics were the most used among nervous system drugs both at admission and discharge, suggesting that hospitalization failed to represent an opportunity for a critical assessment of the appropriate clinical indication for these medications.

The higher prescription in men of drugs from the main anatomical group M is attributable to antigout medications (+6% in men), however the use of anti-inflammatory and anti-rheumatic drugs was prevalent in women (+0.8%). This is in agreement with a higher prevalence of musculoskeletal system and rheumatic disorders in women [35].

Cardiovascular drug classes were slightly more prescribed in men. This observation is not new nor surprising, since the higher prevalence of cardiovascular disease in men [36], the historical misconception that cardiovascular disease belongs to male gender as well as the under-representation of women in cardiovascular clinical trials [29] are all factors contributing to a higher prescription attitude of these drugs in men. At admission, antiplatelets, ACE-inhibitors and statins were the most prescribed cardiovascular medications in men. At discharge the gap between sexes for the prescription of ACE inhibitors was reduced, perhaps as result of better disease identification in the hospital setting, suggesting a previous under-recognition or under-treatment of cardiovascular diseases.

Moreover, our analysis showed that the hospitalization, rather than acting as an opportunity to potentially reduce the medication load, is associated with its overall increase [37], consistently with the well-known poor attitude to discontinue drugs (deprescribing) in several clinical settings [38]. Drugs belonging to the main anatomical group A, in particular proton pump inhibitors (PPI), showed the most marked increase in both sexes. The well established PPI overuse [39] highlights a likely inappropriate prescription of these drugs not free from severe side effects in the elderly [40]. In a previously published analysis from REPOSI more than 50% of patients 65+, between 70 and 84 years of age, were taking 5 or more drugs, mostly chronically. Consistent with our data hospitalization failed to lead to a reduction in the number of therapies at discharge, showing that among patients admitted with polypharmacy, only 3.5% were discharged with fewer than 5 drugs [41].

6. Strengths and limitations

The major strength of the study is the multicenter and prospective data collected of the REPOSI registry that makes the study representative of the overall Italian population of hospitalized elderly women

Table 2
Distribution of the most frequent diseases at hospital admission according to gender.

Diseases at admission	Women (N = 2089)		Men (N = 1946)	
	N	%	N	%
Hypertension	1448	69.3	1290	66.3
Diabetes mellitus	475	22.7	586	30.1
Chronic bronchitis	327	15.7	527	27.1
Other forms of chronic ischemic heart disease	329	15.7	487	25.0
Cardiac dysrhythmias	505	24.2	468	24.0
Hyperplasia of prostate	0	0.0	444	22.8
Chronic kidney disease (CKD)	255	12.2	392	20.1
Heart failure	254	12.2	265	13.6
Gastritis and duodenitis	263	12.6	220	11.3
Disorders of lipoid metabolism	221	10.6	200	10.3
Hypertensive heart disease	251	12.0	196	10.1
Other and ill-defined cerebrovascular disease	207	9.9	157	8.1

Table 3
Distribution of the ten most frequently prescribed drugs at hospital admission and discharge according to gender.

Variables	Women (N = 1819)	Men (N = 1654)	*P* value
Ten most frequent prescribed drugs at admission			
A02BC—proton pump inhibitors	782 (43.0)	729 (44.1)	*0.5198*
B01AC—platelet aggregation inhibitors excl. heparin	668 (36.7)	689 (41.7)	*0.0029*
C03CA—sulfonamides, plain, N (%)	631 (34.7)	596 (36.0)	*0.4078*
C09AA—ACE inhibitors, plain, N (%)	449 (24.7)	475 (28.7)	*0.0072*
C10AA—statins, N (%)	333 (18.3)	379 (22.9)	*0.0008*
C07AB—beta blockers, selective, N (%)	362 (19.9)	289 (17.5)	*0.0668*
C08CA—dihydropyridine derivatives, N (%)	315 (17.3)	277 (16.8)	*0.6555*
C01DA—organic nitrates, N (%)	237 (13.0)	243 (14.7)	*0.1565*
C09CA—angiotensin II antagonists, plain, N (%)	255 (14.0)	205 (12.4)	*0.1579*
B01AA—vitamin K antagonists, N (%)	207 (11.4)	213 (12.9)	*0.1765*
Ten most frequent prescribed drugs at discharge			
A02BC—proton pump inhibitors	1046 (57.5)	985 (59.6)	*0.2210*
B01AC—platelet aggregation inhibitors excl. heparin	684 (37.3)	722 (43.7)	*0.0003*
C03CA—sulfonamides, plain, N (%)	740 (40.7)	680 (41.1)	*0.7965*
C09AA—ACE inhibitors, plain, N (%)	532 (29.3)	512 (31.0)	*0.2779*
C10AA—statins, N (%)	357 (19.6)	416 (25.2)	*<0.0001*
C07AB—beta blockers, selective, N (%)	397 (21.8)	313 (18.9)	*0.0340*
C08CA—dihydropyridine derivatives, N (%)	341 (18.8)	280 (16.9)	*0.1623*
C01DA—organic nitrates, N (%)	271 (14.9)	277 (16.8)	*0.1357*
C03DA—aldosterone antagonists, N (%)	258 (14.2)	263 (15.9)	*0.1579*
B01AA—vitamin K antagonists, N (%)	252 (13.9)	254 (15.4)	*0n2101*

and men. Moreover, the main aim of REPOSI was to investigate polypharmacy in the multimorbid elderly acutely admitted to internal medicine and geriatrics wards, including in the registry all data on drugs therapies. Among limitations, information about medications use at hospital admission may not be fully accurate, being reported by the patient or his/her family. Moreover, we cannot account for the over-the-counter medicines and supplements before admission.

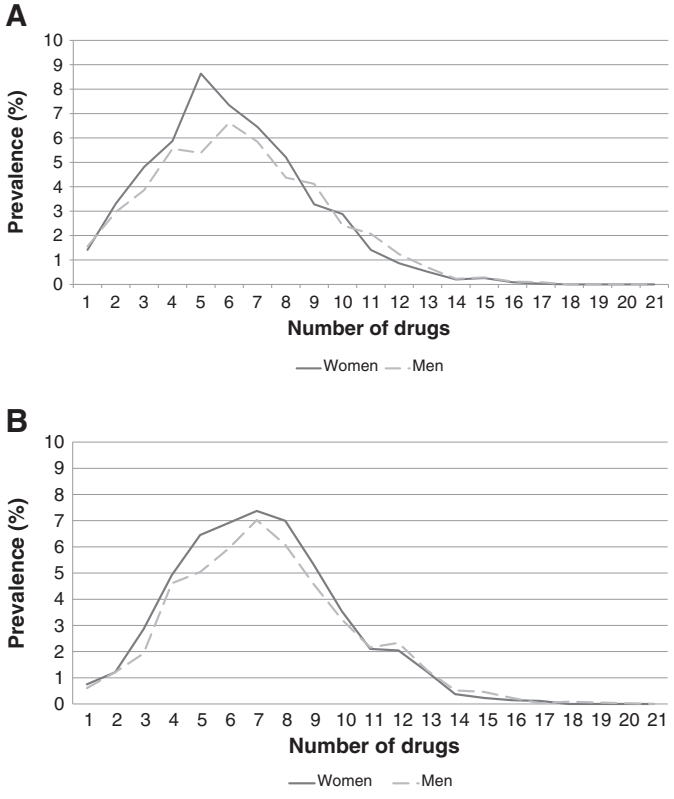

Fig. 3. A. Prevalence (%) of patients according to number of drugs by gender at hospital admission. B. Prevalence (%) of patients according to number of drugs by gender at hospital discharge.

7. Conclusion

Our study showed a gender difference in overall medications pattern in the hospitalized elderly. Neuropsychiatric medication use is prevalent in elderly women, likely related to socio-demographic characteristics of this population rather than to a proper indication. Hospitalization favored more cardiovascular drugs prescription in women, however leaving unchanged the high rate of prescription of neuropsychiatric drugs. Notwithstanding the fact that hospitalization represents a chance for improved disease identification and critical review of therapies, an overall increase of prescriptions was observed, in some instances questionable such as for PPI.

The key starting point for the study's rationale

- Knowledge on gender difference in medication use is largely missing
- Elderly are the largest medication users in the general population often taking multiple drugs on a regular basis.

This study adds

- Information on gender difference in medication prescription and use in a cohort of hospitalized elderly people
- Information on medication use and over-utilization of certain drug classes
- Information on changes in medications pattern due to hospitalization

Conflict of interest

Authors have no conflict of interest to report.

Author contributions

PS and CF equally contributed to the conception, design, and interpretation of data, drafting the article or revisiting it critically for important intellectual content and final approval of the version to be published. MT and CDD equally contributed to data acquisition and

analysis. LP, SC, FS, AM, and MM contributed to revisiting the manuscript. AN and PMM contributed to interpretation of data and revisiting the manuscript critically for important intellectual content and final approval of the version to be published.

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Appendix A

Investigators and co-authors of the REPOSI (REgistro POliterapie SIMI, Società Italiana di Medicina Interna) Study Group are as follows:

*Steering Committee:*Pier Mannuccio Mannucci *(Chair, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milano)*, Alessandro Nobili *(co-chair, IRCCS-Istituto di Ricerche Farmacologiche "Mario Negri", Milano),* Mauro Tettamanti, Luca Pasina, Carlotta Franchi *(IRCCS-Istituto di Ricerche Farmacologiche "Mario Negri", Milano),* Francesco Salerno *(IRCCS Policlinico San Donato Milanese, Milano),* Salvatore Corrao *(ARNAS Civico, Di Cristina, Benfratelli, DiBiMIS, Università di Palermo, Palermo),* Alessandra Marengoni *(Spedali Civili di Brescia, Brescia),* Maura Marcucci *(Unità di Geriatria, Fondazione IRCCS Ca' Granda—Ospedale Maggiore Policlinico & Dipartimento di Scienze Cliniche e di Comunità, Università degli Studi di Milano, Milano, Italia).*

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